Peripherally Acting Mu-Opioid Receptor Antagonists
For Opioid-Induced Constipation
Utah Medicaid Pharmacy and Therapeutics Review

56:92 GI Drugs, Miscellaneous
Methylnaltrexone (Relistor®)
Naloxegol (Movantik®)

Final Report
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University of Utah College of Pharmacy
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Abbreviations:

ALV - Alvimopan
AUC – Area under the curve
BBB – Blood brain barrier
Cmax – Maximum concentration
CrCl – Creatinine clearance
EAPC – European Association for Palliative Care
ENS – Enteric nervous system
GI – Gastrointestinal
ITT – Intent to treat
LES – Lower esophageal sphincter
LIR – Laxative inadequate response
LOS – Length of stay
LTCF – Long-term care facility
MACE – Major adverse cardiovascular event (death, myocardial infarction or stroke)
MEU – Morphine equivalent units
MNTX – Methylnaltrexone
NAL – Naloxegol
NMS – Neuroleptic malignant syndrome
NNH – Number needed to harm
NNT – Number needed to treat
OBD – Opioid bowel disorder
OIC – Opioid-induced constipation
OR – Odds ratio
PAC-QoL – Patient assessment of constipation – quality of life questionnaire
PAC-SYM – Patient assessment of constipation-symptoms questionnaire
PAMORA – Peripherally acting μ-opioid receptor antagonist
PBO – Placebo
RFBM – Rescue-free bowel movement
SAE – Serious adverse event
SBM – spontaneous bowel movement
UC – Usual care
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Executive Summary:

**Introduction:** Constipation is a common side effect of opioid analgesics. Opioid-induced constipation reflects a condition beyond having fewer stools and includes abdominal bloating, the sensation of incomplete bowel movements, straining, gas, abdominal discomfort and hard, dry stools. The prevalence of constipation in the non-malignant pain population receiving opioids is reported to be as high as 81%. Many patients find these symptoms to be more troublesome than their pain. Laxatives are used to prevent and treat opioid-induced constipation but are effective in less than 50% of patients. This is not unexpected, as they do not target the cause, opioid activity at μ-opioid receptors in the enteric nervous system. Many patients discontinue or reduce the dose of their opioid to alleviate symptoms and to have a bowel movement. Opioid induced constipation adversely affects a patient’s quality of life and satisfaction with their pain management regimen. Additionally, it is associated with a significant increase in health care resource utilization and costs.

Two peripherally acting μ-opioid receptor antagonists are indicated for treatment of opioid-induced constipation, naloxegol (Movantik®) for oral use and methylnaltrexone (Relistor®) administered subcutaneously. These opioid analogs have been modified to prevent them from crossing the blood brain barrier, which would lead to a loss of analgesia and the potential development of withdrawal symptoms.

**Clinical Efficacy:** Pivotal randomized, double-blind, placebo-controlled efficacy trials for naloxegol (2 studies) and methylnaltrexone (2 trials) document their ability to reverse opioid-induced constipation in ~50% of patients. In naloxegol trials, the primary endpoint was ≥3 spontaneous bowel movements per week and an increase from baseline of ≥1 spontaneous bowel movement per week in nine or more of the 12 weeks of study and three or more of the final 4 weeks. Methylnaltrexone trials evaluated the percentage of patients having ≥ 3 spontaneous bowel movements per week during the 4 weeks of study. Both agents demonstrated statistical superiority compared to patients treated with placebo. Long-term efficacy was demonstrated with both agents.

**Safety:** These agents are generally well tolerated. Adverse events were most commonly gastrointestinal in nature, typically mild to moderate, more common at higher dosages and most often occurring early in therapy. The adverse events reported most often with both agents were abdominal pain, diarrhea, nausea and vomiting. Significant adverse events occurred similarly among treatment groups. In treated patients, the majority of discontinuations of therapy related to gastrointestinal adverse events. No significant loss of analgesia or symptoms reflective of opioid-withdrawal were observed. Post-marketing surveillance revealed gastrointestinal perforation in 7 patients treated with methylnaltrexone that had underlying pathology. Currently, both agents carry a contraindication for use in patients at risk of gastrointestinal perforation.

**Summary:** A laxative bowel regimen started prophylactically is appropriate for all patients receiving opioid-therapy. Because laxatives do not counter the pharmacologic mechanism of opioid-induced constipation they are often ineffective. The peripherally acting μ-opioid receptor antagonists are a new class of agents that reverse the effects of opioids on receptors within the enteric nervous system producing laxation in ~50% of patients in clinical trials. The fact that
only 50% of patients respond well to this therapy may reflect the multi-factorial cause of
constipation in many patients with chronic pain.

The evidence supports the use of naloxegol and methylnaltrexone in the treatment of opioid-
induced constipation in patients without risk of bowel perforation who have received an opioid
for a minimum of 4-weeks with an inadequate response to laxatives (i.e. stimulant laxative and
osmotic laxative/stool softener). In clinical trials, these agents increase the number of
spontaneous bowel movements and reduce time to laxation. Methylnaltrexone data suggests the
NNT to prevent OIC is in the range of 3-6 and this is likely also true for naloxegol. No
significant loss of analgesia or opioid withdrawal symptoms have been noted. Currently, there is
no evidence supporting use of these agents beyond 12 months or validating superiority over other
pharmacologic therapies. Naloxegol is available orally, while methylnaltrexone is administered
subcutaneously. Adverse events of mild to moderate intensity are most commonly
gastrointestinal in nature, including abdominal pain, nausea, vomiting, diarrhea and flatulence.
No serious adverse events have been reported. These agents are comparable in efficacy and
safety and offer clinicians an additional treatment option for opioid-induced constipation.
**Introduction:** The introduction of peripherally acting μ-opioid receptor antagonists brings attention to an under-diagnosed and under-treated complication of pain management, opioid-induced constipation. Less than half of patients report no constipation or successful prevention or treatment with laxatives. Opioid-induced constipation affects quality of life, health care resource utilization, adherence, absorption concerns for medications/nutrients, adverse events and the potential for serious complications. This review presents evidence concerning the safety and efficacy of both naloxegol (Movantik®) and methylnaltrexone (Relistor®) in the treatment of opioid-induced constipation in chronic non-malignant pain patients, and methylnaltrexone (Relistor®) in the treatment of pain in palliative-care patients with advanced-illness whom have failed laxative therapy.

**Background:**

Chronic pain is reported by at least one in five American adults, ranging from 2-40% (mean of 15%) and affecting 100 million adults. An increase in therapeutic opioid use in the US is also well documented. Currently, narcotic analgesics are the third most commonly prescribed category of pharmaceuticals. Clinically, opioids produce analgesia, confusion, sedation, nausea, vomiting, hypotension, pruritus, urinary retention, respiratory depression, miosis, euphoria, dysphoria, delirium, seizures, motor and cognitive impairment, bowel dysfunction as well as dependence.

Opioid bowel dysfunction (OBD) presents with an array of symptoms associated with short or long term use of opioids and may include; dry-mouth, gastro-esophageal reflux, vomiting, bloating, abdominal distension and pain, anorexia, hard, dry stools, straining or incomplete evacuation.

Opioid-induced constipation is generally considered to be constipation resulting as a side effect of taking opioids for pain management. However, there is a need for a universal definition that could be used in patient care and research a definition of OIC was developed by a Multidisciplinary Working Group of US and international basic science and clinical experts in pain medicine, palliative care, gastroenterology, and gut neurobiology. The number of bowel movements daily or weekly is insufficient to capture patients with OIC. By consensus, OIC was defined as, “A change when initiating opioid therapy from baseline bowel habits that is characterized by any of the following: reduced bowel movement frequency, development of worsening or straining to pass bowel movements, a sense of incomplete rectal evacuation, or harder stool consistency.” The Working Group recommends the development of treatment guidelines and quality of life measures specific for OIC.

Opioid-induced constipation (OIC) is only one manifestation of OBD and is characterized by infrequent stools, straining, hard, dry stools and incomplete evacuation. Many patients consider it the most bothersome of opioid adverse effects. For some patients, constipation is less troublesome than bloating, straining, gas, or abdominal pain. Opioid receptors are located both centrally and peripherally, are stimulated endogenously by endorphins, enkephalins, dynorphins and exogenously by morphine and other μ-opioid receptor agonists. Central opioid effects are mediated by opioid receptor subtypes, mu (μ), delta...
Analgesia occurs predominately through central μ-opioid receptor stimulation. A number of the adverse effects of opioids are caused by central, μ-opioid receptor stimulation, including sedation, drowsiness, sleep disturbances, cognitive impairment, psychomotor impairment, delirium, hallucinations, dreams, nightmares, myoclonus, hyperalgesia and tolerance.

Central stimulation of opioid receptors affects circulating catecholamines and central sympathetic outflow reducing autonomic vasomotor tone and inhibiting nitric oxide generation (inhibitory neurotransmitter). Peripherally, opioids act directly on the enteric nervous system (ENS) at μ-opioid receptors. Motility, absorption, secretion and blood flow are affected. The net effect on the gastrointestinal tract is an increase in segmental longitudinal and circular intestinal smooth muscle contraction, a decrease in peristaltic activity, inhibition of water and electrolyte secretions, stimulation of fluid absorption, increased anal and pyloric sphincter tone and decreased rectal sensitivity, predisposing to OIC.

It is important to remember that non-opioid constipation is a common, under-diagnosed disorder and the development of constipation during opioid therapy does not equal causation.

Concurrent with the increased use of opioids, more patients are presenting with opiate bowel dysfunction. The prevalence of opioid-induced constipation in non-malignant patients treated with opioids, ranges from 15-81% and increases with duration of use. Symptoms are often severe and up to a third of patients stop their opioid in order to have a bowel movement. In the population of cancer patients receiving opioids for pain, opioid-induced constipation is estimated to occur in >85% of patients and in those receiving palliative care it exceeds 94%.

The consequences of chronic constipation impact a patient’s activities of daily living and quality of life. Patients with advanced cancer who receive chronic opioid therapy often report that the constipation causes them more distress than their cancer. Many trade constipation relief for pain relief, which places them at risk of inadequate pain control and the possible development of withdrawal symptoms.

Inpatient and direct costs are significantly increased in the presence of chronic pain, exceeding $60 billion annually. Opioid-induced constipation adversely affects work productivity, daily activities, quality of life, overall health-related quality of life (HRQoL), complicates pain management and increases health care resource utilization (e.g. admission rates, physician and alternate care provider visits, emergency department visits, pharmacy and laboratory costs).
**Prevention and Treatment**

When prevention fails (see below), the goal of treatment of opioid-induced constipation (OIC) is to increase the frequency of spontaneous bowel movements (SBMs) and provide symptom improvement (e.g., straining, stool consistency, feeling of complete evacuation) without impacting pain control. Constipation is common, significant, often the most troubling and persistent side effect of opioid therapy, and should be anticipated.63-66,67,15,36,68,56

**Lifestyle modifications** are recommended as the first-line, non-pharmacologic intervention for patients receiving opioids, although most often inadequate to prevent or treat OIC. Modifications may include increasing water and fluid intake, increasing exercise, increasing or adding dietary fiber or fiber-supplements and optimizing toileting habits.11,12,15,16,45,69

**Pharmacologic Interventions (See Table 1)** Prevention and treatment of OIC includes several approaches. Although μ-opioid receptor antagonists seem reasonable options to antagonize the effects of opioids on the ENS their ability to cross the blood brain barrier (BBB) results in the reversal of central mediated analgesia rendering these agents without merit.22,70,71,70-73 This limitation led to the development of opioid antagonists that do not cross the BBB, the PAMORAs.15

Rotating opioids has been proposed as a modality to limit OIC. Some opioids are associated with less constipation (e.g. fentanyl) and transdermal administration appears to reduce the development of constipation. Unfortunately, rotating opioids may predispose to dosing errors, over-dosage, prescribing errors or other adversities. In fact prescriber or patient errors during rotation have been implicated in opioid over-dosage and death.74-76 Another strategy to combat constipation is via opioid dose reductions.77 This is performed by the addition of a non-opioid co-analgesic (e.g. hydrocodone/acetaminophen, oxycodone/acetaminophen), the addition of an adjuvant analgesic (appropriate to the pain syndrome and mechanism), the application of therapy targeting the cause of the pain, the application of regional anesthesia or neuro-ablative interventions.63 Because OIC develops at a lower dose than required for the treatment of pain, reducing the dose of the opioid may be ineffective to solve OIC.20

Laxatives are traditionally the first medication used to prevent or treat constipation in patients receiving opioids. The adage, “the hand that prescribes opioid shall also prescribe laxatives” is implemented with either oral (or rectal) products, often in combination, and may include; bulk forming laxatives, lubricant laxatives, osmotic laxatives, stimulant laxatives or stool softeners.11,78,63-66 Laxatives may be contraindicated, particularly in palliative-care patients with neutropenia or thrombocytopenia.23 In patients with limited fluid intake, bulk-forming laxatives may lead to pseudoobstruction.15 Despite the number of nonspecific laxative agents available for treatment or prevention of OIC, laxative failure is common and up to 81% of patients still report constipation with symptoms refractory to even the most aggressive laxative regimens.15,23,79,11 Laxative use and overuse may result in electrolyte disturbances, tolerance or dependence to the laxative, kidney stones, kidney failure or the potential for drug-drug or drug-nutrient interactions limiting utility.22 Rescue modalities (e.g., enemas, colonic investigation, and manual disimpaction) are often administered when other options fail. These modalities are often unpleasant, distressing and may carry risks.
The results of an international study involving 489 non-malignant patients receiving opioids found an inadequate response to a single laxative agent in 94% of patients, while 27% failed to respond to two or more laxative agents.\textsuperscript{80} In fact, only 46% of non-malignant patients receiving an opioid had a desired response 50% of the time compared with a laxative response of 84% in control subjects.\textsuperscript{15} A prospective, longitudinal, multi-national study in patients with chronic non-malignant pain and self-reported OIC found most used a laxative at least 4 times in the prior 2 weeks with an inadequate response.\textsuperscript{81}

The National Hospital Ambulatory Medical Care Survey (NHAMCS) data from 2010 found that <1% of patients given a prescription for an opioid were also given a prescription for a laxative. This contrasted with discharge laxative prescriptions for 42% of patients presenting with constipation, demonstrating that most patients receiving opioids are not prescribed laxatives.\textsuperscript{82}

A meta-analysis failed to demonstrate the benefit of one laxative or combination over another in the treatment of OIC. No differences were noted between lactulose and senna, lactulose/senna vs magnesium hydroxide/liquid paraffin, or between misrakasnehan and senna.\textsuperscript{83} Laxative failures are common in OIC and not unexpected as these agents do not target the underlying mechanism of OIC, activation of $\mu$-opioid receptors of the GI tract.\textsuperscript{12, 18,84}

Lubiprostone, a chloride channel activator was approved by the FDA (April, 2013) for use in opioid-induced constipation. The primary response measure, an increase of $\geq$ 1 SBM/week and at least 3 SBMs per week for at least 9 of 12 weeks of study varied in three trials from 15.3% to 27.1% with lubiprostone compared to placebo response rates of 13% to 18.9%. Lubiprostone may not be as effective in patients taking methadone. First dose dyspnea was noted which tended to resolve within 3 hours but can occur with continued dosing. The most common adverse events when used to treat OIC were nausea and diarrhea. This agent should not be used in the setting of possible mechanical bowel obstruction. Dosing is initiated at lower doses in the presence of hepatic impairment.

Pro-kinetic medications initiate or enhance peristalsis and facilitate bolus transport. Dopamine antagonists (e.g. metoclopramide) stimulate peristalsis by releasing acetylcholine. Substituted benzamides (e.g. cisapride) release acetylcholine by acting on 5HT4 receptors and motilides such as erythromycin enhance peristalsis by acting on motilin receptors or by releasing motilin.\textsuperscript{85} These agents are not considered safe for long term use due to the potential for tardive-dyskinesia.\textsuperscript{13,14}
<table>
<thead>
<tr>
<th>Pharmacologic Class</th>
<th>Agents</th>
<th>Time to Laxation</th>
<th>Comments</th>
<th>FDA Approved or Clinical Efficacy Established in OIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laxatives</td>
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<tr>
<td>Stimulant</td>
<td>Bisacodyl Tab, Bisacodyl Suppository, Senna, Casanthranol, Cascara</td>
<td>0.25-1 hour, 0.25-1 hour, 8-12 hours</td>
<td>Abdominal cramps, nausea, vomiting, dependence</td>
<td>No</td>
</tr>
<tr>
<td>Stool Softeners, Surfactant</td>
<td>Docusate</td>
<td>12-72 hour</td>
<td>Nausea, diarrhea, bitter taste</td>
<td>No</td>
</tr>
<tr>
<td>Combination Stimulant – Surfactant</td>
<td>Docusate-casanthranol</td>
<td>8-12 hour</td>
<td>See separately</td>
<td>No</td>
</tr>
<tr>
<td>Osmotic Laxatives</td>
<td>PEG, Lactulose, Glycerin (PR)</td>
<td>0.5-1 hour, 24-48 hour, 0.5-1 hour</td>
<td>Dissolve in 4-8 oz. fluid, flatulence, nausea, bloating, cramping, diarrhea, rectal bleeding, do not use with symptoms of bowel obstruction, risk of electrolyte disturbances</td>
<td>No</td>
</tr>
<tr>
<td>Bulk Forming, Fiber</td>
<td>Psyllium, Methylcellulose, Polycarbophil</td>
<td>12-72 hours</td>
<td>Abdominal pain, flatulence, bloating, rectal pain, requires adequate fluid intake (minimum 8 oz.), caution in fluid restricted patients, rectal bleeding, do not use with gastrointestinal strictures, stenosis, may interfere with absorption of medications, bulk may distend abdomen and cause pain or aggravate constipation</td>
<td>No</td>
</tr>
<tr>
<td>Emollient</td>
<td>Mineral Oil</td>
<td></td>
<td>Not recommended as a laxative; aspiration may cause lipid pneumonia, caution in the elderly, cramps, diarrhea, nausea, vomiting, anal leakage, interferes with absorption of fat soluble vitamins and medications</td>
<td>No</td>
</tr>
<tr>
<td>Saline</td>
<td>Magnesium citrate, Magnesium hydroxide, Magnesium sulfate, Sodium phosphate and bisphonates, Phosphate enema</td>
<td>0.5-1 hour, 5-15 min</td>
<td>Abdominal cramping, watery diarrhea, electrolyte imbalance, use caution in patients with heart failure or kidney insufficiency, may cause magnesium/aluminum toxicity</td>
<td>No</td>
</tr>
<tr>
<td>Other Agents</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Stimulate Peristalsis</td>
<td>Metoclopramide, Erythromycin, Cisapride</td>
<td></td>
<td>Tardive dyskinesia, extrapyramidal reactions, neuroleptic malignant syndrome, fluid retention, limit duration of use, nausea, diarrhea, fatigue, restlessness (Not marketed) Diarrhea, potential changes in gut flora</td>
<td>No</td>
</tr>
<tr>
<td>Chloride Channel Activator:</td>
<td>Lubiprostone</td>
<td>&lt; 24 hours</td>
<td>Nausea, headache, diarrhea, flatulence, abdominal pain, headache; take with food and water, swallow whole; monitor dyspnea; hepatic dosing recommendations; confirm absence of GI obstruction; dyspnea has been reported within 1 hour of first dose</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Peripherally acting \( \mu \)-opioid receptor antagonist agents (PAMORAs) are newer agents that specifically block the peripheral effects of opioids on \( \mu \)-opioid receptors in the enteric nervous system to treat OIC. It has been suggested that up to 50\% of patients with OIC may benefit from treatment with a PAMORA, however, PAMORA resistant constipation may be found in patients with other etiologies which may include medications, advanced age, immobility or advanced illness.\(^{87,88}\) Currently two agents are FDA-approved for the treatment of opioid-induced constipation. Naloxegol (Movantik\textsuperscript{®}) was approved in 2014 for the treatment of opioid-induced constipation in adult patients with chronic non-malignant pain. Methylnaltrexone (Relistor\textsuperscript{®}) was initially approved in 2008 for the treatment of opioid-induced constipation in adult patients with advanced illness who are receiving palliative care, when response to laxative therapy was not sufficient, and expanded in 2014 to include the treatment of opioid-induced constipation in adult patients with chronic, non-malignant pain. The use of PAMORAs are being incorporated within guidelines for management of constipation in patients receiving opioids.\(^{63,83,89}\) (See Table 2)

**Table 2: Guidelines for Prevention and Treatment of Constipation/OIC Mentioning PAMORAs**

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Suggestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Society for Interventional Pain Physicians(^90)</td>
<td>Insufficient data for PAMORAs in chronic, non-malignant pain syndromes.</td>
</tr>
<tr>
<td>Use of Opioid Analgesics in the Treatment of Cancer Pain: Evidence-Based Recommendations from the EAPC (^78,91)</td>
<td>Laxative Failure: Methylnaltrexone</td>
</tr>
<tr>
<td>NICE: Opioids in Palliative Care: Strong Opioids for Pain Relief (Clinical Guideline CG140) – A Guideline Summary (^92)</td>
<td>Laxative Failure: Methylnaltrexone</td>
</tr>
<tr>
<td>NICE: Naloxegol for Treating Opioid-Induced Constipation (Constipation Pathway TA345) (^93)</td>
<td>Laxative Failure: Naloxegol</td>
</tr>
<tr>
<td>Palliative Care for the Patient with Incurable Cancer or Advanced Disease. (Part 2: Pain and Symptom Management.) (^94)</td>
<td>Treatment: Methylnaltrexone</td>
</tr>
<tr>
<td>The Canadian Consensus Development Group Consensus Recommendations for the Management of Constipation in Patients with Advanced Progressive Illness. (^64)</td>
<td>Laxative Failure: Methylnaltrexone</td>
</tr>
<tr>
<td>Expert Working Group of the European Association of Palliative Care Network (^63)</td>
<td>Laxative Failure: Methylnaltrexone</td>
</tr>
</tbody>
</table>
Mechanism of Peripheral Activity
Naloxegol is a PEGylated derivative of naloxone which acts as a μ-opioid receptor antagonist. PEGylation reduces permeability across the blood brain barrier. Preclinical studies documented a 15-fold reduction in CNS penetration in comparison to unconjugated naloxone. CNS penetration is further limited, as the molecule is a substrate for the P-glycoprotein (P-gp) transporter. \cite{95,22,96} The efflux transporter acts a defense mechanism. The transporter is located on the endothelial cells of brain capillaries and limits the accumulation of toxins, xenobiotics and drugs into the brain. By PEGylation and as a substrate for the P-gp transporter, therapeutic doses of naloxegol do not cause antagonism at central μ-receptors. \cite{96}

Methylnaltrexone is a quaternary compound created by N-methylation of an alkyl-substituent on the nitrogen atom of the tertiary opioid antagonist, naltrexone. N-methylation results in a positive charged-derivative (in solution) with limited ability to cross the blood-brain barrier due to both polarity and low lipid solubility. \cite{23,97,98,99-102} The inability of methylnaltrexone to cross the BBB has been confirmed in humans. No loss of analgesia or opioid withdrawal symptoms was noted. \cite{28}

Comparison of PAMORA Agents
Both agents are FDA approved for use in non-malignant patients with opioid-induced constipation. Methylnaltrexone is additionally indicated for opioid-induced constipation in patients with advanced illness who are receiving palliative care, when the response to laxative therapy has been insufficient. The average opioid exposure in clinical trials was 4 weeks for each agent which may increase sensitivity to the medications. Laxatives should be discontinued before use, but may be initiated after 3 days of sub-optimal response. For methylnaltrexone, with a rapid onset of laxation, it is recommended that patients be in close proximity to toilet facilities.

Naloxegol is indicated once daily, in the morning, on an empty stomach, as a 25 mg tablet, swallowed whole. A 12.5 mg tablet is available for those that do not tolerate the 25 mg dosage. Methylnaltrexone is indicated for non-malignant patients as a 12mg, SQ, once daily dosage and for use in palliative-care patients dosed via weight. Methylnaltrexone is available in 8 and 12 mg prefilled syringes and as 12 mg/0.6 ml vials, available individually or in kits containing needle, syringe, and alcohol pads. Once drawn into a syringe, it is stable at room temperature for 24 hours (See Table 3)
### Table 3: Comparison of PAMORA Agents for Opioid-Induced Constipation

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Manufacture</th>
<th>FDA-Approved Indications</th>
<th>Route of Administration</th>
<th>Dosage and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naloxegol</td>
<td>(Movantik®)</td>
<td>AstraZeneca (Approved 2014)</td>
<td>Treatment of opioid-induced constipation in adult patients with chronic non-malignant pain</td>
<td>Oral</td>
<td>Discontinue if/when treatment with the opioid is discontinued</td>
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<td>Be within close proximity to toilet facilities once administered</td>
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<td><strong>In non-malignant pain and OIC</strong></td>
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<td>Dosage: 25 mg once daily</td>
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<td></td>
<td>• Inject one dose daily</td>
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<td>• Reevaluate continued need whenever opioid regimen is changed</td>
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<td><strong>In advanced illness and OIC (weight-based dosing)</strong></td>
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<td></td>
<td>• Inject <strong>every other day</strong>, as needed, no more frequently than one dose per 24-hours:</td>
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<td>- Weight of Adult Patient</td>
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<td>Less than 38 kg</td>
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<td>38 to &lt;62 kg</td>
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<td>62 kg to 114 kg</td>
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<td>More than 114 kg</td>
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<td>From vial: Administer with a 1 mL syringe, 27 gauge x ½ inch needle.</td>
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<td><strong>How Supplied</strong></td>
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<td>• 25 mg tablet</td>
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<td>• 12.5 mg tablet</td>
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<td><strong>Storage</strong></td>
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<td></td>
<td>Store between 20-25 °C</td>
</tr>
<tr>
<td>Methyl 103</td>
<td>Naltrexone (Relistor®)</td>
<td>Salix (Approved 2008, 2014)</td>
<td>Treatment of opioid-induced constipation in adult patients with chronic non-malignant pain</td>
<td>Subcutaneous: Rotate administration: upper arm, abdomen and thigh</td>
<td>Discontinue if/when treatment with the opioid is discontinued</td>
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<td></td>
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<td></td>
<td>Treatment of opioid-induced constipation in adult patients with advanced illness that are</td>
<td></td>
<td>Be within close proximity to toilet facilities once administered</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>receiving palliative care, when response to laxative therapy has not been sufficient.</td>
<td></td>
<td><strong>In non-malignant pain and OIC</strong></td>
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<td></td>
<td></td>
<td></td>
<td>(Use beyond 4 months has not been studied in the advanced illness population).</td>
<td></td>
<td>Dosage: 12 mg subcutaneously once daily</td>
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<td></td>
<td>• Inject one dose daily</td>
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<td></td>
<td>• Reevaluate continued need whenever opioid regimen is changed</td>
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<td></td>
<td><strong>In advanced illness and OIC (weight-based dosing)</strong></td>
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<td></td>
<td>• Inject <strong>every other day</strong>, as needed, no more frequently than one dose per 24-hours:</td>
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<td>- Weight of Adult Patient</td>
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<td>Less than 38 kg</td>
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<td>38 to &lt;62 kg</td>
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<td>62 kg to 114 kg</td>
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<td>More than 114 kg</td>
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<td></td>
<td>From vial: Administer with a 12 mg/0.6 mL vials (Solution drawn into syringe stable 24 hrs.)</td>
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<td></td>
<td></td>
<td>• Single-use vial: One 12 mg/0.6 mL vials (Solution drawn into syringe stable 24 hrs.)</td>
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<td></td>
<td>• 8 mg/0.4 mL single-use pre-filled syringes with needle guard system</td>
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<td></td>
<td></td>
<td>• 12 mg/0.6 mL single-use pre-filled syringes with needle guard system</td>
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<td><strong>Storage</strong></td>
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<td></td>
<td>Store at 20-25 °C room temperature; Protect form light.</td>
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</tbody>
</table>
Pharmacokinetics
Naloxegol: Following a 25 mg oral dose, Cmax is achieved in less than 2 hours with a secondary peak observed 0.4 to 3 hours later in a majority of subjects, suggesting enterohepatic recycling. AUC demonstrated a dose-proportional increase with minimal accumulation following multiple daily doses. The steady state volume of distribution is ~968 to 2140 L with 4.2% plasma protein binding. Metabolism is primarily via the CYP3A enzyme system through N-dealkylation, O-demethylation, oxidation and partial loss of the PEG chain producing six metabolites. The elimination half-life ranges from 6 to 11 hours. Elimination is via the feces (68%) and urine (16%) with 16% and <6% excreted unchanged, respectively.

Methylnaltrexone: Following a 12 mg SQ dose, Cmax is achieved at ~0.5 hours. AUC demonstrated dose-proportional increases but did not accumulate following once daily dosing for seven days. The steady state volume of distribution is ~1.1 L/kg with 11%-15.3% plasma protein binding. Five distinct metabolites are recovered; methyl-6-naltrexol isomers (5%) and methylnaltrexone sulfate (1.3% of total) appear to be the primary metabolism pathways. The elimination half-life is ~8 hours. The majority of the drug is eliminated unchanged in the urine (54%) and feces (17%). The renal clearance of methylnaltrexone is 4-5 fold higher than creatinine clearance suggesting active renal secretion.

Meta-Analyses
Currently, there are no comparative trials of the two FDA-approved agents, naloxegol and methylnaltrexone, in the treatment of OIC. It is difficult to compare these agents across clinical trials as the clinical endpoints or the manner in which they were analyzed, differed. A number of systematic reviews, meta-analysis or Cochrane reviews have been published evaluating the utility of methylnaltrexone, naloxegol and/or alvimopan across studies (See Table 4).

McNicol et al, found the agents effective at reversing opioid-induced oral-cecal transit increases but not statistically beneficial in the treatment of OIC when the data was adjusted for heterogeneity. Becker et al, noted differences across studies in the diagnosis of constipation and questioned the external validity of the data. Sonu et al, noted that although the agents are effective in producing laxation in comparison to placebo, 52% to 62% of patients remained constipated. Ford et al, noted a failure rate with these agents of 46%, a relative risk of failure of 0.69 and a number needed to treat (NNT) to prevent OIC of 4 with a number needed to harm (NNH) of 14. Their subgroup analysis of the methylnaltrexone (MNTX) studies yielded similar findings. Magee et al, calculated the odds ratio (OR) for improvement of OIC to be 3.1 with a NNT of 5.6. Lastly, Candy reported an OR for rescue-free laxation within 4 hours of 6.95 and within 24 hours of 5.42.
Table 4: Meta-Analysis, Systematic Reviews, Cochrane Reviews and Pooled Analysis of PAMORAs for Opioid-Induced Constipation

<table>
<thead>
<tr>
<th>Author</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>McNicol 2008**</td>
<td>The efficacy and safety of peripheral μ-opioid receptor antagonists in the treatment of opioid bowel dysfunction was assessed from 22 articles [2352 opioid antagonist-treated patients: ALV (8 studies), MNTX (6 studies), naloxone (7 studies) and nalbuphine (1 study).] Three studies were excluded, two with insufficient data reported and 1 study with outcome measures that could not be combined with other trials. Reversal of opioid-induced oral-cecal transit increases identified six of ten studies pooled for analysis (5 MNTX and 1 ALV). The majority of the studies were done in healthy volunteers. A single study evaluated transit time changes in patients receiving chronic methadone therapy. Four trials were assessable for constipation (1 each methylnaltrexone and alvimopan and 2 with naloxone).</td>
<td>Both alvimopan and methylnaltrexone were efficacious in reversing opioid-induced increases of gastrointestinal transit times. MNTX studies: GI transit time was reduced 59 minutes vs. PBO (95% CI: -75 to -42). Data was presented on a forest plot and demonstrated weak efficacy. PAMORAs resulted in a NNT of 2.7 (95% CI: 1.9 to 4.8). Statistical significance was lost with a random effects model. Adverse events across trials were similar MNTX vs. PBO and rated as mild to moderate.</td>
</tr>
<tr>
<td>Becker 2007**</td>
<td>A systematic review initially identified 20 trials addressing the use of opioid antagonists in the treatment of opioid-induced constipation. After excluding for small sample size or non-randomized, single blind design, 9 studies using MNTX and 6 studies of ALV were analyzed. Most studies were performed in healthy volunteers, with nonmalignant pain or involving patients in methadone programs. Inconsistency in the diagnosis of constipation questioned the external validity of the well-performed studies.</td>
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<td>Sonu 2015 (Abstract)</td>
<td>Two randomized, placebo-controlled, clinical trials using MNTX and NAL were reviewed to determine the probability of relief from opioid-induced and chronic idiopathic constipation. Statistical significance to relieve OIC was found, vs. PBO Patients remaining constipated: MNTX 52% and naloxegol low/high dose 62%/58</td>
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<tr>
<td>Ford 2013**</td>
<td>A meta-analysis identified 14 studies reflecting 4,101, of whom 2,719 received a μ-opioid receptor antagonist for the treatment of OIC (MNTX in 6 studies, naloxone in 4 studies and ALV in 4 studies). PAMORAs failed in 46.4% of patients vs. PBO patients of 64.1% Treatment resulted in a lower RR of failure compared with placebo (RR=0.69; 95% CI 0.63 to 0.76). The NNT was 4 (95% CI 3 to 6) and the NNH was 14 (95% CI 9-33) The RR of any adverse event (RR=1.11; 95% CI 1.04 to 1.20). MNTX Subgroup treated 1-12 days (n=1,095): a failure to respond 48.7% compared with 64.5% with PBO. RR of failure vs. PBO 0.67 (95% CI 0.56 to 0.72) with a NNT of 3 MNTX Subgroup treated &gt; 2 days RR of failure vs. PBO was 0.79 (95% CI 0.7 to 0.88). Trend toward more AEs in MNTX vs. PBO (RR 1.24; 95% CI 0.98 to 1.57).</td>
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<td>Magge 2012**</td>
<td>Data was extracted and pooled from a review of 3 MNTX studies. Odds ratio (OR, 95% CI) for global improvement was 3.1 (1.97-5.05) with a NNT of 5.6 (4-9)</td>
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<tr>
<td>Candy 2011**</td>
<td>A meta-analysis of 287 palliative care patients enrolled in two randomized, controlled trials assessed the efficacy of MNTX SQ vs placebo to treat OIC. The odds ratio for rescue-free bowel movement within 4 hours was 6.95 (95% CI: 3.83 to 12.61) and within 24 hours was 5.42 (5% CI 3.12 to 9.42).</td>
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</table>
Safety Information

These agents are generally well tolerated. The most common adverse events noted in clinical studies related to the gastrointestinal system (nausea, abdominal pain, diarrhea, flatulence). Other common adverse events included, hyperhidrosis, tremor, headache, dizziness and hot flush at greater than 1%. Caution should be used in patients without an intact blood brain barrier (BBB).

Both agents are contraindicated in patients with impaired structural integrity of the GI tract based on methylnaltrexone data. In reviewing post-marketing, Adverse Event Reporting System (AERS) data, reflecting approximately one year of usage (4/08 to 10/09), Mackey identified 7 cases of gastrointestinal perforation in patients receiving methylnaltrexone. Each patient had a pathological or anatomic abnormality in the upper or lower GI tract, including; metastatic colon cancer with previous hemicolectomy, peptic ulcer, bevacizumab use, volvulus, ALS, peptic ulcer and bowel obstruction. Abdominal pain preceded perforation in four of patients and occurred following the first dose in four patients.\(^{111}\)

Naloxegol is metabolized through the CYP 3A4 and is contraindicated in combination with strong CYP3A4 inhibitors due to the potential for increased exposure to naloxegol and the risk of opioid withdrawal reactions. It is recommended to avoid concomitant use of naloxegol with moderate CYP3A4 inhibitors, grapefruit products, or CYP3A4 inducers (See Table 5).
<table>
<thead>
<tr>
<th>Generic Name Brand Name</th>
<th>Naloxegol <em>(Movantik®)</em></th>
<th>Methylnaltrexone <em>(Relistor®)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Events</strong></td>
<td>Most common adverse events in clinical trials occurring in &gt;3% of patients and at an incidence greater than placebo are abdominal pain, diarrhea, nausea, flatulence, vomiting, headache, and hyperhidrosis.</td>
<td>Chronic Non-malignant Pain: Most common adverse events in clinical trials occurring at &gt;1% and at an incidence greater than placebo are abdominal pain, nausea, diarrhea, hyperhidrosis, hot flush, tremor and chills. Advanced Illness: Most common adverse events in clinical occurring at an incidence &gt;5% and at an incidence greater than placebo are abdominal pain, flatulence, nausea, dizziness, and diarrhea.</td>
</tr>
<tr>
<td><strong>Warnings, Precautions</strong></td>
<td>Gastrointestinal perforation: Consider the overall risk benefit in patients with known or suspected lesions of the GI tract. Monitor for severe, persistent, or worsening abdominal pain; discontinue if symptoms develop. Opioid withdrawal symptoms have occurred during treatment and more frequently in patients receiving methadone. Consider the overall risk benefit in patients with disruptions to the blood-brain barrier. Monitor for symptoms of opioid withdrawal.</td>
<td>Gastrointestinal Perforation: Cases have been reported in adult patients with OIC and advanced illness in conditions affecting structural integrity of the gastrointestinal tract. Consider the overall risk benefit in patients with known or suspected lesions of the GI tract. Monitor for severe, persistent or worsening abdominal pain; discontinue if symptoms develop. Severe or persistent diarrhea: Discontinue Opioid withdrawal symptoms have occurred during treatment. Consider the overall risk benefit in patients with disruptions to the blood-brain barrier. Monitor opioid withdrawal symptoms.</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Patients with known or suspected gastrointestinal obstruction and patients at increased risk of recurrent obstruction, due to potential for gastrointestinal perforation (based on methylnaltrexone data). Patients concomitantly using strong CYP3A4 inhibitors (e.g. clarithromycin ketoconazole), due to increased exposure and potential for precipitating opioid withdrawal. Patients who have had a known serious/severe hypersensitivity reaction</td>
<td>Patients with known or suspected mechanical gastrointestinal obstruction and at increased risk of recurrent obstruction due to the potential for gastrointestinal perforation.</td>
</tr>
<tr>
<td><strong>Drug Interactions</strong></td>
<td>Avoid use with other opioid antagonists. Potential for additive opioid antagonism and risk of withdrawal. <strong>Strong CYP3A4 Inhibitors:</strong> Contraindicated (e.g. ketoconazole, itraconazole, clarithromycin) <strong>Moderate CYP3A4 inhibitors:</strong> Avoid use. If use is unavoidable, reduce the dosage to 12.5 mg/day and monitor for adverse reactions (e.g. diltiazem, erythromycin, verapamil) <strong>CYP3A4 Inducers:</strong> Not recommended (e.g. rifampin, carbamazepine, St. John’s Wort) Avoid grapefruit juice or grapefruit during treatment.</td>
<td>Avoid use with any other opioid antagonists. Potential for additive opioid antagonism and risk of withdrawal. Weak, clinically, non-significant inhibitor of CYP2D6</td>
</tr>
<tr>
<td><strong>Post-Marketing Experience</strong></td>
<td>Gastrointestinal: perforation, cramping, vomiting General: Diaphoresis, flushing, malaise, pain, cases of opioid withdrawal</td>
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</table>
Pharmacodynamics
Effects on Cardiac Repolarization
A third PAMORA was studied for use in the treatment of OIC. In a study evaluating the utility of Alvimopan in OIC, 518 patients receiving opioids for non-malignant pain were treated with Alvimopan 0.5mg twice a day. A non-significant finding of myocardial infarction in 7 of 538 alvimopan treated patients prompted a conservative response from the FDA, although all seven of the patients were at high risk of cardiovascular disease. Further development of alvimopan for OIC was discontinued. Adolor Pharmaceuticals “based this determination principally on its assessment of the cost and timeline for an additional Phase III study relative to the remaining commercial life of alvimopan in OBD.”

Because it was unknown if cardiac adverse effects reflected a class effect, both methylnaltrexone and naloxegol studies were designed to look specifically for cardiac adverse effects, especially major adverse cardiovascular events (MACE - cardiovascular death, myocardial infarction or stroke effects). Neither naloxegol nor methylnaltrexone demonstrated any effect on cardiac repolarization, QTc interval prolongation, blood pressure pulse, platelet aggregation or metabolic changes in pre-clinical or clinical trials.

Special Populations
Neither agent has been tested in children or pregnancy (category C), and exposure through lactation is unknown. Both agents appear safe and effective in the geriatric population. Mild to moderate hepatic dysfunction was not associated with clinically significant effects. 

Adjustments for renal impairments are indicated for both methylnaltrexone and naloxegol. For methylnaltrexone, severe renal impairment (CrCl<30mL/min) did not change Cmax. However, a two-fold increase in total exposure and an 8 to 9-fold decrease in renal clearance was documented prompting the recommendation to reduce the dosage by 50% in this population.

Naloxegol pharmacokinetics in mild, moderate and severe renal impairment did not differ from normal controls except in two patients (one each moderate and severe renal impairment). It is postulated that the increased exposure in these two patients (AUC 1.7 to 2.2-fold increase and Cmax 1.1 to 1.8-fold increase) reflects the effects of renal impairment on gut metabolism, or the downregulation of CYP3A enzyme expression in the gut and liver since naloxegol is primarily eliminated by this enzyme system. At CrCl <60 mL/min, a starting dose of 12.5 mg is recommended which may be increased to 25 mg with consideration of adverse effects.

Methods
A literature search was conducted to identify articles addressing each key question, searching the MEDLINE database (1950 – 2014), Embase (1970 – 2015), the Cochrane Library, the National Institute for Health and Care Institute (NICE), NIH Clinical Trials website, the FDA website, Agency for Healthcare Research and Quality (AHRQ), the Academy of Managed Care Pharmacy (AMCP) and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English were included. Trials evaluating the efficacy of µ-opioid receptor antagonists in opioid-induced constipation are included.
Clinical Evidence - Naloxegol

Naloxegol for Opioid-Induced Constipation in Non-Malignant Pain

Dose-Escalation Study
A phase 2, randomized, double blind, placebo-controlled, dose-escalation study involving 207 patients with chronic, non-malignant pain, randomized to 4 weeks treatment with placebo or 5, 25 or 50 mg of naloxegol solution once daily was performed. The primary endpoint of a change in spontaneous bowel movements from baseline was achieved with 25 and 50 mg naloxegol (2.9 vs 1.0; p= 0.0020 and 3.3 vs 0.5; p=0.0001, respectively). The effect was maintained through the 4-weeks of randomized treatment, with the exception of the 25 mg dose during the second week of treatment. The median change in bowel movements over the entire 4 weeks documented superiority for both the 25 and 50 mg doses of naloxegol compared to placebo (3.0 vs 08; p=0.002 and 3.5 vs 1.0; p=0.0001, respectively) while doses of 5 mg did not demonstrate a difference from placebo. Effects were maintained across opioid dosage strata (30-100 MEU/day or >100 MEU/day). The median time to the first bowel movement was significantly shorter than placebo for the 25 and 50 mg cohorts (6.6 vs 48.6 hours; p=0.0012 and 2.9 vs 44.9 hours; p=0.0016, respectively). PAC and PAC-QOL scores were better at individual time points, but not consistent throughout the study. Naloxegol was generally well tolerated. Common adverse events were abdominal pain, diarrhea and nausea which were mild and transient in the 5 and 25 mg doses and more frequent and severe in the 50 mg dose resulting in higher discontinuation rates. Daily opioid doses remained constant and no changes in opioid withdrawal scores were noted. This phase II dose escalation study confirmed that oral doses of 25 and 50mg QD significantly increased the number of SBMs in patient with OIC over a wide range of opioid doses without interference of central mediated analgesia. Adverse events were mainly gastrointestinal, and more significant with the 50 mg dose. Gastrointestinal adverse events occurred most often during the first week of therapy and resolved by the second week. It is postulated that this may reflect increased bowel functioning following inactivity.20,119

Pivotal Trials
Two identical randomized, placebo-controlled, parallel-group studies (Study-04 and Study-05) evaluated the effects of naloxegol (12.5 or 25 mg) or placebo in outpatients with non-malignant pain and opioid induced constipation during a 12-week randomized treatment period.122 Criteria for enrollment included outpatients aged 18-75 years, receiving daily doses of 30-1000mg MEU, with non-malignant pain who met the definition of opioid-induced constipation (<3SBMs per week with one symptom; hard-lumpy stools, straining or the sensation of incomplete evacuation/anal obstruction present ≥ 25% of bowel movements over the prior 4 weeks). The study included a 2-week period of laxation documentation to confirm the presence of opioid-induced constipation as a baseline. For the primary endpoint (defined as ≥ 3 SBMs per week with an increase of ≥ 1 SBM/week for 9 of the 12 weeks, including 3 of the final four weeks of the study and improvement in at least one measure on the Bristol Stool Scale), naloxegol 25mg performed better than placebo in the ITT population of both studies: Study-04, 44.4% vs 29.4%, and p=0.001; Study-05, 39.7% vs 29.3%, p=0.02. The number needed to treat at 25 mg was 6.7 in Study-04 and 9.7 in Study-05. Patients with an inadequate response to laxatives during the 2-week prescreening period also responded well to naloxegol 25mg: Study-04, 48.7% vs 28.8%, p=0.002; Study-05, 46.8% vs 31.4%, p=0.01. Naloxegol 12.5mg performed
significantly better than placebo in the ITT population of Study-04: 40.8% vs 29.4%, p=0.02; as well as the inadequate response to laxative subset, 42.6% vs 28.8%, p=0.03 but not statistically superior in Study-05. The time to the first spontaneous bowel movement and the mean number of days per week with one or more spontaneous bowel movements was higher with naloxegol 25mg vs placebo in both studies (p<0.001) and with naloxegol 12.5mg in Study-04 (p<0.001). In Study-04 the response time varied from placebo to naloxegol from 35.8 hours to 5.9 hours, respectively and in Study-05, from 37.2 hours to 12 hour. Pain scores, changes in opioid dose and opioid withdrawal symptoms were similar among groups and studies. Gastrointestinal adverse effects occurred more commonly in patients receiving naloxegol 25mg than naloxegol 12.5mg or placebo and led to more discontinuations in this group. Abdominal pain, diarrhea, flatulence, nausea and vomiting typically occurred shortly after initiating treatment and were of mild to moderate severity. Serious adverse events and major cardiovascular events were similar across treatment groups.¹²⁰

Long-term Safety
A long-term safety and tolerability study in 804 patients compared the use of naloxegol 25mg once daily to usual care (UC; a laxative regimen chosen by the investigator based upon clinical experience) over a 52-week period. Patients were rolled into the study from Study-04 and Study-05 or without prior NAL exposure. The completion rate for the naloxegol group was 58.1% and for the UC group 67.3%. Adverse events occurring more commonly in the NAL versus UC group (81.8%, 72.2%) and included abdominal pain 17.8% vs 3.3%), diarrhea (12.9% vs 5.9%), nausea (9.4% vs 4.1%) and headache (9.0% vs 1.1%). There were no differences between groups with regard to serious adverse events or cardiovascular adverse events. Most naloxegol adverse events occurred early, were mild to moderate in intensity and resolved during or after naloxegol therapy. Discontinuation rates were similar between the earlier studies and this study. Patients discontuing therapy with naloxegol reported diarrhea, abdominal pain or vomiting as the reasons. Pain scores and mean daily opioid doses remained stable throughout the study and no attributable opioid withdrawal symptoms occurred in either treatment arm.¹²¹,¹²²

Clinical Evidence - Methylnaltrexone

Methylnaltrexone for Opioid-Induced Constipation in Advanced Illness
Pivotal Trials in Advanced Illness
Methylnaltrexone was added to standard care in two pivotal studies and demonstrated to be more effective than standard care in the relief of opioid-induced constipation in patients with advanced illnesses. Laxation occurred following the first dose and within 30 minutes in ~50% of patients. A similar rate of response was noted over the first 4 administered doses. Overall, MNTX was well tolerated with the most commonly reported adverse events, abdominal pain, nausea and vomiting. No loss of analgesia or withdrawal symptoms were reported.²³,¹²³,¹²⁴ The additional finding that the higher dose of MNTX was less well tolerated and without significant efficacy advantage suggests that patients not responding to the initial doses will likely not respond to dosage increases or continued administration and therefore should not be continued on the medication.¹²⁵

Thomas et al, explored the use of MNTX 0.15 mg/kg or PBO every other day for 14 days in 133 patients with advanced illness (defined as a terminal cancer or end-stage disease with a life
expectancy of >1 month) and opioid-induced constipation. Patients had received opioids for ≥ 2 weeks (utilizing a stable dosage), were using laxatives and had gone ≥3 days without relief of opioid-induced constipation (defined as ≤3 SBM in the preceding week and no “meaningful” BM within 24 hours of the first dose of study drug, or no “meaningful” BM within 48 hours of study drug.) At baseline, patients were receiving a median dose of 100 mg MEU/day and a median use of 2 classes of laxatives. More MNTX treated patients had a RFBM within 4 hours (primary outcome) than those receiving PBO (48% vs 15%, respectively; p< 0.001) as well as a RFBM in ≥2 or the first 4 doses of MNTX (co-primary endpoint) (52% vs 8%, respectively; p<0.001). Treated patients had a higher rate of ≥ RFBMs per week (68% vs 45%; p=0.009). Over 50% of patients had a RFBM within 30 minutes of study drug administration. The effects persisted over 7 doses with 39% of patients receiving MNTX vs 6% of patients receiving placebo have a RFBM in ≥ 4 of seven study doses of MNTX over 13 days. Patients who responded to the first dose of MNTX demonstrated a median time to laxation after dosing for the duration of the study of 6.3 hours vs greater than 48 hours in those receiving PBO (p<0.001).

Serious adverse events were more common among patients receiving MNTX (28% vs 17%) but attributed to underlying disorders or disease progression. Adverse events (abdominal pain, flatulence and vomiting) were similar between groups during the 3-month open-label extension. Patients who receiving PBO in the double-blind phase, had response rates in the open-label phase (45-58%) similar to those that received blinded MNTX. Benefits were sustained over the 3 month open-label extension of the trial with no significant changes to opioid dose requirements for analgesia or opioid withdrawal scores. Life-threatening adverse events occurred in 16% and 15% of MNTX and placebo patients, respectively, all of which were deemed related to primary illness. Two patients were deemed to have serious adverse events during the 3-month extension of the trial related to study drug. One patient had serious muscle spasms and the other serious abdominal and exacerbated pain. No deaths occurring during any phase of the study were attributed to MNTX.

Slatkin et al, explored the effects of a single-dose of SQ MNTX 0.15 or 0.3 mg/kg or PBO in 154 patients with advanced illness (defined as a life expectancy of 1 to 6 months) and opioid-induced constipation. A dose-response relationship for MNTX was not found. The higher dose however, 0.3mg/kg, was associated with more reports of abdominal pain. More patients receiving MNX 0.15 or 0.3 mg/kg had a RFBM within 4 hours of receiving the study drug compared to placebo (61.7% or 58.2% or 13.5%, respectively, p<0.001 for 0.15 and 0.3 mg/kg MNTX vs placebo, respectively). The time following dosing, until a RFBM occurred, was significantly shorter at both the MNTX doses than placebo with results at 1.1h for 0.15 mg/kg, 0.8h for 0.3 mg/kg and >24 hours for PBO in each group, respectively (p<0.001 for both MNTX doses). Of patients who responded to MNTX with a RFBM, 50% responded within 30 minutes of drug administration. Adverse events were seen more commonly in the patients receiving MNTX compared to PBO (76% vs 48%) and included abdominal pain, flatulence and nausea which appeared to be dose-dependent and of mild to moderate intensity in both treatment groups. In the open-label phase of the single-dose study, three patients had serious adverse events related to MNTX therapy. One patient each had, delirium, flushing or diarrhea. The patient with diarrhea died due to metastatic breast cancer, which was exacerbated by diarrhea that resulted in dehydration and cardiovascular collapse.
Advanced Illness, Fixed-Dose Trial
Bull et al, 2015 evaluated the use of two fixed-doses of MNTX in 230 adults with advanced illness, stable doses and regimens of laxatives and opioids and OIC. Patients were randomized to blinded therapy with MNTX SQ QOD at 8 mg (<62kg) or 12mg (>62kg) of PBO for 2 weeks. A RFBM within 4 hours occurred in 62.9% of patients compared with 9.6% receiving PBO (p<0.0001). Secondary endpoints favored MNTX; RFBM less than 4 hours after dosing (p<0.0001), RFBM within 4 hours for at least 4 of 7 doses (p<0.0001), Median time to first-dose laxation (p<0.005). No differences relative to the different doses was observed. Adverse events were similar to other trials with no serious adverse events attributable to MNTX.127

Advanced-Illness Open Label Extension
Lipman et al, 2011 followed 82 advanced-illness patients with OIC who completed a two-week trial evaluating MNTX 0.15 mg/kg SQ QOD compared with PBO over a 3-month open-label extension.123 Patients continued on 0.15 mg/kg MNTX SQ no more than once daily with an increase or decrease in dosage (0.3 mg/kg or 0.075 mg/kg) permitted. Laxation response over the 3 month extension did not change significantly (45.3%, range 45.5-57.7%). The median time to laxation remained ~1 hour. Patients and investigators reported improvement in symptoms. Every patient reported at least one adverse event. Most commonly abdominal pain (30.5%) malignant neoplasm progression (24.4%), nausea (20.7) and vomiting (19.7%). Approximately half of the patients had at least one adverse event likely related to MNTX. Study discontinuation was noted in 7.3% of patients. Serious adverse events occurred in 43.9% of patients, most commonly due to progression of underlying disease. Serious adverse events possibly related to therapy included one patient with muscle spasms and a second patient with abdominal pain and an exacerbation of their pain.

Methylnaltrexone for Opioid-Induced Constipation in Non-Malignant Pain
Pivotal Trial in Non-Malignant Pain
Michna et al, evaluated MNTX as a treatment for OIC in patients (n=460) with chronic non-malignant pain. This double-blind, randomized, placebo-controlled trial compared MNTX 12mg SQ administered daily or QOD to PBO for 28 days. During the first 4 weeks of double-blind therapy, more patients receiving MNX QD or QD had a RFMB within 4 hours of the first dose compared with placebo (33.3% or 35.1% vs 9.9%; p<0.001 for both MNTX groups). Treatment with both MNTX 12mg QD and QOD resulted in a greater mean percent of active injections resulting in a RFBM within 4 hours of study drug administration than PBO (MNTX QD, 28.9% vs 9.4%; and MNTX QOD; 30.2% vs 9.3%; p<0.001 for both MNTX groups). RFBMs following administration of MNTX QD or QOD was more common than with patients receiving placebo (28.9% or 30.2% or 9.4%, P<0.001 for each MNTX vs placebo). Overall, 58.7% of MNTX QD, 45.3% QOD and 38.3% in the placebo group had at least 3 RFBMs per week during the double-blind period resulting in a NNT of 5 for daily dosing MNTX, and a NNT of 14 for QOD dosing. MNTX treated patients documented normalization of bowel texture (p<0.001) and reported sensations of complete evacuation improvement from baseline (p<0.04) compared with PBO. PAC-SYM scores were better in both MNTX groups when compared to patients receiving PBO (33 or 22 vs 18 respectively; p<0.001 for MNTX QD and p<0.014 for QOD dosing).128
The most common adverse event was abdominal pain, reported in 19.3% and 15.0% of patients treated with MNTX QD or QOD, versus 3.7% with PBO. Other adverse events noted more frequently in the MNTX groups were diarrhea, nausea, and hyperhidrosis. One drug-related SAE occurred in a patient who developed extra-systoles on day 1 of therapy which resolved without intervention the same day. Efficacy effects seen in the double-blind phase were durable during the 8-week, open-label phase of the study.\textsuperscript{128}

**Long-Term Efficacy and Safety**

Long-term efficacy was demonstrated in a 48-week, open-label study of SQ MNTX in chronic, non-malignant pain patients with OIC (N=1034). Patients received MNTX at least once weekly and as often as every day. Over the 48 weeks of the study, 34.1% of MNTX injections resulted in a RFBM\textless; within 4 hours of administration and a mean increase of 1.5 RFBM/week from baseline.\textsuperscript{129} Adverse events of mild to moderate intensity were reported in 81.5% of patients. Overall, MNTX was well tolerated and the adverse event profile mimicked the 4-week double-blind, placebo-controlled period of the trial.\textsuperscript{130} The most commonly reported AEs were abdominal pain (24.0%), diarrhea (16.4%), N (15.1%), hyperhidrosis (8.9%) and V (7.2%).\textsuperscript{129,131}

**Conclusion:**

A laxative bowel regimen started prophylactically is appropriate for all patients receiving opioid-therapy. Because laxatives do not counter the pharmacologic mechanism of opioid-induced constipation they are often ineffective. The peripherally acting \(\mu\)-opioid receptor antagonists are a new class of agents that reverse the effects of opioids on receptors within the enteric nervous system producing laxation in \(\sim\)50% of patients in clinical trials. The fact that only 50% of patients respond well to this therapy may reflect the multi-factorial cause of constipation in many patients with chronic pain. The evidence supports the use of naloxegol and methylnaltrexone in the treatment of opioid-induced constipation in patients without risk of bowel perforation who have received an opioid for a minimum of 4-weeks with an inadequate response to laxatives (i.e. stimulant laxative and osmotic laxative/stool softener). In clinical trials, these agents increase the number of spontaneous bowel movements and reduce time to laxation. Methylnaltrexone data suggests the NNT to prevent OIC is in the range of 3-6 and this is likely also true for naloxegol. No significant loss of analgesia or symptoms consistent with opioid withdrawal have been noted. Currently, there is no evidence supporting use of these agents beyond 12 months or validating superiority over other pharmacologic therapies. Naloxegol is available orally, while methylnaltrexone is administered subcutaneously. Adverse events of mild to moderate intensity are most commonly gastrointestinal in nature, including abdominal pain, nausea, vomiting, diarrhea and flatulence. No serious adverse events have been reported. These agents are comparable in efficacy and safety and offer clinicians an additional treatment option for opioid-induced constipation.
Appendix: Evidence Tables

Naloxegol (Movantik®)

<table>
<thead>
<tr>
<th>Reference / Study Design</th>
<th>N</th>
<th>Patient Selection</th>
<th>Treatment Intervention</th>
<th>Results</th>
<th>Adverse Results</th>
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<tbody>
<tr>
<td><strong>Naloxegol Studies – Non-malignant Pain</strong></td>
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<td><strong>Dose- Escalation Study</strong></td>
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<tr>
<td>Webster et al, 2013</td>
<td>207</td>
<td>Outpatients age ≥18 years, Non-malignant pain for ≥2 weeks, OIC confirmed in 2-week run in period</td>
<td>Sequential dose cohorts</td>
<td>Primary Endpoint: Change in SBMs/week from baseline to the end of week 1.</td>
<td>Adverse events at NAL5 and NAL25 were minor and transient. Dose escalation safety committee (DESC) recommended against dose escalation to 100 mg. Discontinuation due to GI AEs (diarrhea, nausea, abdominal pain) most commonly in NAL 50 mg patients (n=10; 71.4%) and 8/10 were in the high-opioid stratum cohort.</td>
</tr>
<tr>
<td>Randomized, double-blind, placebo-controlled, dose-escalation</td>
<td></td>
<td>run in period (≤5 SBMs, &lt;3 SBMs/week &amp; ≥ 1 additional sign or symptom (hard/lumpy stools, straining, sensation of incomplete evacuation or anorectal obstruction))</td>
<td>Randomized to opioid use • 30-100 MEU/day or &gt;100 MEU/day</td>
<td>• NAL 5 1.5 vs 1.2; p=0.7781 • NAL 25 2.9 vs 1.0; p=0.0020 • NAL 50 3.3 vs 0.5; p=0.0001</td>
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<td>Once daily naloxegol oral solution • 5 mg • 25 mg • 50 mg • 100 mg</td>
<td>Secondary Endpoints: Median time from 1st dose of study drug to first laxation</td>
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<td><strong>Pivotal Trials – Non-malignant Pain</strong></td>
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<td>Chey et al, 2014 [120]</td>
<td>652</td>
<td>Outpatients age 18-84 years, Stable opioid ≥ 4 weeks, OIC defined as: &lt;3 SBMs/week with ≥ 1 of: hard/lumpy stools, straining, sensation of incomplete evacuation or anorectal obstruction in &gt;25% of BMs over prior 4 weeks and confirmed with 2-week electronic diary Exclusions: history of cancer, diarrhea or constipation, GI obstruction, risk bowel perforation and interacting meds.</td>
<td>1:1:1 Allocation</td>
<td>Primary End-Point: Response Rate: ≥ 3 or more SBMs over baseline, 9 of 12 weeks, and at least 3 or final 4 weeks (p value vs. placebo)</td>
<td>Any Adverse Event PBO 46.9% NAL12.5 49.3% NAL25 61.2% Discontinuation from AE (Diarrhea, abdominal pain, upper abdominal pain) NAL25 &gt; PBO &gt; NAL12.5</td>
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<td>First of two, identical, randomized, double-blind, parallel-group, placebo-controlled KODIAC-04</td>
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SBM: stool bowel movement, MEU: Morphine Equivalent Units, NAL: Naloxegol
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<tr>
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<th>Treatment Intervention</th>
<th>Results</th>
<th>Adverse Results</th>
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</thead>
<tbody>
<tr>
<td>Chey et al, 2014&lt;sup&gt;230&lt;/sup&gt;</td>
<td>700</td>
<td>See Above (KODIAC-04)</td>
<td>See above (KODIAC-04)</td>
<td>Primary End-Point&lt;br&gt;Response Rate: ≥ 3 or more SBMs over baseline, 9 of 12 weeks, and at least 3 of final 4 weeks (p value vs. placebo)&lt;br&gt;• NAL25 39.7% (p=0.02)&lt;br&gt;• NAL12.5 34.9% (p=NS)&lt;br&gt;• PBO 29.3%&lt;br&gt;Secondary End-Points&lt;br&gt;Response rate in laxative inadequate response (LIR)&lt;br&gt;• NAL25 46.8% (p=0.01)&lt;br&gt;• NAL12.5 42.4% (p=NS)&lt;br&gt;• PBO 31.4%&lt;br&gt;Median Time to First SBM&lt;br&gt;• NAL25 12 hours&lt;br&gt;• PBO 37.2 hours&lt;br&gt;• NAL25 vs. PBO; p&lt;0.001&lt;br&gt;Mean number of days/week with &gt; 1 SBM over 12 weeks&lt;br&gt;• NAL25 vs. PBO; p&lt;0.01&lt;br&gt;Number of SBMs per week compared to PBO&lt;br&gt;• NAL25 p&lt;0.001&lt;br&gt;• NAL12.5 p&lt;0.05&lt;br&gt;Stool consistency and straining vs. PBO&lt;br&gt;• NAL25 and NAL12.5 significantly improved&lt;br&gt;Mean daily opioid doses remained stable</td>
<td>Any Adverse Event&lt;br&gt;PBO 58.9%&lt;br&gt;NAL12.5 59.6%&lt;br&gt;NAL25 69.0%&lt;br&gt;Most Common AEs; percentage&lt;br&gt;Abdominal Pain&lt;br&gt;PBO 7.8&lt;br&gt;NAL12.5 10.9&lt;br&gt;NAL25 17.0&lt;br&gt;NAL 25 9.1&lt;br&gt;Nausea&lt;br&gt;PBO 4.3&lt;br&gt;NAL12.5 6.1&lt;br&gt;NAL25 8.6&lt;br&gt;Diarrhea&lt;br&gt;PBO 4.3&lt;br&gt;NAL12.5 7.8&lt;br&gt;NAL25 9.1&lt;br&gt;Flatulence&lt;br&gt;PBO 3.0&lt;br&gt;NAL12.5 1.7&lt;br&gt;NAL25 6.0&lt;br&gt;Upper Abd. Pain&lt;br&gt;PBO 1.3&lt;br&gt;NAL12.5 2.2&lt;br&gt;NAL25 2.6&lt;br&gt;Vomiting&lt;br&gt;PBO 2.6&lt;br&gt;NAL12.5 3.0&lt;br&gt;NAL25 6.0&lt;br&gt;Headache&lt;br&gt;PBO 3.5&lt;br&gt;NAL12.5 5.2&lt;br&gt;NAL25 5.2&lt;br&gt;Back Pain&lt;br&gt;PBO 1.7&lt;br&gt;NAL12.5 5.2&lt;br&gt;NAL25 5.2&lt;br&gt;Serious AEs&lt;br&gt;PBO 5.2%&lt;br&gt;NAL12.5 6.1%&lt;br&gt;NAL25 3.4%&lt;br&gt;Deaths Related to Study Drug (none)&lt;br&gt;Serious Cardiovascular Events&lt;br&gt;One patient unrelated to study drug&lt;br&gt;One patient related in PBO group&lt;br&gt;Opioid-Withdrawal symptoms no difference</td>
</tr>
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</table>
### Reference / Study Design

| Webster et al, 2014<sup>120</sup> | 52-week, open-label, randomized, parallel-group KODIAC-08 |

#### N Patient Selection

- New patients or rollover patients from Study-04 or Study-05
  - Inclusion criteria: See Chey et al, 2014
  - Exclusion criteria:
    - Diarrhea, constipation
    - Impaired GI integrity
    - Recent GI surgery
    - Inadequate laxative response during OIC confirmation
    - Opioid use for cancer-related pain
    - 5-year history of cancer
    - Increased permeability of BBB
    - Increased risk of ventricular arrhythmia
    - Use of opioid antagonists
    - Use of strong CYP3A4 or P-gp inhibitors

#### Treatment Intervention

- 2:1 Randomization
  - Open Label:
    - NAL - naloxone 25 mg daily
    - Usual Care – Laxative regimen by investigator, modification allowed, rescue laxative allowed

#### Results

- Randomized: 844 patients; 760 new patients, 84 rollover
- Completion rates at 52-weeks
  - NAL (n=327) 58.1%
  - UC (n=189) 67.3%
- Use of breakthrough opioid similar between groups
- Laxative Use: in Usual Care Group
  - Laxative use at study entry 79%
  - No regimen change at completion 73%
- Pain scores remained constant
- Mean daily opioid doses remained constant

#### Adverse Results

- Any AE
  - NAL 437 (81.8%)
  - UC 195 (72.2%)
- AEs causing discontinuation
  - NAL 6 (10.5%)
  - diarrhea, abdominal pain or vomiting

#### Death:

- One in each arm, unrelated to study drug

#### Most Common AEs (≥5% any group); N (%)

<table>
<thead>
<tr>
<th>NAL</th>
<th>PBO</th>
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<tbody>
<tr>
<td>Abdominal Pain</td>
<td>95 (17.8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>69 (12.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>50 (9.4)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>48 (9.0)</td>
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<tr>
<td>Headache</td>
<td>48 (9.0)</td>
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<tr>
<td>Flatulence</td>
<td>37 (6.9)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>33 (6.2)</td>
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<tr>
<td>Nasopharyngitis</td>
<td>33 (6.2)</td>
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<tr>
<td>URI</td>
<td>31 (5.8)</td>
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<tr>
<td>Bronchitis</td>
<td>30 (5.6)</td>
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<tr>
<td>Vomiting</td>
<td>27 (5.1)</td>
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<tr>
<td>Upper abd. Pain</td>
<td>27 (5.1)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>23 (4.3)</td>
</tr>
<tr>
<td>UTI</td>
<td>22 (4.1)</td>
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</tbody>
</table>

- GI AEs with NAL were typically mild or moderate (2.2% severe) occurred in the first 12-weeks of treatment and resolved with continued treatment (<14 days) or after discontinuing

- MACE Events: (2 in each group including 2 deaths, all unrelated to study drug)

- Hypotension and hypertension: Unrelated

- GI perforation: None

- Opioid withdrawal AEs noted in 2 patients in NAL group attributed to a change in the opioid dose (1 patient tapered to lower dose, one as patient ran out of opioid medication)
## Methylnaltrexone Trials

### Advanced Illness – Pivotal Trials

<table>
<thead>
<tr>
<th>Reference / Study Design</th>
<th>N</th>
<th>Patient Selection</th>
<th>Treatment Intervention</th>
<th>Results</th>
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</tr>
</thead>
</table>
| Thomas et al, 200825     | 133| Age > 18 years with advanced illness (defined as incurable cancer or other end-stage disease) with a life expectancy of ≥ 1 month  
Stable opioid use ≥ 2 wks  
Stable laxative ≥ 3 days  
OIC: Less than 3 laxations during the previous week (no meaningful laxation within 24 – 48 hours of the first study dose) | Design: 1:1  
Initial Study: MNTX 0.15mg/kg SQ every other day for 2 weeks or an equal volume of SQ placebo.  
Day 8: If fewer than 3 RFL, the dose could be doubled (0.3mg/kg)  
Duration: 2 weeks with 3 month open label extension:  
Open Label Extension: MNTX 0.15 mg/kg as needed, up to once every 24 hours  
Subsequent dosing: Increased to 0.3mg/kg if no laxation occurred at 4 hours. Decreased to 0.075mg/kg if drug-related AE’s occurred.  
Primary Endpoint:  
Rescue free laxation within 4 hours of initial study dose  
• MNTX 48%  
• Placebo 15%  p<0.001  
Rescue free laxation within 4 hours of first 2 of first 4 doses  
• MNTX 52%  
• Placebo 8%  p<0.001  
Secondary Endpoint:  
Rescue free laxation within 4 hours after each dose for 13 days p<0.005  
Rescue free laxation within 24 hours after study drug, p<0.05  
Percentage of patients with 3 or more laxations per week  
• MNTX 68%  
• Placebo 45%  p=0.009  
Watery rescue free laxation within 4 hours  
• MNTX 16%  
• Placebo 17%  
Change in laxation with dose increases  
• MNTX  n=20  15% → 24%  
• Placebo  n=21  8% → 7%  
Global Clinical Impression of Change scale on days 7 and 14  
• MNTX Majority of status improved  
• Placebo Majority status unchanged  
Pain Scores - Stable throughout in each group  
Himmelsbach Withdrawal Scale - Stable throughout in each group | Incidence of AE similar between groups  
MNTX AE ≥ 5% and 3 percentage points higher than in the placebo group:  
Abdominal pain (17% vs 13%)  
Flatulence (13% vs 7%)  
Nausea (11% vs 7%)  
Increased body temperature (8% vs 3%)  
Dizziness (8% vs 3%)  
MNTX AE - 0.15mg/kg = 0.3mg/kg doses  
SAE: MNTX 28% vs PBO 17%  
Open-label extension  
Most adverse events mild to moderate in intensity  
• Abdominal pain (30%)  
• Malignant neoplasm progression (24%)  
• Nausea (21%)  
• Vomiting (20%).  
AE related to study drug:  
• Muscle spasm (n=1)  
• Abdominal pain (n=1)  
• Exacerbated pain (n=1)  
MNTX 302  
Initial Study: Randomized, double-blind, placebo-controlled trial with 3 month open label extension |
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<tr>
<th>Reference / Study Design</th>
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<tr>
<td>Slatkin et al, 2009\textsuperscript{124} MNTX 301 Double-blind, randomized, placebo-controlled trial with optional 4 week open label phase, and 3-month, open-label extension study. Excerpted from abstract</td>
<td>154</td>
<td>Age ≥ 18 years with advanced illness and life expectancy of 1 to 6 months. Stable opioid and laxative regimens ≥3 days No clinically significant laxation within 48 hours of first study drug dose</td>
<td>1:1:1 Randomization Initial Single Dose Trial: Single SQ dose of MNTX • 0.15mg/kg • 0.3mg/kg or placebo Open-Label (28 day): MNTX 0.15mg/kg SQ as needed as often as every 24 hours Subsequent dosing 2° clinical response: • Increased to 0.3 mg/kg • Decreased to 0.075 mg/kg Open-Label Extension (3 months): MNTX 0.15mg/kg SQ as needed as often as every 24 hours Subsequent dosing 2° clinical response: • Increased to 0.3 mg/kg • Decreased to 0.075 mg/kg</td>
<td>Primary Endpoint Laxation within 4 hours (p&lt;0.0001 each MNTX group vs placebo) 62% 58% 14% Secondary Endpoints Laxation within 30 minutes ~50% Percentage responders with at least one watery diarrhea 27.6% 37.5% 0% Laxation within 24 hours p&lt;0.0001 each MNTX group vs placebo Median time to RFL 1.10 hour 0.8 hour &gt;24 hour (p&lt;0.0001 each MNTX group vs placebo) Median change in pain score = 0 Median change in opioid withdrawal scale = 0 Changes in constipation distress paralleled laxation result Changes in GCIC scale paralleled laxation result</td>
<td>Over the duration of the study, the most common adverse event occurring at ≥5% of patients in MNTX group was abdominal pain, rated mild to moderate, which appeared dose-related. Abdominal pain, flatulence, nausea and dizziness occurred at a higher frequency in the MNTX groups. AEs possible related to MNTX include: • Abdominal pain (N=15) • Increased sweating (N=3) • Increased pain (N=2) • One each of burning at the injection site, vomiting, diarrhea, asthenia, increased blood pressure, dehydration, muscular cramp, loss of consciousness, tremor, delirium, hallucination, dyspnea and flushing</td>
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Open Label Extension Any AE MNTX 81% PBO 80% Discontinue MNTX 6% PBO 7% SAE - Three serious adverse reactions were possibly related to MNTX • Flushing • Delirium • Severe diarrhea, dehydration, cardiovascular collapse

Median interval of 3 days between doses

Open-label phase (n=147) Laxation within 4 hours (1° dose) 61.9% 52.2% 54.2% Open-label and extension phase (1,160 doses administered; n=27 completed trial) Median of 5 doses of MNTX over median duration of 28.5 days
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<tr>
<td>Advanced Illness Fixed-dose Trial</td>
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<tr>
<td>Bull J et al, 2015127</td>
<td>230</td>
<td>Age ≥ 18 years with advanced illness and life expectancy ≥ 1 month with OIC (≤ 3 bowel movements in the last week and no bowel movement in the 24 hours, or no bowel movement in 48 hours receiving stable doses of laxatives and opioids.</td>
<td>1:1 Randomization&lt;br&gt;Initial phase&lt;br&gt;Dose every other day x 2 weeks&lt;br&gt;• MNTX 8mg (&lt;62kg)&lt;br&gt;• MNTX 12mg (≥62kg)&lt;br&gt;• PBO&lt;br&gt;Open-Label Extension&lt;br&gt;Patients completing the initial phase could enroll in the 10 week extension and receive MNTX as needed but not more than once per 24 hours</td>
<td>Primary Efficacy Endpoint:&lt;br&gt;RFBM within 4 hours in 2 of first 4 doses (Percentage, 95% CI)&lt;br&gt;• MNTX 62.9%, (53.5 to 71.7%) (unaffected by weight)&lt;br&gt;• Placebo 9.6%, (4.9% to 16.6%) p&lt;0.0001&lt;br&gt;Secondary Endpoints:&lt;br&gt;• RFBM &lt; 4 hours after first dose p&lt;0.0001&lt;br&gt;• RFBM &lt;4 hours after at least 4 (max 7 doses) (p&lt;0.0001)&lt;br&gt;• Median time to first RFBM after each MNTX dose (p&lt;0.005)&lt;br&gt;• Mean # BMs ≤24 hours after dosing at 2 weeks (p=0.0083)&lt;br&gt;• Mean # RFBM ≤ 24 hours after doing at 2 weeks (p=0.0024)&lt;br&gt;• Patients using rescue laxatives (p=0.0020)&lt;br&gt;Open-Label Extension&lt;br&gt;• Efficacy was consistent with the two-week RCT&lt;br&gt;• Mean pain scores and opioid use remained unchanged</td>
<td>MNTX group AEs: Abdominal pain, nausea Discontinuation rate MNTX 10.3% Placebo 6.1% Serious AEs MNTX 12.1% Placebo 21.1% Open-Label Extension&lt;br&gt;Most commonly reported AEs were abdominal pain (15.4%), diarrhea (7.4%), and flatulence (3.4%) No study drug significant AEs</td>
</tr>
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</table>
| Advanced Illness Open-Label Extension | 82 | See Thomas et al, 2008 Patients completed the 2-week, double-blind, clinical trial, had stable vital signs, and if of child-bearing potential were not pregnant and on adequate birth-control. | Open Label Extension:<br>NMTX SQ 0.15mg/kg (max. Q24hr)<br>Subsequent Dosing: Increased to 0.3 mg/kg for laxation Decreased to 0.075mg/kg for AEs | Underlying Diagnosis: Cancer 54.9%, Cardiovascular disease 10%<br>Laxation response* MNTX group Placebo<br>Results from 2-week study 45.3% 10.8%<br>Month 1 45.5% 48.3%<br>Month 2 57.7% 47.6%<br>Month 3 57.3% 52.1%<br>*doses with laxation/total number of doses<br>Time to rescue-free laxation in responders: <1 hour (range 0-4)<br>Watery bowel movement in 4 hour responders 11%<br>Bowel movement difficulty rated unchanged Improvement in constipation distress 55%<br>Global clinical impression of change at 12 weeks rated as better in more than half of the patients.<br>Pain scores did not change appreciably throughout the study<br>Opioid Withdrawal symptom score ratings for all patients was none or mild. | Incidence of AEs: 100% AEs >7.5% of patients<br>• Abdominal pain 30.5%<br>• Malignant neoplasm progression 24.4%<br>• Nausea 20.7%<br>• Vomiting 19.5%<br>Of Patients with gastrointestinal AE (N=57) 54.4% were at least possibly related 7.3% resulted in drug discontinuation
Serious AEs: 43.9% related to disease progression MNTX Related Serious AEs (n=2)<br>• Muscle spasms<br>• Abdominal pain and pain exacerbation |
### Chronic Non-Malignant Pain – Pivotal Trial

**Reference:** Michna E et al, 2011

**Study Design**
Multi-center, double-blind, randomized, placebo-controlled

<table>
<thead>
<tr>
<th>N</th>
<th>Patient Selection</th>
<th>Treatment Intervention</th>
<th>Results</th>
<th>Adverse Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>460</td>
<td>• Age ≥ 18 years</td>
<td>MNTX 12mg QD</td>
<td></td>
<td>MNTX QD (70/150) 49.3%</td>
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<td></td>
<td>• Chronic pain from a non-malignant condition for at least 2 months and receiving &gt; 50mg oral morphine equivalents daily for at least 2 weeks OIC</td>
<td>MNTX 12mg QOD</td>
<td>Placebo (67/148) 45.3%</td>
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<td></td>
<td>• Fewer than 3 RFBMs weekly, associated with at least 1 of the following signs and symptoms; hard or lumpy stools, straining during bowel movements, or a sensation of incomplete evacuation after a bowel movement.</td>
<td>Placebo</td>
<td>Placebo (62/162) 38.3%</td>
<td></td>
</tr>
</tbody>
</table>

**Design:** 1:1:1 allocation

Patients receive medication for 4 weeks and were eligible to enter and 8-week open-label, as-needed dosing phase with a 14-day follow-up period.

Patients discontinued all laxatives prior to study. In the absence of a BM for 3 days the patient could receive a single dose of bisacodyl (1-4 tablets) once every 24 hours but not within 4 hours of a study dose.

Statistically powered to detect a 15% difference in the proportion of patients having a RFBM within 4 hours after the first dose and the percentage of active injections/patient resulting in a RFBM within 4 hours.

**Primary Endpoints:**

- Proportion of patients with a RFBM within 4 hours of first dose
  - All MNTX 34.2% (NNT~4)
  - Placebo 9.9%
  - MNTX QD 33.3% p<0.001
  - MNTX QOD 35.1% p<0.001

- Percentage of active injections/patient resulting in a RFBM within 4 hours
  - MNTX QD 28.9% p<0.001
  - Placebo 9.4%
  - MNTX QOD 30.2% p<0.001
  - Placebo 9.3%

**Secondary Endpoints:**

- Time to first RFBM after injection
  - All MNTX 46% p<0.001
  - Placebo 25.3%

- Adjusted mean change from baseline in weekly number of RFBM
  - MNTX QD 3.1 p<0.001
  - MNTX QOD 2.1 p<0.01
  - Placebo 1.5

- Patients with ≥ 3 RFBMs per week (blinded)
  - MNTX QD 58.7% (NNT~5)
  - MNTX QOD 45.3% (NNT~14)
  - Placebo 38.3%

- Bristol Stool Form Scale, Straining Scale score, Sense of Complete Evacuation Scale score in both MNTX groups improved with MNTX

- Opiate withdrawal scales – MNTX = PBO

- PAC-QOL Questionnaire
  - Day 28: MNTX QD improvement p<0.001
  - Day 28: MNTX QOD improvement p<0.014

- Rescue Laxative Use
  - MNTX QD n=58 38.7% p<0.001
  - MNTX QOD n=73 49.3% p=0.03
  - Placebo n=100 61.7%

**Adverse Results**

- Most AE mild to moderate in severity and similar between groups.
  - GI AE: MNTX > PBO
    - abdominal pain, nausea, diarrhea
  - Hyperhidrosis: MNTX > PBO
  - SAE: MNTX = PBO
    - One 50yo patient had extra systoles during the first double blind treatment day, which resolved on the same day.
<table>
<thead>
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</tr>
</thead>
</table>
| Webster et al, 130 (abstract) | 1034 | Patients with non-malignant pain, OIC ≥ 1 month after 14 day screening Stable opioid regimen | MNTX SQ 12mg  
- At least once weekly (max. once daily)  
- Duration 48 weeks  
Routine laxatives permitted | Doses resulting in a RFBM within 4 hours  
- 34.1% (monthly mean rate 33.0% to 37.4%)  
Change in number of BMs per week compared to baseline  
- +1.5  p<0.001 monthly compared to baseline  
Improvements were noted in straining and stool consistency  
From Salix131: Mean number of doses per week ~5 | Discontinuations 54%  
AEs 15% |


129. Webster LR, Michna E, Khan A, Maller E, Tzanis E, Israel R. Subcutaneous Methylnaltrexone Provides Long-Term Laxation in Patients with Chronic Non-Malignant Pain and Opioid-Induced Constipation. *Neuropathology and Motility*. 2011;23:44.


