Brand Name: Movantik

Generic Name: Naloxegol

Manufacturer[3]: AstraZeneca

Drug Class[1,2]: Peripherally Acting Mu Opioid Receptor Antagonist (PAMORA)

Labeled Uses[1,2,3,4.] Opioid-induced constipation, Chronic non-cancer pain

Mechanism of Action:[1,2,3,4.]

A mu-opioid receptor antagonist derivative of naloxone that is specific to peripheral tissues (eg, gastrointestinal tract) due to pegylation that decreases passive permeability and CNS penetration at recommended dosages

Pharmacokinetics[1,2,3,4.]:

Absorption:

T_{max}	< 2 hours
V_d	968-2140L
$t_{½}$	6-11 hours
Clearance	61.5 – 87.8 L/hr
Protein binding	4.2%
Bioavailability	n/a

Metabolism: Naloxegol is extensively metabolized in the liver primarily by CYP3A. It is both a substrate of CYP3A and P-glycoprotein. No metabolites are currently known to be active.

Elimination: Naloxegol is primarily excreted through the feces into urine (68%). It is also partially eliminated through the kidneys (16%) with less than 6% as the unchanged drug.

Efficacy:

Chey WD, Webster L, Sostek M, Lappalainen J, Barker PN, Tack J. Naloxegol for Opioid-Induced Constipation in Patients with Noncancer Pain. *PRA Interna tional Salt Lake City (LW); AstraZeneca Pharm N Engl J Med*. 2014;370:2387-2396. doi:10.1056/NEJMoa1310246.

Study Design: Two identical multicenter, randomized, double-blind, placebo-controlled, Phase 3 trials

Description of Study:

Methods:

Outpatients with non-cancer pain with confirmed OIC (opioid induced constipation) and LIR (inadequate response to laxatives) were randomly assigned to receive a daily dose of 12.5 or 25 mg of naloxegol or placebo. There were 652 participants in study 4 and 700 participants in study 5 that were assigned to either 12.5mg naloxegol or 25mg naloxegol or placebo. Eligible patients reported symptoms of active opioid-induced constipation. Opioid-induced constipation was confirmed over a 2-week period on the basis of data from daily electronic diaries. Patients who met these criteria were then stratified on a 1:1:1 ratio to receive naloxegol 25 (214), naloxegol 12.5 (213) or placebo (214) once daily for 12 weeks. Efficacy and safety were evaluated using the same electronic diaries used in the pre-screening to evaluate for opioid induce constipation. Analysis was based on the intent-to-treat population consisting of all patient randomized into the study.

Outcome Results:

The response rate as compared with placebo was increased by 11.4 percentage points in the 12.5mg group (95% [CI], 2.4 to 20, P=0.02) and by 15.0 percentage points with the 25-mg group (95% [CI], 5.9 to 24, P=0.001) dose. In study 05 a significantly higher response rate was seen with the 25mg dose (P=0.02) but not with the 12.5mg (P=0.20) dose in compared with placebo the differences in the response rate between active treatment and placebo were 5.6 percentage points (95% CI, −2.9 to 14.1) with the 12.5-mg dose and 10.3 percentage points (95% CI, 1.7 to 18.9) with the 25-mg dose. The time to the first post dose spontaneous bowel movement was significantly shorter with both naloxegol doses than with placebo in study 04 and was significantly shorter with the 25-mg dose than with placebo in study 05 ($P<0.001$ for all comparisons). The number of spontaneous bowel movements per week increased in association with naloxegol treatment over the 12-week period, with both studies showing a significantly greater effect in the naloxegol groups than in the placebo group. The incidence of overall adverse events and the incidence of adverse events leading to study discontinuation were higher in the 25-mg group than in the 12.5-mg group or the placebo group.

Limitations:

The study was sponsored by AstraZeneca the manufacturer of naloxegol and multiple authors had affiliations with AstraZeneca introducing potential conflicts of interest. Patients were responsible for submitting data for all the primary endpoints via a personal electronic diary. Only 50% of patients were verified to have a laxative inadequate response as defined by the investigators. There was no data that showed precisely what laxatives each patient used prior to completing the survey and at what amount.. The medication was also not objectively compared to currently available treatments of opioid induced constipation (Relistor and Entereg).

Conclusion:

These studies showed that naloxegol use in patients with opioid induced constipation that have shown to be laxative resistant is an appropriate option. Study four demonstrated that both

doses of naloxegol had higher response rates than placebo and study 5 demonstrated that only the 25mg had a higher response rate than placebo. This study was limited to adult patients with noncancer pain and more studies need to be conducted to assess its efficacy in pediatric patients and cancer patients. Also more studies should be done to evaluate its comparative efficacy to already approved peripherally acting mu opioid receptor antagonists

Webster, L., Chey, W. D., Tack, J., Lappalainen, J., Diva, U. and Sostek, M. (2014), Randomised clinical trial: the long-term safety and tolerability of naloxegol in patients with pain and opioid-induced constipation. Alimentary Pharmacology & Therapeutics, 40: 771–779. doi: 10.1111/apt.12899

Study Design: Multicenter, open-label, randomized, parallel-group phase 3 study

Methods:

804 patients were randomized 2:1 to receive naloxegol 25mg/day or usual care (investigator chosen laxative regimen) using a computer generated randomization scheme. In the usual care group patients were not allowed to use any other laxatives than those prescribed by the investigator. Patients in the naloxegol group were not allowed to use any other laxatives during the treatment period but were permitted to use bisacodyl as a rescue medicine. Safety and tolerability were evaluated by the incidence, nature, intensity and relatedness to treatment of all adverse events. The effect of treatment on opioid requirements and pain management was assessed as well. An opioid withdrawal scale was used to assess centrally mediated opioid withdrawal symptoms (mHOWS).

Outcome Results:

Pain history and baseline total opioid dose and history were similar between treatment groups for newly randomized patients confirming that naloxegol did not impact pain therapy. Use of breakthrough medication was similar as well (naloxegol, 36.0%; usual care, 34.8%). The mean exposure to the medication was 268 days with naloxegol and 296.7 in the usual care arm. A majority of patients had treatment emergent adverse events with naloxegol, most commonly being: abdominal pain, diarrhea, nausea, headache, flatulence, bronchitis and upper abdominal pain. 10.5% of patients withdrew from the naloxegol group due to the gastrointestinal adverse events. Only 1.8% of patients withdrew from the usual care group. It is to be noted that nine patients with abdominal pain discontinued treatment with naloxegol.

Limitations:

The study was sponsored by AstraZeneca the manufacturer of naloxegol and multiple authors had affiliations with AstraZeneca introducing potential conflicts of interest. This was an open label trial so the patients were knowledgeable of potential risk and harms of naloxegol prior to treatment. This could result in a confounding bias in the reporting of adverse events and the decision to continue in the study. The usual care regimen was investigator defined and varied so no particular laxative agent was compared to naloxegol. The adverse event reporting could vary based on what the investigator decided to prescribe. If adverse events did occur in the usual care

group they were allowed to switch therapy, while in the naloxegol group they were not which led to higher discontinuation rates due to adverse events. It is also noted that the safety was not evaluated compared to a placebo so the rate and occurrence of adverse events with no treatment could be obtained. It is also noted that the 12.5mg tablet was not evaluated.

Conclusion:

In this study it was shown naloxegol is safe and relatively tolerable for up to 12 months. The most common adverse events being abdominal pain, diarrhea and nausea which were most likely due to its mechanism of action at mu opioid receptors in the gastrointestinal system. It was shown that the medication was tolerable for the majority of patients and that the findings were consistent with that of previous phase three trials that evaluated, safety and efficacy.

Webster L, Dhar S, Eldon M, Masuoka L, Lappalainen J, Sostek M. A phase 2, double-blind, randomized, placebo-controlled, dose-escalation study to evaluate the efficacy, safety, and tolerability of naloxegol in patients with opioid-induced constipation. *Pain*. 2013. doi:10.1016/j.pain.2013.04.024.

Study Design: A phase 2, double-blind, randomized, placebo-controlled, dose-escalation study

Description of Study:

Methods:

In this study men and women who were 18 years of age and older had to be currently receiving 30-1000mg of morphine equivalent doses to treat malignant or nonmalignant cancer pain. A two week run in period was required to confirm opioid induced constipation, during this time patients had to discontinue all laxatives. Bisacodyl was the only laxative allowed and only if the patient had not had a spontaneous bowel movement in more than 72 hours. Patients were required to enter bowel movements, pain scores, break-through use of pain medications and rescue bisacodyl doses daily in an electronic diary. Patients were randomized in a 1:1 ratio of naloxegol to placebo within each cohort and were stratified based on their total daily morphine equivalent units. There were three cohorts of naloxegol once daily (5mg, 25mg and 50mg). The primary endpoint was the change in spontaneous bowel movements per week from baseline to the end of week one.

Outcome Results:

Efficacy was similar between stratification groups (low baseline opioid use vs. high opioid use). The median change in bowel movements for the low dose opioid group per week was 0.8 bowel movements for 5mg, 3.3 bowel movements for 25mg and 2.5 bowel movements

for 50mg. The median changes in bowel movements for the high dose opioid group were 2.0 bowel movements for 5mg, 2.4 bowel movements for 25mg and 5.3 bowel movements for the 50mg dose. The changes in bowel movements per week for naloxegol compared with placebo were statistically significant for both the 25mg and 50mg naloxegol in both high and low baseline opioid usage. Gastrointestinal adverse events increased with increasing naloxegol dose; 39.4% in the 5mg cohort, 46.7% in the 25mg cohort and 60% in the 50mg cohort. A total of 32 patients discontinued from treatment, 15 due to adverse events primarily reporting abdominal pain, diarrhea and nausea. Lastly, patients in the 25-mg cohort experienced statistically significantly lower PAC-SYM mean scores for rectal symptoms at week 2, stool symptoms at weeks 2 and 4 After analysis the 25mg dose was deemed as a safe and tolerable dose to be utilized in phase three studies.

Limitations:

The study was sponsored by AstraZeneca the manufacturer of naloxegol and multiple authors had affiliations with AstraZeneca introducing potential conflicts of interest. Pediatric patients were not evaluated in this study. Patients self-reporting may not always be completely accurate. Lack of an active control group, short treatment duration and a small population sample are all limitation of this trial.

Conclusion:

In conclusion it can be stated that naloxegol at a dose of 25mg appears to be tolerable and statistically significantly increased SBM's. The 5mg did not show a significant change in SBM's as compared to placebo and was not chosen for phase three trials. The 50mg dose had more significant adverse events than the other strengths and was not chosen for phase three trials. Overall none of the dosages resulted in an increase in opioid use nor withdrawal symptoms. This was important since the medication at higher concentrations could potentially antagonize the effects of concurrent opioid therapy. The adverse events were primarily GI related (nausea, vomiting and abdominal pain). Chronic opioid treatment would require chronic treatment of constipation and therefore require longer studies evaluating safety and efficacy in this population, which was completed in later trials.

Contraindications[1,2,3,4].

Gastrointestinal Obstruction: Can increase the risk for gastrointestinal perforation

Concomitant use of strong CYP3A4 inhibitors: Can increase exposure to naloxegol which can precipitate opioid withdrawal symptoms.

Hypersensitivity: Serious or severe hypersensitivity to naloxegol or any of its ingredients.

Precautions[1,2,3,4].

Gastrointestinal Perforation: Patients with diffuse or localized reduction of the structural integrity in the wall of the GI tract have had reported cases of gastrointestinal perforation while on other peripherally acting mu opioid receptor antagonists. Monitor for the development of severe and worsening abdominal pain and discontinue naloxegol in these patients**.**

Opioid Withdrawal: Clusters of symptoms associated with opioid withdrawal has occurred with patients who were taking naloxegol. Those who were currently on methadone were shown to have a higher frequency of GI related adverse events related to withdrawal. Monitor patients for opioid withdrawal, especially in those with disruptions of the blood brain barrier, since this might result in opioid withdrawal or decreased analgesia.

Adverse Effects:

Occurring in >10% of patients

Gastrointestinal

Abdominal Pain (12% to 21%)

Occurring in >1% to <10% of patients

Central Nervous System

Headache (4%)

Dermatologic

Hyperhidrosis (3%)

Gastrointestinal

Diarrhea (6% to 9%)
Nausea (7% to 8%)
Flatulence (3% to 6%)
Vomiting (5%)

Miscellaneous

Uncommon (<1%) but serious
Anxiety
Arthritis
Back pain
Chills
Gastrointestinal Perforation
Irritability
Joint Pain
Yawning

Drug Interactions[1,2,3,4.]

Co-administration with moderate CYP3A4 inhibitors (diltiazem, erythromycin, verapamil):

Can increase naloxegol concentrations leading to increased risk of adverse reactions. If unavoidable reduce dosage to 12.5mg

Co-administration with strong CYPA3A4 inhibitors (ketoconazole, itraconazole, clarithromycin):

Can increase naloxegol concentrations and result in adverse events.

Co administration with weak CYP3A4 inhibitors (quinidine, cimetidine):

Clinically significant increases in naloxegol concentrations are not expected however monitor for adverse events

Grapefruit or Grapefruit juice:

Avoid consumption of grapefruit or grapefruit juice while on Naloxegol since it can increase plasma naloxegol concentrations.

Co-administration with strong CYP3A4 inducers (rifampin, carbamazepine, St. John's Wort):

Can significantly decrease plasma concentration of naloxegol and may reduce its efficacy.

Opioid Antagonists

Avoid use of other opioid antagonists since there is a potential for additive effects and an increased risk of opioid withdrawal.

Dosing/Administration[1,2,3,4.]

Adult Dosing

Initial dose: 25mg orally once daily in the morning; if not tolerated reduce to 12.5mg orally once daily

Renal impairment

The dose for patients with a creatinine clearance of <60ml/min is 12.5mg once daily. If tolerated, may increase to 25mg.

Hepatic impairment

In mild or moderate hepatic impairment. No dosage adjustment is required. However no data has been published for severe hepatic impairment and use should be avoided.

Conclusion:

Naloxegol is an effective therapy for patients with chronic non-cancer pain and opioid induced constipation refractory to usual care treatment with laxatives. Naloxegol has many drug interactions since it is metabolized by the CYP3A4 pathway. It is contraindicated with concomitant use of strong CYP3A4 inhibitors and requires a dose reduction with concomitant use of moderate CYP3A4 inhibitors. Studies determining naloxegol's efficacy in the setting of laxative resistance should be reevaluated with more specific criteria to accurately assess laxative resistance. Studies should also be done to evaluate the comparative efficacy between the other commercially available peripherally acting mu opioid receptor antagonists and commonly used laxatives in the setting of opioid induced constipation. The medication appears to be safe and relatively tolerable with no life-threatening toxicities reported. However the gastrointestinal side

effects are of marked concern due to the risk of gastrointestinal perforation which can occur in patients with disorders that impact the structural integrity of the gastrointestinal tract. Providers should obtain a complete history prior to initiating this drug. In conclusion naloxegol is a safe and effective drug that can increase the amount of spontaneous bowel movements and the amount of days per week that a bowel movement will occur in patients with non-cancer chronic pain diagnosed with opioid induced constipation.

Recommended References:

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Prepared by: Nikolas K. Naleid, Doctor of Pharmacy Candidate