Drug Substance: Movantik
Study Number: ESR-15-11000
Tufts IRB #12043
Version: Protocol version #19
Date: September 10, 2018

Impact of Naloxegol (Movantik) on Prevention of Lower Gastrointestinal Tract Paralysis in Critically Ill Adults Initiated on Scheduled IV Opioid Therapy: A Randomized, Double-Blind, Placebo-Controlled, Phase II, Single-Center, Proof of Concept Study

Sponsor:

Tufts Medical Center, Boston, MA through an Investigator-Initiated Research Grant from AstraZeneca Pharmaceuticals

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Abbreviations

Abbreviation	*Explanation*
APACHE	Acute Physiologic and Chronic Health Evaluation
COWS	Clinical Opioid Withdrawal Scale
CVP	Central venous pressure
DSMB	Data safety monitoring board
ECG	Electrocardiogram
FDA	Food and Drug Administration
GI	Gastrointestinal
ICDCSC	Intensive Care Delirium Screening Checklist
ICU	Intensive care unit
INR	International normalized ratio
IV	Intravenous
IRB	Institutional Review Board
LAR	Legally authorized representative
MC	Medical center
NRS	Numerical rating scale
OIC	Opioid induced constipation
PAMORA	Peripherally acting Mu opioid receptor antagonist
SAE	Serious adverse event
SAS	Sedation-Agitation Score
SBM	Spontaneous bowel movement
SOFA	Sequential organ failure assessment
WOCBP	Women of childbearing potential

1. INTRODUCTION

1.1 Background

Among the more than 5 million adults who are admitted to an ICU each year in the USA, most receive IV opioid therapy. Overall, IV opioid use in critically ill adults is increasing given the greater awareness of untreated pain in this population and a recent level 1 recommendation in the Society of Critical Care Medicine's Pain, Agitation and Delirium Practice Guidelines for Critically Ill Adults that an analgesia-first (analgo-sedation) approach be used to optimize patient safety and comfort and improve tolerance with mechanical ventilator support [1]. In critically ill adults with acute respiratory distress syndrome, high-dose infusions of opioids are frequently used to depress respiratory drive and reduce oxygenation needs.

Paralysis of the lower gastrointestinal (GI) tract, defined as the inability to pass stool due to impaired peristalsis, is a common sequelae of opioid use in the critically ill. [2] As outlined in the 2012 recommendation's from the European Society of Intensive Care Medicine's Working Group for Defining Gastrointestinal Function in Intensive Care Patients, paralysis of the lower GI tract, defined as the absence of stool for 3 or more days, in the absence of mechanical GI obstruction, is the preferred terminology for opioid-associated bowel dysfunction rather than constipation given that the symptoms of constipation (e.g., painful defecation, abdominal pain, and a feeling of incomplete bowel evacuation) are not possible to evaluate in most patients in the ICU. Paralysis of the lower GI tract occurs in up to 72% of critically ill adults. [4-7]

The frequent use in the ICU of tube feed formulations having low fiber, a lack of patient mobility, and restrictive fluid policies will further magnify the impact of opioids on the prevalence of lower GI tract paralysis in this population. [8-12]. Lower GI tract paralysis will often lead to nausea and vomiting, aspiration, compromise the ability to administer enteral nutrition (and thus reach nutritional goals), greater abdominal pain, and has been shown to delay extubation. Constipation in the critically ill has recently been reported to be associated with greater delirium [13] One recent randomized study found that aggressive use of laxatives to prevent lower GI tract paralysis in critically ill adults was associated with lower daily organ dysfunction [as measured by the Sequential Organ Failure Assessment (SOFA) score][14] The lower GI tract paralysis that occurs in the critically ill often responds poorly to stimulant and osmotic laxative therapy. [10, 11]

1.2 Rationale for conducting this study

While stool softeners are routinely administered to patients on opioids, laxative-based bowel protocols are frequently not initiated in the ICU until signs of lower GI tract paralysis start to become evident. Even if laxatives were used earlier and more aggressively in the ICU care to prevent lower GI tract paralysis, a large proportion of patients receiving continuous IV opioid therapy would still not fully respond, and laxative-associated safety issues would increase. <u>There is therefore an important unmet need for a safe and efficacious medication to prevent lower GI tract paralysis in critically ill adults who are initiated on IV opioid therapy</u>. [10, 11]

Naloxegol, a pegylated naloxone tablet formulated for once daily oral administration, is a peripherally acting μ opioid receptor antagonist with established efficacy and safety in treating opioid-induced

constipation (OIC) in non-ICU patients receiving scheduled moderate to high dose opioids for the treatment of chronic non-cancer pain. [10] Naloxegol has a mechanism of action, efficacy, convenience of administration, and safety profile that make it an ideal candidate for use as a preventative medication for lower GI tract paralysis in critically ill adults receiving continuous IV opioid therapy. A Phase II, proof of concept study to evaluate the efficacy and safety of naloxegol as a strategy to prevent lower GI tract paralysis in these high-risk critically ill adults, and to serve as guide for future larger RCTs in this area, is crucial in filling a major knowledge and care gap in critical care practice.

Despite the prevalence of lower GI tract paralysis in the ICU, large knowledge gaps exist regarding its epidemiology, the optimal way to define it, and the ideal methods that should be used to characterize its severity and resolution. Moreover, the fact that that no lower GI tract paralysis prevention strategy has ever been evaluated in the critically ill using a randomized, controlled design makes it unclear what a reasonable treatment effect should be and what the variability would be for any particular efficacy outcome that is chosen.

Therefore, while a strong rationale can be made that naloxegol may safely and effectively prevent lower GI tract paralysis in critically ill adults administered opioids, there is an important need for a rigorous Phase II proof of concept study to help justify and inform future research efforts with naloxegol in this population. Such a Phase II proof of concept investigation should be randomized and double-blind and carefully evaluate the validity and feasibility of the different endpoints that can used to evaluate naloxegol safety and efficacy in the ICU patient at high risk for lower GI tract paralysis. This Phase II proof of concept investigation will allow for a much better characterization of how lower GI tract paralysis develops (and resolves) in the critically ill and also help define the variability that exists around each of the clinical endpoints that are evaluated. The recent finding that resolution of constipation will reduce organ dysfunction suggests that abdominal pressure monitoring may serve as an important secondary outcome in any study focused on evaluating the efficacy of a new intervention to reduce lower GI tract paralysis in critically ill adults. [14] This Phase II proof of concept study is critical in not only justifying the potential completion of larger investigations in this area but also to ensure, if they are justified, that they are correctly designed in terms of sample size, primary and secondary outcomes and how potential confounders are identified and managed. While larger investigations that have the power to evaluate important outcomes like nutrition delivery, delirium, use of early mobilization, duration of mechanical ventilation, length of ICU stay, ICU mortality and healthcare costs are critical when evaluating the true clinical benefit/impact of naloxegol as a lower GI tract paralysis prevention strategy in the critically ill, given the substantial time, effort and expense of conducting large multicenter studies in this area, it is critical that future research efforts be meticulously planned through thoughtful and rigorous Phase II proof of concept investigations like the one proposed.

1.3 Research hypothesis

Naloxegol will prevent lower GI tract paralysis in critically ill adults initiated on scheduled intravenous opioid therapy and its use will not lead to safety concerns.

1.4 Benefit/risk and ethical assessment

The package insert for naloxegol contains warnings that necessitate an assessment of the risk/benefit in the context of its planned use in this protocol.

Potential Benefits

Lower GI tract paralysis occurs frequently in the ICU as a result of opioid initiation and is associated with substantial patient morbidity including discomfort, underfeeding, prolonged mechanical ventilation, delirium and potentially worsening organ dysfunction. The administration of currently available laxative(s) frequently does not prevent lower GI tract paralysis and thus there is a need for efficacious and safe therapies to prevent lower GI tract paralysis secondary to opioid use in critically ill adults. Naloxogol (Movantik) is new oral gut-selective Mu-receptor antagonist that is FDA-approved for the treatment of opioid-induced constipation in non-critically ill adults without cancer. In two large randomized controlled studies of patients with opioid-induced constipation (many of who were received one or more laxative treatments) it has been shown to be efficacious in quickly resolving opioid-induced constipation. If naloxegol is shown to be effective in preventing opioid-induced lower GI tract paralysis, it will represent an important advance in the care of the critically ill.

Potential Risks

a. Naloxegol is contraindicated in patients with known or suspected gastrointestinal obstruction and patients at increased risk for recurrent obstruction due to potential for gastric perforation.

   The following steps have been taken in the protocol to minimize the risk for this adverse event: Patients with proven or suspected gastric obstruction are excluded from the study.

b. Naloxegol is contraindicated in patients concomitantly taking strong CYP3A4 inhibitors (e. g., clarithromycin, ketcononazole) given the likehood that the concomitant use of these agents will lead to supratherapeutic serum concentration (which could potentially induce opioid withdrawal).

   The following steps have been taken in the protocol to minimize the risk for this adverse effect: Patients taking a strong CYP3A4 inhibitor are excluded from the study. If there is a clinical need to use a strong CYP3A4 inhibitor medication (and another therapeutic option without these properties is not available) then the subject will be removed from the study.

c. In the package insert, it is stated that naloxegol is contraindicated in patients concomitantly taking strong CYP3A4 inducers (e.g. rifampin, carbamazepine, St. John's Wort) as it could significantly decrease plasma naloxegol concentratios and may decrease the efficacy of naloxegol (Movantik).

   The following steps have been taken in the protocol to minimize the risk for this effect. Patients taking a strong CYP3A4 inducer are excluded from the study. If there is a clinical need to use a strong CYP3A4 inducer medication (and another therapeutic option without these properties is not available) then the subject will be removed from the study.

d. Cases of gastrointestinal perforation have been reported with the use of another peripherally acting mu opioid receptor antagonist (PAMORA) when used in patients who have a diffuse or local reduction in the structural integrity in the wall of the gastrointestinal tract.

   The following steps have been taken in the protocol to minimize the risk for this adverse effect. The following patients are excluded from the study: i. admitted with an acute GI condition (e.g., clinical evidence of acute fecal impaction/complete obstruction, acute surgical abdomen, acute GI bleeding), ii. having a condition affect affecting GI motility or function (e.g. inflammatory bowel disease

requiring immunosuppressive therapy, symptomatic Clostridium difficile, active diverticular disease, surgery on the colon or abdomen within 60 days of ICU admission or iii. having a history of constipation at the time of ICU admission.

e. The effect of severe hepatic impairment (e.g. Cirrhosis with a Child-Pugh Class scale score of B or C) on the pharmacokinetics of naloxegol has not been evaluated.

The following steps have been taken in the protocol to minimize the risk for this adverse effect: Patients with severe hepatic impairment are excluded from the study.

f. Naloxegol has been very rarely associated with signs of opioid withdrawal.

The following steps have been taken in the protocol to minimize the risk for this adverse effect:

i. Patients having an acute disruption of the blood brain barrier (that could potentiate naloxegol absorption to the CNS) are excluded from the study.
ii. Patients taking scheduled opioids at the time of ICU admission are excluded.
iii. Each study patient will be carefully monitored before and 2 hours each study dose for signs of opioid withdrawal using the Clinical Opioid Withdrawal Scale (COWS) score.

g. No data regarding use of naloxegol in pregnancy and its use in a pregnant female taking opioids may precipitate opioid withdrawal in the infant.

The following step has been taken in the protocol to minimize the risk for this adverse effect. All female patients will be screened with a pregnancy test prior to study enrollment and if found to be pregnant will be excluded from the study.

h. No data regarding use of naloxegol in lactating mothers and its use in a lactating female taking opioids may precipitate opioid withdrawal in the fetus.

The following step has been taken in the protocol to minimize the risk for this adverse effect. All lactating females will be excluded from the study.

i. In the package insert, it is recommended that maintenance laxative therapy be discontinued before starting naloxegol and that laxative therapy should only be resumed in those patients who have OIC symptoms and after no sooner than 3 days after naloxegol was initiated.

This recommendation is based on the treatment of OIC in an outpatient setting and is not based on the usual clinical practices that are used to prevent lower GI tract paralysis in the ICU. Given that half the patients in the study will be randomized to placebo (in a blinded fashion), it is important that normal ICU lower GI tract paralysis prevention practices are incorporated into the research protocol. It is standard practice that all patients initiated on opioid therapy in the medical ICU at Tufts MC are started on scheduled docusate therapy and then managed with a step-wise laxative therapy (in a similar fashion to the laxative protocol developed for the study) as symptoms of lower GI tract paralysis develop and persist. The study laxative protocol accounts for patients who do have a SBM (i.e., laxative therapy is down-titrated/stopped), and stool softness and frequency is carefully being monitored as part of the study, so it is not expected that study patients, regardless of study

assignment, will receive a greater amount of laxative therapy than is clinically necessary to prevent lower GI tract paralysis.

j. Scheduled use of opioids (≥ 100 mg morphine equivalents per day in the week prior to ICU admission) is a study exclusion criteria. This is information may be considered sensitive information and should be carefully collected in a de-identified fashion.

During the study screening process, the patient's medical record will be reviewed to see if the patient has a history of opioid use (both prescribed and non-prescribed). In addition, at the beginning of the consent discussion, the patient (legally authorized representative) will be asked whether the patient has used an opioid in the past week. If such use is not detected (i.e., through both methods), the patient will be deemed NOT to meet this study exclusion criteria. The study screening log (where the reason(s) for patient exclusion is documented) are completed de-identified so this information regarding opioid use will remain protected. If this opioid use history information is already documented in the patient record, then the patient will be excluded from study participation and the study team will never meet with the patient/authorized representative. If this opioid use history information is not documented in the patient record, but then identified through a discussion with the patient (or legally authorized representative), it will remain in the confidence of the investigative team (ie. not provided to the medical team) and documented in a de-identified fashion only on the study screening log as an exclusion criteria.

k. Removal of urinary (foley) catheters in the ICUs at Tufts MC is an important quality improvement initiative, will a urinary catheter be used solely for research purposes and is there a risk to inserting the bladder pressure transducer into a foley catheter that is already in place?

The answer is never. The bladder pressure that is being measured for research purposes requires that a bladder catheter be in place (to aseptically insert the bladder pressure transducer into the bladder catheter, thus creating a closed system). When the ICU team decides that a urinary catheter is no longer required for patient care then all bladder measuring will cease. If a subject is enrolled in the study who does not have a urinary catheter in place, a urinary catheter will NOT be inserted for research purposes. The study investigators met with the Tufts Med Center Urinary Tract Infection Committee chaired by Shira Doron, MD, last fall to discuss two issues

1. The Tufts Medical Center Urinary Tract Infection Committee felt that the insertion of the pressure tranducer into the red foly port (ie breaking the seal) would not lead to a clinically significant enough risk for a caUTI that would preclude abdominal pressure monitoring as part of the study.

   Action: The investigators will raise the fact that there may be a very small risk for caUTI with abdominal pressure monitoring in the research protocol (in the risk/benefit portion) and will include a statement of this risk in the study ICF.

2. The Tufts Medical Center Urinary Tract Infection Committee was concerned that foley catheters may be left in place longer for abdominal pressure monitoring than would be clinically required (particularly given that ICU clinicians may sometimes "search" for an excuse to keep the foley catheter in place). Dr. Devlin (on behalf of Dr. Garpestad) emphasized that there was no intent, on the part of the investigators, to keep a foley in place longer than was clinically necessary. In no instance, would a foley be inserted solely for abdominal pressure monitoring.

The investigators will incorporate in the research protocol that MICU service will be formally asked each morning whether the foley catheter can come out of the patient (and to emphasize to the MICU team that a foley catheter should only remain in the patient if there is a clinical need). The answer to this question will be formally documented on the daily bedside study data collection form.

2. STUDY OBJECTIVES

Given that there is no one "gold-standard" way to characterize the efficacy of naloxegol to prevent lower GI tract paralysis in critically ill adults administered scheduled opioids, given the Phase II, proof of concept nature of this investigation we plan to consider multiple outcomes to evaluate naloxegol's efficacy in this population. Since the original April 2015 protocol submission, in an effort to help better define those outcomes that are most relevant to clinicians when they are considering the efficacy (and safety) of a preventative strategy like naloxegol in their critically ill patients at risk for lower GI tract paralysis, we informally surveyed clinicians at Tufts Med Center (and elsewhere). Of note, time to the first spontaneous bowel movement (SBM) (which is directly related to our primary outcome of prevention of lower GI tract paralysis) was suggested most frequently as the most clinically relevant outcome when evaluating a new lower GI tract paralysis prevention intervention. Clinicians noted that once a patient receiving scheduled opioid therapy has their first SBM (and remained on any particular lower GI tract prophylaxis regimen) that the patient should ideally be expected to have a SBM at least daily. Therefore, these clinicians felt that comparing the ICU days without a SBM (noting that when 3 days without a SBM is met, the definition for lower GI tract paralysis is met) was also a clinically meaningful way to compare naloxegol with placebo. While most respondents questioned whether it was necessary (or even possible) to rigidly define a SBM (e.g., based on a specific fecal output volume), they suggested that we collect the following data for each SBM [1. Stool volume (i.e., small, medium or large) and 2. Stool consistency (i.e. using the Bliss stool scale score)] Clinicians generally felt that the other outcomes that were proposed in the previous version of this protocol (for both efficacy and safety) in April 2015 were all appropriate and should all be collected given the pilot nature of this investigation. With the recently published study by Palacio de Azeda et al [13] that found that the use of an aggressive daily lactulose and enema protocol reduced the average daily SOFA (organ severity) score, and that highlighted that there may be an important connection between lower GI tract paralysis and abdominal pressure, we would like to incorporate collection of daily SOFA scores and thrice daily measurement of abdominal pressure as an efficacy outcome in the study. Lastly, a recent paper found a strong relationship between delirium and lower GI tract paralysis in the critically ill and thus we propose to monitor each subject twice daily for delirium. [12].

Overall Study Aim

The overall aim of this Phase II, proof of concept study is to evaluate the efficacy and safety of naloxegol (versus placebo) in preventing lower GI tract paralysis in critically ill adults initiated on scheduled intravenous (IV) opioid therapy.

2. 1 Primary objective

The primary objective of this single-center, Phase II, proof of concept study in critically ill adults initiated on scheduled IV opioid therapy is to compare the incidence of lower GI tract paralysis [from the time of a study enrollment (i.e., randomization) to ICU discharge, death or 10 days of study drug administration (whichever comes first)] between naloxegol 25mg daily and placebo-treated groups.

Note:
1. For the purposes of the study, any rectal output will be considered a SBM as long as it not temporally related to the insertion of a rectal tube or the insertion of a suppository (as per the study laxative protocol (Appendix 1).
2. Patients with preexisting lower GI tract paralysis are excluded from the study.
3. Patients not expected to survive their ICU stay are excluded from the study.

2. 2 Secondary objectives

To compare the efficacy of naloxegol (with placebo) in critically ill adults initiated on scheduled IV opioids on each of the following outcomes:

During the period from time of scheduled opioid therapy initiation (IV fentanyl equivalent dose ≥ 100 mcg/day) until ICU discharge, death or 10 days of study drug administration (whatever comes first):
(Note: there are up to three days to enroll and randomize subject after the initiation of scheduled opioid therapy).

a. Incidence of lower GI tract paralysis (≥ 3 days without a SBM)
b. Time to first SBM (in hours)
c. Days without a SBM
d. Average daily opioid requirement [in IV fentanyl equivalents (mcg)].

Note:
1. For the purposes of inclusion in the study, only opioids administered by the IV route will be considered but to calculate the daily opioid requirement all opioids administered (regardless of route) will be considered. All enteral/oral opioids will be reduced by 50% when converting to the IV fentanyl equivalent.
2. Administration of opioids will be mandated by the ICU team (as per routine clinical practice based on the ICU team evaluation of regular pain assessment scores) and will not be protocolized as part of the study.
3. While IV fentanyl is the most common IV opioid used in the medical ICU at Tufts MC, other opioids (e.g. IV and oral hyromorphone, oral oxycodone) are used at times. Choice of opioid during routine patient care is currently not protocolized in the ICUs at Tufts MC and will not be protozolized as a part of this study. The choice and amount of opioid administered each day will be collected as part of the study.

During the period from time of study enrollment (i.e., randomization) to ICU discharge, death or 10 days of study drug administration (whatever comes first):

e. Time to first SBM
f. Daily characterization of each SBM for size (small, medium or large)
g. Daily characterization of each SBM for consistency (using the Bliss Stool Scale)
h. Daily characterization of use of the study laxative guidelines.
i. Daily volume of enteral nutrition administered.
j. % of daily enteral nutrition goal met.
k. Daily fluid balance (i.e., 24 hr ins and outs)
l. Daily maximal pain scale score (using nurse-administered 10 point rating scale)

m. Daily Sedation Assessment Scale (SAS) score
    a. Average
    b. Presence of coma (SAS = 1 or 2)
n. Daily presence of delirium using the Intensive Care Delirium Screening Checklist (ICDSC)
    a. Proportion of patients ever found with delirium (ICDSC ≥ 4]
    b. Days with delirium
    c. Proportion of patients ever found with subsyndromal delirium [ICSDC = 1 to 3]
    d. Days with subsyndromal delirium
o. Daily total sedation administered (in midazolam equivalents)
p. Occurrence of lower GI tract paralysis requiring consultation by a gastroenterologist or a surgeon.
q. Days without mechanical ventilation support.
r. Duration of ICU stay.
s. In patients having a clinical reason for foley catheter placement, abdominal pressure measurement every 8 hours:
   i) % patient of patients having abdominal pressure ≥ 12 mmHg; ii) % patient of patients having abdominal pressure ≥ 20 mmHg; iii) Average daily maximal abdominal pressure score
t. Time from first initiation of ≥ 100 fentanyl equivalents to administration of first dose of study medication.

2. 3 Safety objectives

To compare the safety of naloxegol (with placebo) in critically ill adults initiated on scheduled IV opioids for each of the following outcomes:

During the period from time of study enrollment (i.e. randomization) to ICU discharge, death or 10 days of study drug administration (whatever comes first):

a. Diarrhea:
    a. Daily presence
    b. Time from study drug initiation to first episode of diarrhea
    Note: Diarrhea is defined where ≥ 3 loose or watery stools 24 hour period as defined by a Bliss stool scale score of 3 (loose and unformed stool) or 4 (liquid stool)].

b. Days without a diaper or rectal tube
c. Days without a rectal tube
d. Daily difference in the pre-dose and post-dose Clinical Opioid Withdrawal Scale (COWS) score (as evaluated by the bedside nurse before and 2 hours after the administration of the daily study drug dose).

3. STUDY PLAN AND PROCEDURES

This study will be conducted at Tufts Medical Center in Boston, MA. No study-related procedures will be conducted at Northeastern University.

3.1 Overall study design and study flow chart

This will be a Phase II, proof of concept, single-center, randomized, double-blind, placebo-controlled pilot study to assess the efficacy and safety of naloxegol for preventing lower GI tract paralysis in 36 (18 naloxegol; 18 placebo) medical critically ill adults who require scheduled IV opioid therapy.

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Table 1. Study Plan

Study period	**ICU admission and initiation of scheduled opioid**	**Treatment Period (maximum of 10 days)**										**Study drug stopped or early termination**	**Discharge from ICU**	
Study day	**Maximum of 72 hrs to enroll patient**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**			
Screening	√													
Randomization		√												
Use of study laxative guideline		√	√	√	√	√	√	√	√	√	√	√		
Administration of study medication		√	√	√	√	√	√	√	√	√	√			
Baseline demographic information	√	√												
Inclusion/Exclusion criteria	√													
Pregnancy test for WOCBP	√													
Efficacy outcomes														
Monitoring that is a routine part of care at Tufts MC														
Bedside nurse														
Documentation of all SBMs	√	√	√	√	√	√	√	√	√	√	√	√		
Volume of enteral nutrition administered		√	√	√	√	√	√	√	√	√	√	√		
Fluid balance		√	√	√	√	√	√	√	√	√	√	√		
Sedation assessment SAS q6h)		√	√	√	√	√	√	√	√	√	√	√		
Pain assessment (numerical rating q6h)		√	√	√	√	√	√	√	√	√	√	√		
Delirium assessment (ICSDC q12h)		√	√	√	√	√	√	√	√	√	√	√		
Investigative team														
Documentation of study laxative guideline use		√	√	√	√	√	√	√	√	√	√	√		
% of daily enteral nutrition goal achieved		√	√	√	√	√	√	√	√	√	√	√		
Daily opioid requirements	√	√	√	√	√	√	√	√	√	√	√	√		
Daily sedative requirements		√	√	√	√	√	√	√	√	√	√	√		

Serum creatinine to calculate creatinine clearance	√	√	√	√	√	√	√	√	√	√	√			
Monitoring that is not a routine part of care at Tufts MC														
Bedside nurse														
Characterization of each SBM for size		√	√	√	√	√	√	√	√	√	√	√		
Characterization of each SBM using the Bliss Scale		√	√	√	√	√	√	√	√	√	√	√		
Measurement of bladder pressure in subjects with a foley catheter in place for a clinical reason (to estimate abdominal pressure) q8h		√	√	√	√	√	√	√	√	√	√			
Investigative team														
Requirement for mechanical ventilation	√	√	√	√	√	√	√	√	√	√	√	√		
SOFA score calculation (daily)		√	√	√	√	√	√	√	√	√	√	√		
Occurrence of lower GI tract paralysis requiring a GI or surgical consult		√	√	√	√	√	√	√	√	√	√	√		
Safety outcomes														
Monitoring that is a routine part of care at Tufts MC														
Bedside nurse														
Presence of diarrhea	√	√	√	√	√	√	√	√	√	√	√	√		
Investigative team														
Presence of a diaper or rectal tube		√	√	√	√	√	√	√	√	√	√	√		
Monitoring that is not a routine part of care at Tufts MC														
Bedside nurse														
Characterization of diarrhea using the Bristol Scale		√	√	√	√	√	√	√	√	√	√	√		
Evaluation for opioid withdrawal using the COWS scale before and 2 hours after each daily study dose		√	√	√	√	√	√	√	√	√	√			

Additional assessments not included in table:

1. Baseline demographics [age, gender, APACHE II score, Charlson comorbidy scale score, primary reason for ICU admission (based on APACHE III criteria)], baseline comorbidities potentially associated with an increased risk for lower gastrointestinal tract paralysis, treatments

received at the time of ICU admission or administered after ICU admission that might influence SBM frequency and/or lower gastrointestinal tract paralysis incidence, and primary reason(s) for scheduled opioid initiation.

2. Evaluation for adverse events

Impact of Level of Sedation on Patient Assessments: Patients admitted to the Medical ICU at Tufts MC are generally maintained in an awake or lightly sedated state. For a patient who may require a short period of deeper sedation all of the following assessments above will be able to be still evaluated/collected **except**: COWS

3.2 Rationale for study design, doses and control groups.

There are many potential sources of bias in study that investigating the efficacy of safety of naloxegol for the prevention of lower GI tract paralysis in critically ill adults and thus a double-blind, placebo-controlled study is the gold standard study design to use. There is no reason to suggest that a dose of greater than 25mg daily of naloxegol (the current FDA-approved dose for the treatment of opioid induced constipation) is not the appropriate dose for this pilot investigation. As outlined in the current package insert, the study dose will be reduced to 12.5mg daily when patients are concomitantly administered a moderate CYP314 inhibitor or who have renal dysfunction (calculated creatinine clearance ≤ 60 ml/min). Given that this is a randomized study, the treatment and control groups should be identical. Initiation of docusate 100mg twice daily is a standard of practice in all patients receiving an opioid who are admitted to the medical ICU service at Tufts Medical Center. Given that it remains unknown if naloxegol is efficacious in preventing lower GI tract paralysis in critically ill adults and that half the patients will be administered placebo, all patients will be managed with an aggressive standardized laxative protocol that is based on the most common clinical practices in the ICUs at Tufts Medical Center.

4. SUBJECT SELECTION CRITERIA

The investigators will maintain a screening log for the duration of the study.

Each patient will meet all of the inclusion criteria and none of the exclusion criteria. A study screening sheet will be completed by a member of the investigative staff and confirmed by a second member of the investigation staff before randomization will occur.

All patients consecutively admitted to the medical ICU service who are admitted to the MICU, CCU, SICU or NCCU at Tufts Medical Center will be screened on a daily basis (through review of the ICU admission note, available laboratory data, the medication administration record, and the patient flowsheet by one of the study investigators who will determine if the patient meets all inclusion and exclusion criteria for participation in the study.

When the patient is found to meet all inclusion and no exclusion criteria, and Drs. Garpestad, Preston or Roberts have reviewed and signed the screening form, and the patient's primary ICU attending has approved their enrollment, the subject/legally authorized representative will be approached (either in person or by phone (ie. invited to come to Tufts MC to discuss the study) during the periods of 7am to 7pm.

4. 1. Inclusion criteria

a. Admitted to the medical ICU service.

b. Age ≥ 18 years.

c. Expected by the medical ICU attending physician to require admission to the MICU service for ≥ 48 hours.

d. Intravenous opioid administration in the prior 24 hours of ≥ 100 mcg fentanyl equivalents (including both scheduled and "as needed" therapy).

e. No objections from the MICU or attending physician for enrollment.

4. 2 Exclusion criteria

a. Scheduled use of morphine, oxycodone, hydromorphone, fentanyl ≥ 100 mg morphine equivalents per day in the week prior to ICU admission as evaluated by medical record review and/or interview with patient and/or family.

b. Scheduled use of methadone at any dose in the week prior to ICU admission as evaluated by medical record review and/or interview with patient and/or family.

c. History of constipation (as defined by the scheduled use of bisacodyl, senokot, lactulose, PEG 3350 (Miralax) and/or Fleet enema) prior to ICU admission as evaluated by medical record review and/or interview with patient and/or family.

d. Current scheduled use a medication affecting gastric motility (i.e., metoclopramide, domperidone, erythromycin and loperamide).

e. Current use of medication known to be a strong CYP3A4 inhibitor (itraconazole, lopinavir/ritonavir, clarithromycin, ritonavir, ketoconazole, indinavir/ritonavir, voriconazole, nefazodone).

f. Current use of a medication known to be a strong CYP3A4 inducer (rifampin, carbamazepine, St. John's Wort).

g. Known serious or severe hypersensivity to naloxegol (Movantik) or any of its excipients.

h. Patients admitted with a history of a neurologic condition that may affect the permeability of the blood-brain barrier (e.g. multiple sclerosis, recent brain injury, Alzheimer's disease, uncontrolled epilepsy, acute stroke, acute meningitis).

i. Patients admitted with an acute GI condition (e.g., clinical evidence of acute fecal impaction/complete obstruction, acute surgical abdomen, acute GI bleeding).

j. Patients with a condition affecting GI motility or function (e.g. inflammatory bowel disease requiring immunosuppressive therapy, symptomatic Clostridium difficile, active diverticular disease, surgery on the colon or abdomen within 60 days of ICU admission.

k. Patients with underlying cancer who are at heightened risk of GI perforation such as those with underlying malignancies of the GI tract or peritoneum, recurrent or advanced ovarian cancer, vascular endothelial growth factor inhibitor treatment.

l. Current use of total parenteral nutrition

m Administration of enteral nutrition through a jejeunal tube.

n. Severe hepatic dysfunction

[Defined as either: i. INR ≥ 2.0 (not related to warfarin therapy) AND total bilirubin ≥ 2 or ii. Diagnosis of liver cirrhosis as defined by Child-Pugh classes B or C or iii. acute liver disease is the primary reason for admission to the ICU.]

o. Inability to enroll in study and initiate study medication within 72 hours of the patient being first initiated on IV opioid therapy after ICU admission.

p. Unreliable method for enteral, gastric and/or oral medication administration (e.g., no feeding tube, NG tube is on suction).

q. Current or previous use of an opioid antagonist agent (e.g., naloxogel, methylnaltrexone) agent in the past 30 days.

r. Patients expected to expire within 24 hours.

s. Pregnant or actively lactating females.

t. Current participation in another interventional clinical study.

u. Inability to obtain informed consent from either the subject or their legally authorized representative.

5. STUDY CONDUCT

5. 1 Restrictions during the study

Restrictions regarding laxative use, restricted medications and requirements for change in the study drug dose are provided in Section 5.6

5.2 Subject enrollment, randomization and the initiation of the investigational product

5.2.1 Informed Consent Process

All patients consecutively admitted to the medical ICU service who are admitted to the MICU, CCU, SICU or NCCU at Tufts MC will be screened on a daily basis (through review of the ICU admission note, available laboratory dat, the medication administration record, and the patient flowsheet by one of the study investigators who will determine if the patient meets all inclusion criteria and has no exclusion criteria participation in the study. An enrollment screening sheet (submitted to IRB) will be reviewed and signed by either Dr. Garpestad, Dr. K. Roberts or Dr.Preston before the patient/LAR is approached for consent.

For non-English speaking patients (legally authorized representatives) who are invited to participate in the study, and an IRB-approved Short Form consent exists for their language, the IRB-approved consent Short Forms per the IRB's Short Form policy will be used during the consent discussion.

Informed consent will be obtained by Drs. Garpestad, Devlin, Duprey, Faugno, K. Roberts, or Preston. Approval will be obtained from the subject's Medical ICU attending physician before a consent discussion occurs. Dr. Devlin is a critical care pharmacist researcher with more than 20 years of

experience in obtaining patient consent from critically patients (or their legally authorized representatives). In the numerous ICU clinical trials he has served as a co-investigator/research coordinator at Tufts Medical Center he has led consent discussions for more than 400 patients. Over the past 6 months, Dr. Duprey has been trained by Drs.Garpestad and Devlin to conduct high quality consent discussions for this study. During March/April 2017, Drs. Garpestad and/or Devlin carefully evaluated 5 different consent discussions conducted by Dr. Duprey using an IRB-approved review metric and found that Dr. Duprey can conduct high-quality consent discussions that meet all of the criteria of the Tufts MC IRB. Drs. Devlin, Duprey and Faugno will always ensure that Dr. Garpestad (or Dr. Preston or Dr. K. Roberts) will always be available to participate in a consent discussion should questions (medical or otherwise) come up that Dr. Devlin, Dr. Duprey or Dr. Faugno feel he is not qualified to answer. Given Drs Devlin, Faugno and Duprey's experience in consent discussions with ICU patients/their representatives, there are no plans to have the PI or a medical Co-I be present during all or part of the consent process unless the ICU patient (or their representative) have questions that Dr. Devlin. Faugno, or Duprey cannot answer.

All patients will be evaluated by a member of the investigative team to determine if they have the mental capacity to provide consent for study participation. For the purposes of this study, a patient will be deemed to be cognitively intact if they have an ICDSC=0 (i.e. neither delirium nor subsyndromal delirium) and are not sedated. It is expected that the vast majority of patients will be not able to initially provide consent given their critical care illness and the use of scheduled opioids that have sedative properties. In addition, it is estimated that about two-thirds of the potential subjects will be mechanically ventilated and thus all be received sedative medications. Furthermore, close to 70% of patients of all patients admitted to the ICU have delirium or subsyndromal delirium, cognitive states that prevent obtaining consent from subjects. Drs. Garpestad, Preston, K. Roberts , Devlin, Duprey and Faugno will each be able to determine whether the subject is able to provide informed consent. As per the ICF, a legally recognized representative will be recognized in the following order: healthcare proxy (that is documented and verified) > spouse >adult child > parent of guardian > adult sibling.

Before the enrollment of a decisionally-impaired subject Drs. Garpestad, Preston, K. Roberts, Devlin, Faugno and/or Duprey will confirm that the study is not prohibited by law for this subject. The legally authorized representative will be contacted and invited to meet face-to-face with one of the investigators to provide written consent at Tufts Medical Center. Permission will be obtained from the primary provider for the participation of the patient in the study before the legally authorized representative is contacted. All consent discussions with a legally authorized representative will take place in location at Tufts MC that is both private and quiet (e.g., an ICU conference room). The legally authorized represenative (or the patient) will be provided with a copy of the consent form to read and all questions will be answered prior to their signing the consent. All sections of the ICF will be carefully reviewed including the fact that the legally authorized representative is free to discontinue the participation of the subject at any time for any reason. No research related activities will occur prior to the consent being signed. The original signed ICF will be stored in the locked office of the investigator. A copy of the signed ICF will be given to the legally authorized representative and the methods (as outlined in the ICF) to research a member of the research team if they have additional questions will be emphasized. The investigator's recognize the potential vulnerability of the legally authorized representative in this setting (ie. having a relative who is critically ill) and thus will terminate the consent discussions in any situation where the legally authorized representative appears to be uncomfortable or apprehensive about providing consent for their relative to participate in the study. In an effort to help recognize situations where the legally authorized representative may be apprehensive about providing consent, written informed consent will be obtained in the presence of the patient's nurse. The patient's nurse is ideally suited to serve as a

witness because they in fact may have met the legally authorized representative before. This procedure is frequently used for research studies in the ICUs at Tufts MC when consent is obtained from a legally authorized representative. The investigator conducting the consent discussion with the legally authorized representative will confirm with the legally authorized represensative that the subject will be withdrawn from the study if they appear to be unduly distressed.

Telephone Consent:

In situations where it not possible for the LAR to physically come to Tufts Medical Center for an in person consent discussion (for example, lives outside of Boston area, inclement weather, LAR's schedule, study consent time frame, etc.), Drs. Garpestad, Devlin, Faugno or Duprey will conduct telephone consent:

1) E-mail, fax, (or mail) the ICF to the LAR. (If mailed, 2 copies will be mailed, so the LAR can keep a copy.)
2) The LAR will be instructed to contact Drs. Garpestad, Devlin, Faugno or Duprey after reviewing the ICF.
3) The person consenting the LAR will have the same consent discussion via phone that they would have had in person (including asking questions to gauge comprehension and answering the LAR's questions)
4) A witness will be present during telephone consent (at Tufts Medical Center with the investigator conducting the consent process)
5) If the LAR consents, the LAR will complete and sign the ICF (in all appropriate sections) and either e-mail a scanned PDF, fax, (or mail) the signed and dated ICF to the research team.
6) The LAR should be instructed to keep one signed copy of the ICF for his/her own records.
7) Once the ICF (signed & dated by the LAR) is received by the research team, the Investigator who explained the study should sign the appropriate signature line with the current date (the date they receive the ICF and sign, not the date they consented the LAR).
8) Ensure all signatures and dates are accurately documented. Any errors should be noted in a note or memo to file.
9) Document in a separate note to file/progress note, or with a note under the PI signature line on the ICF that consent was obtained over the phone with the actual date and mailed/e-mailed/faxed back. For example "*Discussed with [LAR name] via telephone on [insert date], and received signed consent form on [insert date].*"

No study-relacted activities will be conducted prior to consent being obtained.

The investigative staff will regularly remind the ICU team that informed consent is indeed a process and that obtaining a signature on the ICF is part of that process. In all interactions with the subject (and their family) the investigative team will introduce ourselves so that the subject (and their family) can associate us with the study. We will also educate them on the study procedures as they progress. The trial requires that we explicitly interact with the subject through the study period. The patients cognitive status will be evaluated twice daily using the Intensive Care Delirium Screening Checklist (ICDSC) and their sedation level will be evaluated four times daily using the SAS. When subjects are deemed to have an ICDSC score = 0 (ie.,neither subsyndromal delirium or delirium) and have a SAS of 4 (ie. are awake) they will be considered to potentially have the potential capacity of providing informed consent. It should be noted there are other reasons besides delirium and sedation that would make a subject incapable for re-consent

other than delirium. The subject's clinical team will also be asked to determine of they are now relying on the subject for decision making capacity. Based on this process, on the day that the investigative team first determines that the subject has adequate decision making capacity to provide their own consent, the subject will be re-consented (in those situations where a legally authorized representative had originally provided consent). During this consent discussion the subject will be educated about the research that has been completed to date (in addition to what additional research activities lie ahead). If the subject does not wish to remain in the study, all study-related activities will stop and no research data collected to date will be used. This re-consent process and its result will be documented in the patient record.

5.2.2 Procedures for randomization

Subjects meeting all inclusion criteria and no exclusion criteria will be randomized by a pharmacist in the Tufts Medical Center investigational drug pharmacy to one of two study groups (ie. (naloxegol or placebo) on the first day. Randomization (in blocks of 4) will take place by means of a computer-generated random-number table and will be developed by a pharmacist in the Tufts Medical Center investigational drug pharmacy. This randomization schedule will assign each subject a study number, which will be used to identify treatment allocation (ie. naloxegol or placebo) and all study data that is collected during the study.

5.3 Procedures for handling subjects incorrectly enrolled, randomized or initiated on the investigational product.

Both the investigative team and the research pharmacists in the investigational drug pharmacy have extensive experience in conducting randomized, double-blind, medication-based trials in the ICUs at Tufts Medical Center. An investigational screening sheet is always completed and verified by a secondary member of the investigative team before a patient/family is approached for consent and before randomization occurs. Should the very unlikely situation occur that a patient is mistakenly enrolled in the study or consent is withdrawn by the patient (family member), a member of the investigative team will contact the study PI, the patient's primary physician and the investigation drug pharmacy regarding this issue. In all situations the Tufts Med Center IRB and AstraZeneca will be informed of this occurrence in a timely fashion.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

Subjects and all ICU caregivers will be unaware of the treatment assignments for the duration of the study. The fact that AstraZeneca will be providing "the official" Movantik 12.5mg and 25mg placebo tablets for use in the study make it next to impossible for either the clinical or investigative team to know whether active drug or placebo drug is being administered.

All investigators will remain blinded until the final study data set is analysed. The study biostatistician will complete all analysis (including that required for intermittent analysis by the DSMB using a group A vs. group B approach. The research pharmacist at Tufts Medical Center (or his/her designate) will have access to a computer randomization program in order to assign study treatment and he/she will be the only person who will have access to the treatment assignment group.

5.4.2 Methods for unblinding the study

If needed for medical reasons, a member of the investigative team will contact the research pharmacist (or designate) on a 24/7 basis to unblind the patient. In this instance the research pharmacist will provide the treatment allocation to a member of the clinical team. The investigative team will remain blinded in all situations where a member of the clinical team is provided with the treatment allocation. Any episode of unblinding will be documented by the research pharmacist.

5.5 Treatments

5.5.1 Identity of investigation products(s)

The following investigative products will be used in this protocol:

Treatment:

Movantik 25mg tablet
OR

Movantik 12.5 mg tablet (for use in those situations where the protocol calls for the lower drug dose)

Control:

Placebo (Movantik) 25 mg tablet

OR

Placebo (Movantik) 12.5 mg (tablet) (for use in those situations where the protocol calls for the lower drug dose)

Naloxegol placebo tablets and naloxegol active drug tables appear identical, even when crushed.

5.5.2 Doses and treatment regiments

Treatment arm:

Naloxegol 25 mg daily [administered orally (or enterally)]

A lower dose of naloxegol (12.5mg mg daily) will be administered in the following two situations:

a. A patient who is receiving a moderate CYP3A4 inhibitor that includes diltiazem, erythromycin, fluconazole, or verapamil (at any dose)
b. A patient with a calculated creatinine clearance (using the modified MDRD approach) ≤ 60 ml/min

This based on the following information included in the Movantik package insert:

1 **Under drug interactions: The concomitant use of naloxegol and a moderate CYP3A4 inhibitor may increase naloxegol serum concentrations.** If use cannot be avoided, the dose of naloxegol should be reduced to 12.5mg daily. The investigators are hesitant to exclude all medical ICU patients receiving a moderate CYP3A4 inhibitors from the study given that the list of medications in this list is long and many are used with a high prevalence in the ICU (e.g. diltiazem, erythromycin, fluconazole, or verapamil). With a 12.5 mg naloxegol tablet (and matching placebo) available from AstraZeneca, it will be feasible to administer the lower 12.5 mg daily naloxegol dose to subjects with this potential interaction without compromise the rigor or blinding of the study.

2 **Under dosage and administration: The starting dose for patients with a creatinine clearance ≤ 60 ml/min is 12.5 mg daily.** This dose recommendation is based on the fact that some patients with a creatine clearance ≤ 60ml/min who were exposed to naloxegol 25mg daily were shown to exhibit markedly higher systemic exposure to naloxegol compared to subjects with normal renal function. Given that naloxegol is metabolized through the cytochrome P450 system of the liver, the reason for these high levels is not understood. The investigators are hesitant to exclude all medical ICU patients with a calculated creatinine clearance ≤ 60 mL/min given that this population represents more than 50% of the medical ICU population. With a 12.5 mg naloxegol tablet (and matching placebo) available from AstraZeneca, it will be feasible to administer the lower 12.5 mg daily naloxegol dose to subjects with renal dysfunction without compromise the rigor or blinding of the study.

Note:

- Renal function often changes (either worsens or improves) during the ICU stay. Therefore, the creatinine clearance will be calculated daily. For a patient whose creatinine clearance drops to ≤ 60ml/min during the study, the study drug dose will be reduced from 25mg daily to 12.5mg daily. For a patient whose creatinine clearance improves to ≥ 60ml/min during the study, the study drug dose will be increased to 25 mg daily.
- It is possible that medications with moderate CYP3A4 activity may either be clinical required or stopped during the period of the study. If a patient requires the initiation of a medication with moderate CYP3A4 activity while receiving study medication (and other therapeutic alternatives without this property do not exist), then the study drug dose will be reduced to 12.5 mg daily. If a medication with moderate CYP3A4 activity is stopped during the period of study drug administration then the study drug dose will be increased to 25mg daily on the day after the CYP 3A4 moderate inhibitor is stopped.
- If a patient enrolled in the study requires a strong CYP3A4 medication (and another therapeutic alternative without this property does not exist), then the patient will be removed from the study.

Control arm:

AstraZeneca Naloxegol 25 mg placebo daily [administered orally (or enterally)}

A lower placebo dose of 12.5mg will be used for either of the above situations (ie. #1 or #2) where the 12.5mg daily dose is warranted.

Study drug administration:

If oral study drug medication is not possible (e.g. intubation) then the study drug will be administered via a gastric or enteral tube as recommended in the Movantik package insert. Tube feeds (if being

administered) will be held for one hour and then the feeding tube will be flushed with 30 mL of sterile water (using a 60 mL oral syringe) given that no data exists as to whether naloxegol may bind to enteral nutrition. Given that naloxegol (or matching placebo) is formulated as an easily crushed, film-coated tablet, the bedside nurse will crush the naloxegol (or matching placebo) tablet, mix in 60 mL of sterile water and draw up the contents (of the medication and sterile water) in a 60 mL oral syringe and administer via the gastric or enteral tube over 3-5 minutes. The bedside nurse will rinse the vessel used to crush the medication with another 30mL of sterile water, draw up the contents into the oral syringe and administer over 3-5 minutes. Tube feeds will then be restarted at the same pre-dose rate (i.e., if the patient was receiving tube feeds at the time of the study dose) one hour after the study drug dose is administered. This is a method of administration of enteral drug administration that has been used in other ICU clinical studies where data on the enteral administration of the crushed tablet does not exist.

5.5.3 Additional study drug

Under no circumstances will additional study drug (other than that described in 5.5.1) be administered to a subject.

5.5.4 Labeling

Each dose of study medication (whether naloxogol or placebo) will be packaged in a unit of use package by the investigation drug service at Tufts Medical Center and hand delivered to subject's bedside each morning. Each package will be labeled with the following: subject's name, bed number, naloxegol or placebo, strength, the study number and a patient-specific bar code. All normal medication administration screening and documentation procedures for medication administration in the medical ICU at Tufts Medical Center will be used (e.g. bar scanning, computerized medication administration profile etc) to prevent any potential sources for medication-related error.

5.5.5 Storage

All study medication (and placebo) will be stored in Tufts Medical Center Investigational Drug Pharmacy based on the most recent storage recommendations from AstraZeneca. This storage area is in a completely different area of the pharmacy from where normal medication stock is stored. All usual study drug accountability procedures (as outlined in the policies and procedures of the Tufts MC Investigational Drug Pharmacy) will be used for this study. Among the research team, Drs. Devlin and Duprey will be the primary liasons with members of the Tufts MC Investigational Drug Pharmacy.

5.6 Concomitant and post-study treatment

All patients enrolled in the study will be initiated on the following:

1. Docusate 100mg twice daily administered orally (or enterally).

AND

2. Study Laxative Guideline (see Appendix 1)

A standard laxative guideline does not currently exist in any ICUs at Tufts Medical Center. Therefore in an effort to standardize the administration of laxatives in the study, the investigative team developed a study laxative guideline that is similar to current laxative prescribing practices in the medical ICU at Tufts MC for patients that do not have spontaneous bowel movement for ≥ 3 days. Realizing the importance of having a formal, tiered laxative guideline that mimics that which is used in routine practice for medical ICU patients at Tufts Medical Center, the investigators basically formalized the approaches that are most commonly used in practice to develop (what is felt) to be a reasonably aggressive guideline. It should be noted that if study patient fails to have spontaneous bowel movement at 6 days (despite ever more intensive laxative treatment steps occurring), the patient will be removed from the study and the clinical ICU team will have the option of administering SC methylnaltrexone or intervening in whatever way these see fit to treat the constipation. Of course, prior to study day #6, if the medical ICU team feels that a subject's constipation is severe enough to warrant study removal (and perhaps methylnatrexone administration) then the subject would be removed from the study earlier. It will be communicated to each subject's ICU physician that the study laxative guideline does not have to be rigidly followed if the subject's physician deems that a deviation from the guideline is required based on their clinical evaluation of the subject.

5.7 Treatment compliance

Given that study drug administration will only occur in an ICU, and all drug will be administered by an experienced ICU nurse, treatment compliance should not be an issue. The usual medication administration and documentation system will be employed for the study that involves the bedside nurse bar-scanning each study drug dose (to ensure correct patient and correct schedule) and the exact time each daily study drug dose is administered will be documented. The investigative team will be in the ICU each morning to monitor all study procedures completed over the past 24 hours and will be available by pager on a 24/7 basis for any questions that the bedside nurse or any other member of the ICU clinical team may have regarding the study. The study procedures outlined in Table 1 that will be completed by a member of the investigative team will be completed by Dr. Devlin, Dr. Duprey, Dr. Faugno or Dr. Garpestad.

5.8 Discontinuation of investigational product

5.8.1. Procedures for discontinuation of a subject from investigational product

Study drug administration will be stopped when one of the following occurs**:**

1. The subject experiences an adverse event potentially attributable to the study drug that is deemed, in the opinion of principal investigator, to warrant discontinuation of therapy.
2. The patient requires use of the Level 4 Study Laxative Guideline (i.e., methylnaltrexone)
3. Scheduled opioid therapy is stopped for ≥ 24 hours and the patient has had ≥ 1 SBM since the time of study enrollment.
4. The patient has been administered 10 days of study medication.
5. The patient is discharged from the ICU.
6. The patient dies in the ICU.
7. The patient requires a strong CYP3A4 inhibitor medication (and no other therapeutic alternative medication without this property can be used)
8. The patient develops excessive diarrhea defined as ≥ 3 SBMs with a Bliss Score of 3 or 4 in a 24 hour period. When excessive diarrhea first occurs, study medication will be held. In addition, all laxatives

will be stopped (including docusate) and the investigative team will work with the subject's clinical team to identify other possible causes for the excessive diarrhea (e.g. enteral nutrition formulation choice, C. difficile infection etc). In a further 24 hours (48 hours after the last study medication dose), if excessive diarrhea persists, the study medication will be permanently discontinued. However, if the subject no longer has excessive diarrhea in a further 24 hours (48 hours after the last study medication dose), study medication will be resumed at the original dose. If excessive diarrhea occurs again after study medication is resumed, then the study medication will be permanently stopped.

Non-study naloxegol is currently not available at Tufts Medical Center given that is has not been added to the Tufts Medical Center medication formulary so there is no chance that a patient will be initiated on naloxegol after removal from the study while still a patient at Tufts Medical Center. The care team for all patients removed from the study (who may been receiving naloxegol) will be notified that they should formally evaluate the patient for appropriate laxative orders, particularly in those situations where opioid therapy is continuing or where the patient has not had recently had spontaneous bowel movement.

5.9 Withdrawal from study

While 5.8.1 lists the reasons why study drug administration will cease, post-study drug discontinuation outcomes like duration of ICU stay will still be collected.

Should consent for study participation be withdrawn all study data collection activities will cease and no study data collected before the time of withdrawal will be used.

6. COLLECTION OF STUDY VARIABLES

6. 1 Recording of data

As outlined above in Table 1, study data that is not routinely documented on the ICU flowsheet or within the other section of the patient record (e.g. Soarian) will be documented by the bedside nurse on a daily nursing bedside data collection form (Appendix 9) . All other study data will be collected by the investigative team (Drs. Devlin, Duprey, Faugno or Garpestad) on the daily investigative team data collection form (Appendix 10).

6.3 Efficacy

6.3.1 List each efficacy variable

<u>As outlined in Table 1</u>:

Any SBMs
Characterization of each SBM for size (small, medium or large)
Characterization of each SBM for consistency (using the Bliss Stool Scale)
Use of the study laxative guideline
Daily volume of enteral nutrition administered
Daily enteral nutrition goal
Daily fluid balance (i.e., 24 hr ins and outs)

Pain scale score (using nurse-administered 10 point rating scale) every 6 hours
Opioid requirement [in IV fentanyl equivalents (mcg)](all IV, SC, oral or transdermal use)
Daily Sedation Assessment Scale (SAS) score (by nurse every q6h)
Delirium using the Intensive Care Delirium Screening Checklist (ICDSC) (by nurse q12h)
Daily total sedation administered (in midazolam equivalents)
Occurrence of lower GI tract paralysis requiring consultation by a gastroenterologist or a surgeon
Requirement for mechanical ventilation support
Abdominal pressure (estimated by nurse measurement of bladder pressure every 8 hours

6.4 Safety

6.4.1 List of each safety variable

As outlined in Table 1:

Presence of diarrhea
Presence of diaper
Presence of rectal tube
Difference in the pre-dose and post-dose Clinical Opioid Withdrawal Scale (COWS) score (as evaluated by the bedside nurse before and 2 hours after the administration of the daily study drug dose).

6.4.2 Definition for a serious adverse events and unanticipated problems:

Serious Adverse Event:

Events of a serious nature even if not related to the study (e.g. resulted in death, was life-threatening, resulted in hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacitation, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed above).

Unanticipated Problem:

An event that meets all of the following criteria: 1) was unexpected; 2) was related or probably related to participation in the study, 3) may place subject(s) or others at greater risk of harm than previously recognized.

Please note that these can include:

i. events that are identified in the ICF, but that are more severe and longer lasting than expected.
iii events that were not expected to occur during the course of the study and that are not identified in the ICF(s).
iv. any event about which the Principal Investigator is unsure, whether or not it meets the above criteria

6.4.2 Recording and Reporting of adverse events

All reportable new information that occurs in the study will be reported by the investigative team (sponsor) to the IRB as per the IRB's reportable new information policy and to the study sponsor based on the sponsor's reporting requirements that are outlined as follows:

All reportable new information that occurs in the study will be reported by the investigative team (sponsor) to the IRB as per the IRB's reportable new information policy and to the study sponsor based on the sponsor's reporting requirements that are outlined as follows:

The Sponsor is responsible for safety reporting of adverse events or adverse drug reactions that arise during the Study in accordance with the Code of Federal Regulations Title 21, Part 312, section 312.32 and 312.33to (i) the US Food and Drug Administration (FDA) ; (ii) any overseeing Institutional Review Boards; and (iii) all Investigators under this IND.

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

The investigator will notify AstraZeneca (the Company) of all suspected unexpected serious adverse drug reactions (SUSARs) at the same time that the expedited IND safety reports are sent to the FDA.

When reporting to AstraZeneca, a cover page should accompany the MedWatch 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 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.

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 at least <<on a monthly 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 in the study database. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

Note: As with any other clinical study, the patient's physician may elect to discontinue the study drug at any time should an adverse effect develop that is felt to be attributable be to study drug administration.

7. BIOLOGICAL SAMPLING PROCEDURES

No biological samples are being collected as part of this study.

8. ETHICAL AND REDULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

8.2. Subject data protection

The ICF will incorporate wording that complies with relevant data protection and privacy legislation. All subjects will be de-identified using an unique subject number. Confidentially risks will be minimized given that no PHI or identifying information (other than a subject study code) will be used to identify study subjects. Demographic data for each subject will be maintained in a password-protected computer in Dr. Devlin's locked office. Only Drs. Garpestad, Devlin, Duprey and Faugno will engage in data collection for this study and all will be done on the hospital premises. All data entry will be entered on a data collection form on which patient identifying information will be excluded. De-identified data entry into department research computers is password protected. Data will only be reported in aggregate form in any abstract or publication of the study results. All study data will be kept locked in the investigators office. In additional to the investigative team, the Tufts MC IRB, the Medical Gastrointestinal Research Team at AstraZeneca, and the FDA will also have access to this data. Data is not being sent outside of Tufts Medical Center. Only the Tufts Medical Center Investigational Pharmacy will have access to the randomization (allocation) code. The bedside nurse is not a member of the research team (please see Section 9).

8.3 Ethics and regulatory review

The Tufts Medical Center Institutional Review Board (IRB) will approve the final study protocol, including the final version of the ICF. The investigator will ensure the distribution of these documents to the applicable to the IRB and to other members of the investigative team. The opinion of the IRB will be obtained in writing. The investigator will submit this written IRB approval to AstraZeneca or its representative before enrollment of any patient into the study occurs. This study protocol will be re-approved by the IRB annually.

8.4 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the PI and AstraZeneca. If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the studyprotocol. The amendment is to be approved by the IRB. If a protocol amendment requires a change to a center's ICF, AstraZeneca and the IRB are to approve the revised ICF before the revised form is used. If local regulations require, any administrative change will be communicated to or approved by the IRB.

8.5 Audits and inspections

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

9. STUDY MANAGEMENT

9.1 Study personnel:

Neither the MICU team (ie. physicians) nor the bedside nurse will be part of the research team. As outlined in Table 1, the vast majority of the monitoring that the bedside nurse will be completing for the study will take place within the scope of their regular job duties. The study monitoring that the bedside nurse will be asked to conduct outside of their regular duties will take no more than 10 minutes in total to conduct over a standard 12 hour nursing shift and are all within the scope of practice of an ICU nurse. The MICU team has no specific study-related activities to perform over and above maintaining an awareness that their patient may be in the study and contacting a member of the research team with any questions or concerns.

9.2 Study drug administration

Study medication will be administered by an experienced ICU bedside nurse. The investigative team will be in the ICU each morning to monitor all study procedures over the past 24 hours and is available by pager on a 24/7 basis for any questions that the bedside nurse or any other member of the ICU clinical team may have. The subject's bedside ICU nurse (or his/her designate) will be present in the ICU (and close to the subject's bedside) on a 24-7 basis during entire period of study drug administration.

9.3 Facilities and equipment for managing emergencies

All interventions, tests and procedures will occur while the subject is admitted to an ICU at Tufts MC under the care of the Medical ICU team. Each subject will be monitored on a 24/7 basis by a critical care nurse and a physician member of the ICU team is always in house to respond quickly to any emergencies. A member of the research team will always be available by pager on a 24/7 basis. Dr. Garpestad is a board-certified intensivist who has extensive experience in managing critically ill patients and any potential emergencies that may occur in this population. Drs. Devlin and Duprey are experienced critical care pharmacists who are used to working with critical care nurses and physicians to identify and help resolve drug-related problems and emergencies in the ICU setting. All critical care nurses at Tufts

Medical Center are well-trained to help identify and resolve with the ICU medical team emergencies that occur in their patients.

9.4 Training of study site personnel

The PI will educate each research team member on their roles and responsibilities. This education and the roles and responsibilities of each research team member will be documented in the study regulatory binder(s). Although neither the Medical ICU team nor bedside nurses will be members of the research team, a member of the investigative team will provide the Medical ICU nurses and physicians an overview of the study protocol and the specific data that will be collected as part of the study.

9.4 Study agreement

An agreement between AstraZeneca and Tufts Medical Center will be in place before any study-related activities take place.

9.5 Study time line and end of study

Protocol Finalization	December, 2016	Month 1
Execution of research agreement	January 2017,	Month 2
IRB approval	January 2017	Month 2
First subject enrolled	May 2017	Month 6
Subject #18 enrolled (50% enrollment)	February 28, 2018	Month 14
Subject #36 enrolled (100% enrollment)	December 31, 2018	Month 23
Publication	March 31, 2019	Month 27

10. DATA MANAGEMENT

All study-related forms (including the original signed ICF) will be kept in a locked investigators office. One copy of the of the signed ICF will be included in the patient record and another copy will be provided to the patient/legally authorized representative. All study records will kept for whichever of the following is longest: at least 7 years or for 2 years after the FDA approval of withdrawal of the FDA application.

Robin Ruthazer, MPH, a senior biostatistician from the Institute for Clinical Research and Health Policy Studies at Tufts Medical Center will work closely with the rest of the research team to provide direction, guidance, and assistance regarding data management and analysis. Ms. Ruthazer has worked with our group on prior studies. Drs. Devlin, Faugno and Duprey will check all subject case report forms (CRFs) for completeness at the time of data collection. All data collection forms including the CRFs will be stored in a locked cabinet in Dr. Devlin's locked office at all times. Drs. Devlin and Duprey will conduct all data entry into MS Excel. Both have extensive experience in entering data into MS Excel for other investigations our group has completed. Drs. Garpestad will monitor the integrity of data entry. Data will be stored in a specified directory on Dr. Devlin's computer, which is password-protected which will be located in his locked office (in a secure building) and backed up regularly.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of efficacy variables

Please see table 1 and study objectives section

11.2 Calculation or derivation of safety variables

Please see table 1 and study objectives section

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

All patients will be analyzed in the groups to which they were randomly assigned, according to the intention-to-treat principle.

12. 2 Methods of statistical analysis

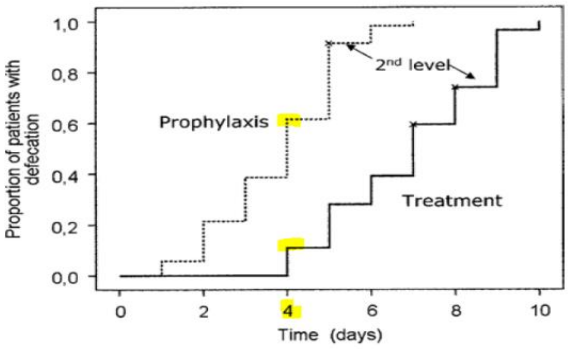
Baseline characteristics of patients will be compared using standard univariate methods (chi-square test, t-test) to confirm the randomization was successful in achieving comparable groups. To test the primary outcome (incidence of lower GI tract paralysis), given that there may be censoring (i.e., subject may die or withdraw from study before developing lower GI tract paralysis), we will present Kaplan-Meier curves for the naloxegol and placebo groups for the time to first development of lower GI tract paralysis (≥ 3 days without a SBM after study randomization) during the ICU stay up to 10 days and compare the curves using a log-rank test. If all subjects complete the study (e.g., no deaths, no withdrawal or loss-to-follow-up for other reasons), then we will instead compare the proportion of patients that develop lower GI tract paralysis after study randomization during the ICU stay up to 10 days between the naloxegol and placebo groups using a chi-square test. The secondary outcome, time to first SBM will be estimated using a Kaplan Meier time to event analysis and compared between groups using a log-rank test. The secondary outcome of the number of ICU days without a SBM will be compared between the naloxegol and placebo groups using the Poisson regression for count data and adjusting for total number of days in the ICU (up to a maximum of 10) as an offset term in the Poisson model. The secondary outcome of the average daily opioid requirements will be compared between groups using either a student t-test or nonparametric Wilcoxan rank-sum test if the assumptions of the student t-test fail to be met. Length of mechanical ventilation and ICU stay will be reported as medians and interquartile ranges and will be compared using the Wilcoxon Rank Sum Test. For all statistical tests of hypotheses, a two-sided p-value of ≤ 0.05 will be considered as statistically significant. As this is a Phase II proof of concept study a p value of <0.10 may still be worth consideration for future study, however. All statistical analyses will be performed using SPSS 17.0. (SPSS, Chicago, IL) or other comparable commercially available statistical software.

12.2.1 Interim analyses

As outlined in the DSMB procedure, planned interim analyses will occur to evaluate safety after the enrollment of 10 subjects and after the enrollment of 20 subjects.

12.2.2 Determination of sample size

For the power analysis, the 4-day estimates of failure to defecate (i.e., failure to have a SBM) from the Kaplan-Meier plot presented in the Guardiola et. al. paper [4] was used as the estimate of lower GI tract paralysis. The figure below shows that the estimate of the percent of patients who *failed to defecate* (1 minus plotted proportion with defecation) by day 4 was 40% in the Prophylaxis group (i.e., the intervention group) vs. 90% in the non-prophylaxis (Treatment) group (i.e., the control group) (see yellow highlights in figure). We believe the 4-day estimate will be strongly related to the primary outcome of lower GI tract paralysis (≥ 3 days without a SBM).



For this Naloxogol randomized trial, we propose enrolling 36 subjects, 18 per group. The statistical power table below shows this sample size yields over 95% power using an alpha of 0.05 if the true day 4 estimated freedom of event (defecation) rates are 90% (Placebo) vs. 40% (Prophylactic treatment), all subjects have complete follow-up, and the analysis is done using the log-rank test to compare survival curves. As sensitivity analysis, the table also shows the power of the study with this sample size under different scenarios. Because this is not the final definitive study to determine efficacy, a less stringent alpha of 0.10 may be justified for this Phase II proof-of-concept study which, if positive, would be followed by a confirmatory study [15]. While we expect most subjects to finish the study (based on the inclusion criteria), we have shown the impact on the power if approximately 20% of subjects do not finish the study. We have also varied the estimated proportion of patients failing to defecate by day 4 (i.e., not having a SBM) in the placebo group from 90% to 70% and in the prophylactic treated group from 40% to 50%.

Statistical Power of Log-Rank Test with n=18 subjects per group (36 total)

Complete study	ALPHA	Proportion Failing to Defecate at Day 4 (Placebo vs. **Prophylactic Treated**)				
		90% **vs.** 40%	90% **vs.** 50%	80% **vs.** 40%	80% **vs.** 50%	70% **vs.** 40%
100%	**0.05**	**99.8%**	**98.4%**	**92.7%**	**76.0%**	**76.0%**
	0.10	100.0%	99.4%	96.2%	84.9%	84.9%
80%	0.05	**99.7%**	**97.6%**	**90.8%**	**72.5%**	**72.5%**
	0.10	99.9%	99.0%	95.1%	82.2%	82.2%

12.3 Data monitoring committee

A Data and Safety Monitoring Board (DSMB) will be formed for this study. The DSMB will consist of an intensivist, gastroenterologist and a pharmacist who have experience in the management of

gastrointestinal-related conditions in the critically ill. The study biostatistician, Robin Ruthazer, will also be a part of the DSMB in a consultative role. The DSMB will review all subject data (in a blinded fashion) after the enrollment of the first 10 subjects in the study and then after the enrollment of the first 20 subjects. Any unanticipated SAE will also automatically trigger a DSMB review. The DSMB will meet at least once every 6 months in the event that the pace of study enrollment does not trigger a DSMB meeting in a particular 6 month period. DSMB members will not be associated with the study. The study biostatistician will remain blinded until the final results of the study are analyzed. If the DSMB requires the A group and B group coding, then the research pharmacist will send a confidential email to the DSMB that contains the A and B assignments. The charter for the DSMB is listed under Appendix 9.

13. LIST OF REFERENCES

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3. Guardiola B[1], Llompart-Pou JA, Ibáñez J, et al. Prophylaxis versus treatment use of laxative for paralysis of lower gastrointestinal tract in critically ill patients. J Clin Gastroenterol. 2016 Feb;50(2):e13-8.

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Appendix 1. Study Laxative Guideline

No spontaneous bowel movement in ≥ ***3 days[A]?***

Step 1: Initiate: Senna one tablet (8.6 mg) PO/NG daily AND polyethylene glycol 3350 17 g PO/NG daily. If SBM occurs then stop step 1 therapy but keep patient on docusate.

No spontaneous bowel movement in ≥ ***4 days[A]?***

Step 2: Increase Senna to 2 tablets (17.2 mg) PO/NG daily AND polyethylene glycol 3350 to 34 g PO/NG daily and insert a bisacodyl suppository 10mg PR x 1. If bowel movement occurs then stop all laxative study protocol therapy but keep patient on docusate.

No spontaneous bowel movement in ≥ ***5 days[A]****?*

Step 3: Repeat Step 2 AND if no spontaneous bowel movement within 2 hours of administering the bisacodyl suppository, administer a 10oz bottle of magnesium citrate sodium phosphate. If bowel movement occurs then stop all study laxative protocol but keep patient on docusate.

No spontaneous bowel movement in ≥ ***6 days[A]?***

Step 4: **Discontinue study medication (but do not unblind patient assignment).** Repeat Step 3, initiate methylnatrexone (Relistor) sc x once and consider a consultation to gastroenterology or surgery. [Note: If patient weight is 38-62 kg then methylnaltrexone dose = 8mg; if patient weight is 62-144 kg then methylnaltrexone dose = 12mg].

[A]From the day of initiation of scheduled opioid therapy (ie. IV fentanyl ≥ 100mcg/day or equivalent)

Appendix 2. Riker Sedation-Assessment Scale (SAS) Score

Score	Outcome
7	Dangerous agitation pulling at ET tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side-to-side
6	Very agitated requiring restraint and frequent verbal reminding of limits, biting ETT
5	Agitated, anxious or physically agitated, calms to verbal instructions
4	Calm and cooperative, easily arousable, follows commands
3	Sedated, difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again
2	Very sedated, arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable, minimal or no response to noxious stimuli, does not communicate or follow commands

Appendix 3 Numerical Pain Rating Scale

1 **10**

No pain **Severe Pain**

Appendix 4 Intensive Care Delirium Screening Checklist

Date:		
Time:		
1. Altered level of consciousness Choose **ONE** from A-E. Note: May need to reassess patient if recent administration of sedation therapy		
A. Exaggerated response to normal stimulation — Riker/SAS = 5, 6, or 7 — Score 1 point		
B. Normal wakefulness — Riker/SAS = 4 — Score 0 points		
C. Response to mild or moderate stimulation (follows commands) — Riker/SAS = 3 — Score 1 point **Score 0 if LOC related to recent sedation/analgesia**		
D. Response only to intense and repeated stimulation (e.g. loud voice and pain) SAS = 2 ****Stop assessment**		--
E. No response — SAS = 1 ****Stop assessment**		--
2. Inattention Score 1 point for any of the following abnormalities: A. Difficulty in following commands OR B. Easily distracted by external stimuli OR C. Difficulty in shifting focus **Does the patient follow you with their eyes?**		
3. Disorientation Score 1 point for any one obvious abnormality: A. Mistake in either time, place or person **Does the patient recognize ICU caregivers who have cared for him/her and not recognize those that have not? What kind of place are you in? (list examples)**		
4. Hallucinations or Delusions Score 1 point for either : A. Equivocal evidence of hallucinations or a behavior due to hallucinations (Hallucination = perception of something that is not there with NO stimulus) OR B. Delusions or gross impairment of reality testing (Delusion = false belief that is fixed/unchanging) **Any hallucinations now or over past 24 hrs? Are you afraid of the people or things around you? [fear that is inappropriate to clinical situation]**		
5. Psychomotor Agitation or Retardation Score 1 point for either: A. Hyperactivity requiring the use of additional sedative drugs or restraints in order to control potential danger (e.g. pulling IV lines out or hitting staff) OR B. Hypoactive or clinically noticeable psychomotor slowing or retardation **Based on documentation and observation over shift by primary caregiver**		
6. Inappropriate Speech or Mood Score 1 point for either: A. Inappropriate, disorganized or incoherent speech OR B. Inappropriate mood related to events or situation **Is the patient apathetic to current clinical situation (ie. lack of emotion)?** **Any gross abnormalities in speech or mood? Is patient inappropriatelydemanding?**		
7. Sleep/Wake Cycle Disturbance Score 1 point for: A. Sleeping less than four hours at night OR B. Waking frequently at night (do not include wakefulness initiated by medical staff or loud environment) OR C. Sleep ≥ 4 hours during day **Based on primary caregiver assessment**		
8. **Symptom Fluctuation** Score 1 point for: fluctuation of any of the above items (ie. 1 – 7) over 24 hours (e.g. from one shift to another) **Based on primary caregiver assessment**		
TOTAL ICSDC SCORE (Add 1 – 8)		

A total ICSDC Score ≥ 4 has a 99% sensitivity correlation for a psychiatric diagnosis of delirium

Appendix 5. Bliss Stool Scale Score

Stool Consistency Classification System (Adopted from Zimmaro Bliss, *et al.* J. Wound Ostomy Contin. Nurs., 2001)

1	2	3	4
Hard and Formed	**Soft but Formed**	**Loose and Unformed**	**Liquid**
			
Having a hard or firm texture & retaining a definite shape like a banana, cigar or marbles.	Retaining same general shape in the collection bag; does not spread all over the bottom of the bag or has a texture that appears like peanut butter.	Lacking any shape of its own; spreads over the bottom of the collection bag; having a texture that appears like hot cereal.	Like water.

Appendix 6. Clinical Opioid Withdrawal Scale Score

APPENDIX 1
Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:_____ Date and Time ____/____/____:_____

Reason for this assessment:_____

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset**: *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

This version may be copied and used clinically.

Source: Wesson, D. R., & Ling, W. (2003). The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*, 35(2), 253–9.

Appendix 7. Child Pugh Classification

1. CRITERIA FOR CHILD-PUGH CLASSIFICATION

Table 1 Criteria for Child-Pugh Classification

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

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

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

Appendix 8. DSMB Charter

The Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to Tufts Medical Center to monitor participant safety, data quality and evaluate the progress of the study. Dr. Erik Garpestead, Tufts Medical Center is conducting the Impact of Naloxegol (Movantik) on the Impact of Naloxegol (Movantik) on Prevention of Lower Gastrointestinal Tract Paralysis in Critically Ill Adults Initiated on Scheduled IV Opioid Therapy: A Randomized, Double-blind, Placebo-Controlled, Pilot Study. **This study is funded as an investigator initiated study by AstraZeneca.**

The DSMB responsibilities are to:

- evaluate the progress of the trial, including periodic assessments of data quality and timeliness, recruitment, accrual and retention, participant risk versus benefit, performance at the trial site, and other factors that can affect study outcome;
- consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- review study performance, make recommendations and assist in the resolution of problems reported by the Principal Investigator;
- protect the safety of the study participants;
- make recommendations to the Principal Investigator, the Institutional Review Board at Tufts Medical Center and, if required, to the Food and Drug Administration (FDA) concerning continuation, termination or other modifications of the trial based on adverse effects of the treatment under study;
- ensure the confidentiality of the study data and the results of monitoring; and,
- assist the Institutional Review Board at Tufts Medical Center by commenting on any problems with study conduct, enrollment, sample size and/or data collection.

The DSMB will discharge itself from its duties when the study is complete.

Membership

Paul Wischmeyer M.D., E.D.I.C. Professor of Anesthesiology and Pediatrics (Nutrition Section), Associate-Chairman for Clinical and Translational Research, Director of Nutrition Therapy Services, University of Colorado School of Medicine, will serve as both Chair and Safety Officer for the DSMB and is responsible for overseeing the meetings, developing the agenda in consultation with the Principal Investigator. Dr. Wischmeyer will also serve as the safety officer and thus be the primary contact for serious adverse event reporting.

Rob MacLaren, PharmD, Professor of Pharmacy, U of Colorado School of Pharmacy and Critical Care Pharmacy Specialist, U of Colorado Medical Center. Dr. MacLaren has extensive critical care research experience, some of which is in the GI area. Dr. MacLaren has previously served on study DSMBs

Thormika Keo, MD, PhD, an attending gastrotenterologist from the Dallas VA hospital will serve as the third member of the DSMB.

Robin Ruthazer, MPH, Senior statistician, Data Design and Research Center, Tufts Medical Center, Boston, MA will serve in a consultative role to the DSMB.

At least 2 members of the DSMB must be present at a meeting to constitute a quorum.

Board Process

Dr. Wischmeyer in is his role as the DSMB's safety officer, will receive all reports of serious and/or unanticipated adverse events (AE) for patients enrolled in the study and determine within 7 days of receiving each AE report whether the DSMB needs to be convened. Please note that any unanticipated serious event will automatically trigger a DSMB review.

Meetings of the DSMB will be held after the enrollment of the first 10 subjects in the study and then after the next 10 subjects. Any unexpected serious event will also automatically trigger a DSMB review. The DSMB will meet at least once every 6 months regardless of the pace of study enrollment. An emergency meeting of the DSMB may be called at any time by the Chair should participant safety questions or other unanticipated problems arise.

Meetings shall be closed to the public because discussions may address confidential participant data. Meetings will be attended by the Principal Investigator and members of his/her staff. The study biostatistician will be invited to attend at the prerogative of the DSMB chair. Meetings may be convened as conference calls as well as in-person.

Meeting Format

DSMB meetings will consist of open and closed sessions. Discussion held in all sessions is confidential. The Principal Investigator and key members of the study team attend the **open sessions.** Open session discussion will focus on the conduct and progress of the study, including participant accrual, protocol compliance, and problems encountered. No study data (other than SAE reports and screening logs) will be presented in the open session. A member of the study staff will keep minutes of each open session and submit them within one week to Dr. Garpestad.

The **closed session** will be attended by the DSMB members. The study statistician may be present, at the request of the DSMB. The study biostatistician, R. Ruthazer, will provided a blinded copy of the study data for patients enrolled to date (ie. group #1 vs. group #2) to the DSMB members no less than 7 days prior to the scheduled DSMB meeting. The investigators will not see this report. The code to unblind this report will only be provided by the Tufts Medical Center research pharmacist should the DSMB specifically request it. A member of the DSMB will keep minutes of each closed session and submit them within one week of the meeting to Dr. Garpestad who will forward this report to the Tufts MC IRB.

Each meeting must include a recommendation to continue or to terminate the study made by a formal DSMB majority or unanimous vote. Should the DSMB decide to issue a termination recommendation, the full vote of the DSMB is required.

A recommendation to terminate the study may be made by the DSMB at any time by majority vote. The Chair should provide such a recommendation to Dr. Garpestad immediately by telephone and email that will then be communicated to Dr. Garpestad.

Meeting Materials

DSMB interim report templates will be prepared by the study staff, typically the statistician, to be reviewed by the DSMB members at the first meeting. Interim data reports generally consist of two parts:

- Part 1 - Open Session Report and
- Part 2 - Closed Session Report

Format and content of the reports for both the open and closed sessions and plans for interim analyses should be finalized and approved at the initial DSMB meeting, although changes throughout the trial may be requested by the Board.

The reports will list and summarize safety data and describe the status of the study. All meeting materials should be sent to the DSMB at least 7 to 14 days prior to the meeting. The reports are numbered and provided in sealed envelopes within an express mailing package or by secure email as the DSMB prefers.

1. **Part 1 - Open Session Reports:** Open session reports generally include administrative reports by site that describe participants screened, enrolled, completed, and discontinued, as well as baseline characteristics of the study population. Other general information on study status may also be presented. Listings of adverse events and serious adverse events as well as any other information requested by the DSMB may also be in the open session report, but none of the specific patient data should be presented in a group #1 vs. group #2 fashion – even if the groups remain blinded to the investigators. The DSMB may direct additions and other modifications to the reports on a one-time or continuing basis.

2. **Part 2 – Closed Session Report:** Closed session reports generally present the same information as presented in the open session but also included the subject data in a blinded fashion by treatment group (e.g. group #1, group #2,) that will be focused on all safety outcomes/data. The Closed Session reports should be destroyed at the conclusion of the meeting. If the meetings are held by telephone, printed copies of the closed reports should be destroyed immediately following the meeting. If a study has an interim analysis, it is also discussed in the closed session.

Reports from the DSMB

A formal report containing the recommendations for continuation or modifications of the study will be prepared by the DSMB Chairperson. The draft report will be sent to the DSMB members not later than four weeks after the meeting. Once approved by the DSMB members, the DSMB Chair will forward the formal DSMB recommendation to the Principal Investigator. It is the responsibility of the Principal

Investigator to distribute the DSMB recommendation to all co-investigators and to ensure that copies are submitted to all the IRBs associated with the study.

As previously stated, the formal DSMB report must include a recommendation to continue or to terminate the study. This recommendation should be made by formal majority vote. A termination recommendation may be made by the DSMB at any time by majority vote. In the event of a split vote in favor of continuation, a minority report should be contained within the regular DSMB report. The report should not include unblinded data or discussion of the unblinded data.

Confidentiality

All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.

Appendix 9. Daily Nursing Data Collection Form.

Subject ID: _____Subject Initials: _____ ICU Room: *Date (of day shift):_____ Study day#_____
*Note: this monitoring form goes from 07:00h to 06:59h the next day

Time of study drug administration : ____h (note: should be around 0900h; if patient on tube feeds, please hold 1 hour before & after administration ; if patient is eating, administer 1 hour before or 2 hours after breakfast)
[Complete study drug administration instructions on next page]

Clinical Opioid Withdrawal Scale (COWS) Score to be completed 1 hour before and 2 hours after study drug administration (see next page)

Spontaneous Bowel Movements (from 0800h to 07:59h)	**Time**	**Size (indicate small (S), medium (M) or large (L) (Use best judgment)**	**Bliss Stool Scale Score (see next page and on wall)**	**Comments**
#1				
#2				
#3				
#4				
#5				
#6				
#7				
#8				

Does the patient have a urinary (foley) catheter in place for a clinical reason (s) Yes_____ No____
Was the patient's ICU physician asked about whether the urinary (foley) catheter can be removed? Yes No_____
Was the study laxative protocol utilized? Yes ____ No ____ If YES, which level? ____

Time frame	Day Shift (0700 – 14:59h)	Afternoon shift (15:00-22:59H)	Night shift (23:00-06:59h)

Abdominal pressure score			
Time of evaluation			

For any questions regarding this study please page Matthew Duprey, PharmD or John Devlin, PharmD at pager #2742
initials of investigational team member completing/verifying form_____ date _____

Clinical Opioid Withdrawal Scale (COWS) Score	1 hour before admin Time: _____	2 hours after admin Time: _____
Heart Rate: 0 = 80 bpm or below 1 = 81 to 100 bpm 2 = 101-120 bpm 4 = 121+ bpm		
Sweating over past ½ hour not accounted for by room temperature or patient activity: 0 = no chills or flushing 1 = patient reports chills or flushing 2 = flushed or observable moistness on face 3 = beads of sweat on brow or face 4 = sweat streaming off face		
Restlessness: 0 = able to sit or lie still 1 = patient reports difficulty sitting/lying still, but is able to do so 3 = frequent shifting or extraneous movements of legs/arms 5 = unable to sit/lie still for more than a few seconds		
Pupil Size: 0 = pupils pinned or normal size for room light 1 = pupils possibly larger than normal for room light 2 = pupils moderately dilated 5 = pupils so dilated that only the rim of the iris is visible		
Bone or Joint Aches (if Patient was Having Pain Previously, only the Additional Component Attributed to Opiate Withdrawal Scale): 0 = not present 1 = mild diffuse discomfort 2 = patient reports severe diffuse aching of joints/muscles 4 = patient is rubbing joints or muscles and is unable to sit still because of discomfort		
Runny Nose or Tearing Not Accounted for by Cold Symptoms or Allergies: 0 = not present 1 = nasal stuffiness or unusually moist eyes 2 = nose is running or tearing 4 = nose constantly running or tears streaming down cheeks		
GI Upset: Over Last ½ Hour: 0 = no GI symptoms 1 = stomach cramps 2 = nausea or loose stool 3 = vomiting or diarrhea 5 = multiple episodes of vomiting or diarrhea		
Tremor Observation of Outstretched Hands:		

0 = no tremor 1 = tremor can be felt by patient, but not observed 2 = slight tremor observable 4 = gross tremor or muscle twitching		
Yawning Observation During Assessment: 0 = no yawning/intubated 1 = yawning once or twice during assessment 2 = yawning three or more times during assessment 4 = yawning several times/minute		
Anxiety or Irritability: 0 = none 1 = patients reports increasing irritability or anxiousness 2 = patient obviously irritable/anxious 4 = patient so irritable or anxious that participation in the assessment is difficult		
Gooseflesh Skin: 0 = skin is smooth 3 = piloerection of skin can be felt or hairs standing up on arms 5 = prominent piloerection		
Total Score: 5-12 = Mild 13-24 = Moderate 25-36 = Moderately Severe More than 36 = Severe Withdrawal		

Study Drug Administration Instructions

If oral study drug medication is not possible (e.g. intubation) then the study drug should be administered via a gastric or enteral tube.

Tube feeds (if being administered) should be held for one hour and the feeding tube will be flushed with 30 mL of sterile water.

Crush the naloxegol (or matching placebo) tablet, mix in 60 mL of sterile water and draw up the contents (of the medication and sterile water) in a 60 mL oral syringe and administer via the gastric or enteral tube over 3-5 minutes.

Rinse the vessel used to crush the medication with another 30 mL of sterile water, draw up the contents into the oral syringe and administer over 3-5 minutes.

Restart tube feeds at the same pre-dose rate (i.e., if the patient was receiving tube feeds at the time of the study dose) one hour after the study drug dose is administered.

Drug Substance: Movantik
Study Number: ESR-15-11000
Tufts IRB #12043
Version: Protocol version #19
Date: September 10, 2018

Appendix 10. Investigative Team Daily Data Collection Form.
IRB # 12043 Impact of Naloxegol (Movantik) on Prevention of Lower Gastrointestinal Tract Paralysis in Critically Ill Adults Initiated on Scheduled IV Opioid Therapy: A Randomized, Double-Blind, Placebo-Controlled, Phase II, Single-Center, Proof of Concept Study. PI: Erik Garpestad, MD

Subject ID: _____Subject Initials: _____ ICU Room: *Date (of day shift):_____ Study day#_____
*Note: this monitoring form goes from 0700h to 06:59h the next day

Time frame	Day Shift (0700 – 14:59h)	Afternoon shift (15:00-22:59H)	Night shift (23:00-06:59h)
Fentanyl (mcg)			
Hydromorphone (mg)			
Morphine (mg)			
Oxycodone (mg)			
Hydrocodone (mg)			
Methadone (mg)			
Other Opioids: Name and Dose			
Diazepam (mg)			
Lorazepam (mg)			
Midazolam (mg)			
Dexmedetomidine (mcg)			

Propofol (mg)			
Haloperidol (mg)			
Quetiapine (mg)			
Volume of enteral nutrition administered (mL)			
Enteral nutrition goal (mL)			
% of enteral nutrition goal reached			
Fluid balance (+ or –) (mL)			
Lowest SAS			
Highest SAS			
ICDSC score (if evaluated during this shift)			
Lowest pain assessment score			
Highest pain assessment score			
Current Laxative Guideline Step (ie. 1, 2, 3 or 4)			
Laxatives administered (list all agents and doses)			
Requirement for mechanical ventilation? (Y/N)			
Presence of rectal tube? (Y/N)			

(Please note time of insertion if new)			
GI or Surgical consult for lower GI tract paralysis? Y/N			
SOFA Score (worst values over study day)			
Serum creatinine (worst value over study day)			
Calculated creatinine clearance (worst value over study day)			

initials of investigational team member completing/verifying form_____ date _____

Daily SOFA Calculator

Pt Study ID: |__|__|__| *Pt Initials:* |__|__|__|

From: |__|__| |__|__| |_2|_0|__|__| |__|__| : |__|__| *To:* |__|__| |__|__| |_2|_0|__|__| |__|__| : |__|__|
YEAR HH MM DD MM YEAR HH MM DD MM

Please retain this worksheet at the site with the CRF.

Calculate SOFA score using values from the 24 hour period prior to randomization.

A. Please circle appropriate score

Organ System	0	1	2	3	4	Score
RESPIRATION PaO_2/FiO_2 (mmHg)	>400	301-400	201-300	101-200 with respiratory support	< 100 with respiratory support	
CARDIOVASCULAR Vasopressors (mcg/kg/min)	No hypotension	MAP < 70mmHg and No vasopressors	Dopamine ≤ 5 or Any dose Dobutamine	Dopamine > 5 or Epinephrine ≤ 0.1 or Norepinephrine ≤ 0.1	Dopamine >15 or Epinephrine > 0.1 or Norepinephrine > 0.1 or any dose Vasopressin	
LIVER (bilirubin) (mg/dl)	<1.2	1.2 – 1.9	2.0 – 5.9	6.0 – 11.9	≥ 12	
COAGULATION Platelets (x $10^3/\mu L$)	>150	101-150	51-100	21-50	≤20	
RENAL Creatinine (mg/dL)) or urine output mL/hr	<1.2	1.2 - 1.9	2.0 -3.4	3.5 – 4.9 or < 500 ml/day	≥ 5.0 or < 200 ml/day	
					TOTAL SOFA=	

B. Please record below the actual values used in the scoring above.

PaO_2 |__|__|__|

FiO_2 |__| . |__|__|

MAP |__|__|__|

Bilirubin |__|__|__| µmol/L

Platelets |__|__|__| x 10^3/µL

Creatinine |__|__|__| µmol/L or Urine output |__|__|__|__| mL/day

initials of investigational team member completing/verifying form_____ date _____

Appendix 11. Investigative Team Baseline Data Collection Form

Case Report Form

Patient Initials ___ ___ ___

Patient Study Number: ___ ___ ___

Date of Randomization: ___/___/____ **Time: ___:___** (24 hr. clock)
mm dd yyyy

Enrolled by: (please print) _____

Signature: _____ **Date: ___/___/____**

Background Information regarding enrollment:

_____

_____

_____

Subject's Contact Information:

Primary phone number: (_____) _____-_____

Secondary phone number: (_____) _____-_____

Address: _____
Street Apt

_____ _____ _____

City State Zip

Subject's Legally Acting Representative: **Name: _____**

Relationship: _____

Primary phone number: (_____) _____-_____

Secondary phone number: (_____) _____-_____

Address: _____
Street Apt

_____ _____ _____
City State Zip

initials of investigational team member completing/verifying form_____ date _____

Baseline Characteristics

Pt Number ____ ____ ____	Patient Initials ____ ____ ____	Date ____/____/_____

1. Date of Birth: ____/____/_____ **2. Age: ____ ____** years

3. Gender: M ☐ F ☐

4. Height: ____ ____ inches **5. Weight: ____ ____ ____** kg

6. Hospital admission date: (to study hospital) **____/____/_____**

7. ICU admission date: (in study hospital) **____/____/_____**

8. Location prior to hospitalization (includes hospitalization at Tufts Medical Center and any outside hospital)

☐ Home alone
☐ Home with a spouse
☐ Home with other family member/friends
☐ Rehabilitation
☐ Senior housing (w/ minimal assisted living)
☐ Assisted living facility
☐ Long term care facility
☐ Other: _____

9. Location immediately prior to this ICU admission:

☐ Tufts emergency department
☐ Tufts hospital ward
☐ Tufts operating room following elective surgery
☐ Tufts operating room following emergency surgery
☐ ICU at outside hospital, admit date: ____/____/_____
☐ Ward at outside hospital, admit date: ____/____/_____
☐ Other: _____

10. Prior ICU stay during this hospital admission: ☐ Yes ☐ No

If YES, specify unit: _____

11. Was a tracheotomy present on admission to ICU? ☐ Yes ☐ No

If YES, was it performed during this hospital admission? ☐ Yes ☐ No

12. Start date of mechanical ventilation: Date: ____/____/_____ Time: ____:____ (24hr clock)

13. Admission APACHE III Diagnosis Code (Please see attached)**: ____ ____**

If "other" has been selected in any category, please specify: _____

14. APACHE II Score (Please see eattached)**:** Calculate APACHE II score using values from the 24 hour period prior to randomization.

APS: ____ Age Points: ____ Chronic Health Points: ____

Total APACHE II: ____

initials of investigational team member completing/verifying form_____ date _____

Pt Number ____ ____ ____	Patient Initials ____ ____ ____	Date ____/____/_____

15. Baseline SOFA Score (Please see attached)**:** Calculate SOFA score using values from the 24 hour period prior to randomization.

Total SOFA: ____

16. Last Spontaneous Bowel Movement (Per medical record review/family interview)**:**

Date: ____/____/_____ **Time: ____:____** (24 hour clock)

17. Current infusions at randomization: (check all that apply)

Fentanyl:	☐ Yes ☐ No	Start date: ____/____/_____	Time: ____:____	Rate: _____mcg/hr	
Hydromorphone:	☐ Yes ☐ No	Start date: ____/____/_____	Time: ____:____	Rate: _____ mg/hr	
Morphine:	☐ Yes ☐ No	Start date: ____/____/_____	Time: ____:____	Rate: _____ mg/hr	
Midazolam:	☐ Yes ☐ No	Start date: ____/____/_____	Time: ____:____	Rate: _____ mg/hr	
Lorazepam:	☐ Yes ☐ No	Start date: ____/____/_____	Time: ____:____	Rate: _____ mg/hr	
Propofol:	☐ Yes ☐ No	Start date: ____/____/_____	Time: ____:____	Rate: _____ mcg/kg/min	
Dexmedetomidine:	☐ Yes ☐ No	Start date: ____/____/_____	Time: ____:____	Rate: _____ mcg/kg/hr	
Other: _____		Start date: ____/____/_____	Time: ____:____	Rate: _____ ___/hr	

18. Opioid Medications at randomization: (check all that apply)

Fentanyl:	☐ Yes ☐ No	Start date: ____/____/_____	Dose in last 24 hours ____ mcg
Hydromorphone:	☐ Yes ☐ No	Start date: ____/____/_____	Dose in last 24 hours ____ mg
Morphine:	☐ Yes ☐ No	Start date: ____/____/_____	Dose in last 24 hours ____ mg

Oxycodone: ☐ Yes ☐ No Start date: ____/____/_____ Dose in last 24 hours ____ mg
Hydrocodone: ☐ Yes ☐ No Start date: ____/____/_____ Dose in last 24 hours ____ mg
Methadone: ☐ Yes ☐ No Start date: ____/____/_____ Dose in last 24 hours ____ mg
Other: _____ Start date: ____/____/_____ Dose in last 24 hours ____ mg

19. Reason for Opioid Initiation: (check all that apply)

☐ Analgesia for Mechanical Ventilation
☐ Cancer Pain
☐ Wound Care
☐ Postoperative Pain
☐ Periprocedural Pain

initials of investigational team member completing/verifying form_____ date _____

Baseline APACHE II Calculator

Pt Study ID: |__|__|__| **Pt Initials:** |__|__|__|

From: |__|__| |__|__| |2|0|__|__| |__|__| : |__|__| **To:** |__|__| |__|__| |2|0|__|__| |__|__| : |__|__|
1) DD MM YEAR HH MM DD MM YEAR HH MM

Please retain this worksheet at the site with the CRF.
Calculate APACHE II score using values from the 24 hour period prior to randomization.
Please circle appropriate range on form

A. Physiologic Variables Points

PHYSIOLOGIC VARIABLE	HIGH ABNORMAL RANGE					LOW ABNORMAL RANGE				PT SCORE
	4	3	2	1	0	1	2	3	4	
Temperature –core (°C)	≥ 41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤ 29.9	
MAP (mmHg)	≥ 160	130-159	110-129		70-109		50-69		≤ 49	
Heart Rate	≥ 180	140-179	110-139		70-109		55-69	40-54	≤ 39	
Respiratory Rate (non-ventilated or ventilated)	≥ 50	35-49		25-34	12-24	10-11	6-9		≤ 5	
Oxygenation: [A-aDO_2 = (FiO_2 x 710) – (PCO_2 x 1.25) – PO_2]					FiO_2 =		PCO_2 =		PO_2 =	

Drug Substance: Movantik
Study Number: ESR-15-11000
Tufts IRB #12043
Version: Protocol version #19
Date: September 10, 2018

a. If $FiO_2 \geq 0.5$ record A-aDO_2	≥ 500	350-499	200-349		< 200					
b. If $FiO_2 < 0.5$ record only PaO_2					$PO_2 > 70$	PO_2 61-70		PO_2 55-60	$PO_2 < 55$	
Arterial pH	≥ 7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	< 7.15	
Serum Na (mEq/L)	≥ 180	160-179	155-159	150-154	130-149		120-129	111-119	≤ 110	
Serum K (mEql/L)	≥ 7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		< 2.5	
****Serum Creatinine ** (mg/dL)**	> 3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6			
Hematocrit (%)	≥ 60		50-59.9	46-49.9	30-45.9		20-29.9		< 20	
WBC (10^3/µL)	≥ 40		20-39.9	15-19.9	3-14.9		1-2.9		< 1	
Glasgow Coma Score (GCS)	Score = 15 minus actual GCS (see below)									
Serum HCO_3 (venous mEq/L) - not preferred, use only if no ABG's	≥ 52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.0	< 15	
ACUTE PHYSIOLOGY SCORE (APS): Sum of the 12 individual variables										

**** Acute Renal Failure – double the creatinine points for ARF (cr > 2.5 mg/dL in a subject with prior normal kidney function)**

B. Age Points - Assign points to age as follows:

AGE (yrs)	POINTS
≤ 44	0
45-54	2
55-64	3
65-74	5
≥ 75	6

AGE SCORE =

C. Chronic Health Points - If the patient has a history of :

severe organ insufficiency or is immunocompromised assign points as follows:

a. For nonoperative or emergency postoperative pt -- 5 points
b. For elective postoperative pt -- 2 points

CHRONIC HEALTH SCORE

D. APACHE II SCORE - Sum of A + B + C

A. APS points	
B. Age points	
C. Chronic Health points	

GLASCOW COMA SCALE		
1) Parameter	2) Response	Points Assigned (please circle)
Eyes Open	Spontaneously	4
	On spoken command	3
	On pain	2
	No response	1
Best Motor Response	To spoken command	6
	To painful stimulus:	
	Localized pain	5
	Flexion withdrawal	4
	Flexion abnormal	3
	Extension	2
	No response	1
Best Verbal Response	*(Not on ventilator)*	
	Oriented & converses	5
	Disoriented & converses	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No response	1
	(On ventilator)	
	Appears oriented	5
	Questionably oriented	3
	Generally unresponsive	1

Drug Substance: Movantik
Study Number: ESR-15-11000
Tufts IRB #12043
Version: Protocol version #19
Date: September 10, 2018

APACHE II SCORE = ☐

CHRONIC HEALTH DEFINITONS ***Please check all that apply***

Organ insufficiency or immuno-compromised state evident prior to this hospital admission and conform to the following criteria:

☐ **LIVER**: Biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma

☐ **CARDIOVASCULAR**: New York Heart Association Class IV

☐ **RESPIRATORY**: Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction i.e. unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mmHg), or respirator dependency

☐ **RENAL**: Receiving chronic dialysis

☐ **IMMUNO-COMPROMISED**: The patient has received therapy that suppresses resistance to infection i.e. Immuno-suppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection (i.e. leukemia, lymphoma, AIDS)

initials of investigational team member completing/verifying form_____ date _____

Baseline SOFA Calculator

Pt Study ID: |__|__|__| *Pt Initials:* |__|__|__|

From: |__|__| |__|__| |_2|_0|__|__| |__|__| : |__|__| *To:* |__|__| |__|__| |_2|_0|__|__| |__|__| : |__|__|
DD MM YEAR HH MM DD MM YEAR HH MM

Please retain this worksheet at the site with the CRF.

Calculate SOFA score using values from the 24 hour period prior to randomization.

A. Please circle appropriate score

Organ System	0	1	2	3	4	Score
RESPIRATION PaO_2/FiO_2 (mmHg)	>400	301-400	201-300	101-200 with respiratory support	< 100 with respiratory support	
CARDIOVASCULAR Vasopressors (mcg/kg/min)	No hypotension	MAP < 70mmHg and No vasopressors	Dopamine ≤ 5 or Any dose Dobutamine	Dopamine > 5 or Epinephrine ≤ 0.1 or Norepinephrine ≤ 0.1	Dopamine >15 or Epinephrine > 0.1 or Norepinephrine > 0.1 or any dose Vasopressin	
LIVER (bilirubin) (mg/dl)	<1.2	1.2 – 1.9	2.0 – 5.9	6.0 – 11.9	≥ 12	
COAGULATION Platelets (x $10^3/\mu L$)	>150	101-150	51-100	21-50	≤20	
RENAL Creatinine (mg/dL)) or urine output mL/hr	<1.2	1.2 - 1.9	2.0 -3.4	3.5 – 4.9 or < 500 ml/day	≥ 5.0 or < 200 ml/day	
					TOTAL SOFA=	

B. Please record below the actual values used in the scoring above.

PaO_2 |__|__|__|

FiO_2 |__| . |__|__|

MAP |__|__|__|

Bilirubin |__|__|__| µmol/L

Platelets |__|__|__| x 10^3/µL

Creatinine |__|__|__| µmol/L or Urine output |__|__|__|__| mL/day

initials of investigational team member completing/verifying form_____ date _____