

**Food and Drug Administration  
Center for Drug Evaluation and Research**

**Briefing Document**

**Anesthetic and Analgesic Drug Products  
Advisory Committee Meeting**

**June 11-12, 2014**

**Meeting**

The committee will discuss the potential cardiovascular risk associated with products in the class of peripherally-acting opioid receptor antagonists and the necessity, timing, design and size of cardiovascular outcomes trials to support approval of products in the class for the proposed indication of opioid-induced constipation in patients taking opioids for chronic pain.

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought data regarding the safety of certain opioid receptor antagonists for the treatment of opioid-induced constipation to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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Opioid Antagonists for the treatment of Opioid Induced Constipation**

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## **1 Introduction**

### ***1.1 Statement of Purpose***

The purpose of the Anesthetic and Analgesic Drug Products Advisory Committee meeting is to discuss a potential cardiovascular risk associated with products in the class of peripherally-acting opioid receptor antagonists and the necessity, timing, design and size of cardiovascular outcomes trials to support approval of products in this class for the proposed indication of opioid-induced constipation (OIC) in patients taking opioids for chronic non-cancer pain. A potential cardiovascular safety signal observed in the development program for one opioid antagonist (Entereg) has raised questions regarding the amount and type of clinical safety data necessary to support approval of other opioid antagonists intended to treat OIC. Key considerations include the size of the target population, the existence of multiple treatments, and the fact that patients with opioid induced constipation are not necessarily refractory to currently available treatments.

Two opioid receptor antagonists are currently approved and marketed in the U.S. Methylnaltrexone (Relistor) is approved for the treatment of OIC in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient (the clinical trials primarily enrolled patients with incurable cancer). Alvimopan (Entereg) is approved to accelerate time to upper and lower GI recovery following surgeries that include partial large or small bowel resection surgery with primary anastomosis. Entereg is approved with a Risk Evaluation and Mitigation Strategy (REMS) because of an imbalance in myocardial infarctions (more infarctions on alvimopan) seen in one long-term study in patients with OIC (chronic pain setting). It is restricted to use in hospitalized patients, and limited to a total of 15 doses. Only hospitals that have registered in and met all of the requirements for the Entereg Access Support and Education (E.A.S.E.™) program may use Entereg.

Relistor and other drugs in this class have been in development for the treatment of OIC in patients with chronic non-cancer pain, not associated with advanced illness. Patients enrolled in clinical trials to support marketing approval for this indication are not required to be refractory to laxatives or to have an inadequate response to laxatives. Given the prevalence of chronic pain conditions treated with opioids in the U.S., approval of opioid antagonists for OIC in this population would represent a relatively large number of patients treated with these drugs. Controlled, long-term safety data, similar to that which generated the potential CV safety signal for Entereg, seem critical for preliminary assessment of CV risk for the development of other drugs in this class. However, it's important to note that a key underlying assumption of this paradigm is whether or not the cardiovascular event rate imbalance observed in the Entereg OIC program actually represents a true signal of increased cardiovascular risk.

The cardiovascular safety data that resulted in the Entereg REMS will be presented to offer the Committee an opportunity to reflect on the strength of the cardiovascular safety signal that was observed. The clinical trial designs for mu opioid receptor antagonists have been summarized in this briefing document, along with available cardiovascular safety data. There are commonalities as well as differences between the clinical development programs. For example, the phase 3 Relistor OIC program did not include an adequately controlled safety extension phase, whereas the naloxegol (Movantik) program did. Lack of comparative longer-term safety data, makes it difficult to assess a safety signal, including cardiovascular safety. Given this limitation, the sponsor of Relistor (Salix) was advised that additional controlled CV safety data must be submitted for review, prior to approval, for OIC in a chronic non-cancer pain population. Available data across peripherally restricted opioid antagonists, from

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products in various stages of development, is presented to this advisory committee to familiarize the committee with the scope of the safety data available for these agents. Sponsors have suggested that variability in product receptor target binding affinity mitigate or negate concerns regarding a potential class effect for all opioid antagonists; relevant data is presented to allow discussion of these concerns.

Given the cardiovascular adverse events observed in the Entereg OIC program, as well as concerns raised about the interpretability of uncontrolled safety extension studies, the Division of Gastroenterology and Inborn Errors Products (DGIEP) has considered various approaches to obtaining adequately controlled safety data, including cardiovascular outcomes trials. DGIEP has recommended sponsors conduct a controlled clinical trial of adequate duration and size to characterize the CV safety signal for presentation at an Advisory Committee meeting to allow proper assessment of CV risk pre-approval. However, cardiovascular outcome trials could be required pre-approval, post-approval, or be initiated pre-approval, with a pre-specified plan to submit the NDA when an interim analysis (after a given number of CV events) excludes a pre-specified level of risk. In the latter case, such a trial would continue to completion post-approval, if an Advisory Committee deemed it necessary. Sponsors, however, have raised serious concerns about the feasibility of cardiovascular outcomes trials, given the relatively low frequency of major adverse cardiovascular events (MACE) in patients with chronic pain.

In order to provide perspective on the background risk for the incidence of MACE in the OIC population, demographic information from OIC clinical trials (for mu opioid receptor antagonists) are presented in this document. This briefing document also includes a brief statistical overview on how cardiovascular outcomes trials are designed, to assist discussion and help answer questions regarding the determination of study sample sizes needed to evaluate CV risk associated with any given drug. Strengths and limitations of alternative approaches to randomized, controlled outcomes trials are also presented.

### **1.2 Opioid Induced Constipation (OIC)**

Opioid induced bowel dysfunction is a term used to describe the adverse effects on the gastrointestinal system due to opioid therapy. Opioid induced constipation is (OIC) one of the symptoms reported by patients who are thought to have opioid induced bowel dysfunction.

An international group of researchers using the World Health Organization's (WHO) World Mental Health Survey instrument in 10 developed countries has estimated that approximately 37% of adults in these populations (age-standardized) have common chronic pain conditions<sup>1</sup>. In the United States, this amounts to at least 116 million people in 2011<sup>2</sup>. Chronic pain, by definition, is neither self-limiting nor curable and in the U.S. a variety of chronic non-cancer pain conditions are treated with opioid medications. Use of chronic opioid therapy for chronic non-cancer pain has increased substantially, in part due to a growing consensus that opioid therapy is appropriate for some patients with chronic non-

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<sup>1</sup> Tsang et al. *J Pain*. 2008 Oct;9(10):883-91.

<sup>2</sup> Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington (DC): National Academies Press (US); 2011. 2, Pain as a Public Health Challenge. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK92516/>



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cancer pain<sup>3</sup>. In one U.S. survey, the proportion of office visits for chronic musculoskeletal pain in which any opioids were prescribed doubled from 8% in 1980 to 16% in 2000; over the same two decades, the proportion of office visits in which prescriptions for potent opioids were given increased from 2% to 9%<sup>4</sup>.

In a meta-analysis of 11 placebo-controlled, randomized trials, OIC affected an average of 41% of patients taking opioids for up to 8 weeks<sup>5</sup>. Examination of the demographic information from phase 3 trials of treatments for OIC associated with non-cancer pain reveals the mean duration of opioid exposure prior to study entry is approximately 3-5 years. The majority of OIC patients with chronic pain who are willing to participate in clinical trials are female (approximately 60%), and have a median age of approximately 50 years.

### **1.3 Mechanism of Action**

The current class of opioid antagonists being developed for OIC targets peripheral receptors in the gastrointestinal tract. Opioids exert their effects via opioid receptors (subtypes mu, delta, and kappa). Most clinically used opioid agonists are relatively selective for the mu ( $\mu$ ) receptors, which are expressed in the central and peripheral nervous system, including the myenteric and submucosal plexi of the gastrointestinal system. Activation of mu receptors by exogenous opioids leads to analgesia as well as major side effects such as sedation, bowel dysfunction, respiratory depression and dependence. Multiple lines of evidence have demonstrated that mu, delta, and kappa receptors are expressed in other peripheral tissues, including vascular, cardiac, and airway/lung. Multiple lines of evidence have implicated activation of  $\delta$ -opioid and  $\kappa$ -opioid receptors in the myocardium as having an important role in cardioprotection during ischemic injury.<sup>6,7,8,9</sup>

The opioid antagonists discussed here have higher affinity for human  $\mu$  than for human  $\delta$  receptors. (Comparative data for human  $\kappa$  opioid receptors is not available). Peripheral opioid antagonists that are approved or currently in development for OIC differ in their chemical structures and opioid receptor binding affinities. Table 1 displays some of these factors.

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<sup>3</sup> The American Academy of Pain Medicine, the American Pain Society: The use of opioids for the treatment of chronic pain: A consensus statement from the American Academy of Pain Medicine and the American Pain Society. Clin J Pain 13:6-8, 1997

<sup>4</sup> Caudill-Slosberg MA, Schwartz LM, Woloshin S. Office visits and analgesic prescriptions for musculoskeletal pain in US: 1980 vs. 2000. Pain. Jun 2004;109(3): 514-519.

<sup>5</sup> Camilleri, M. Opioid-Induced Constipation: Challenges and Therapeutic Opportunities. Am J Gastroenterol 2011; 106: 835-842.

<sup>6</sup> J Mol Cell Cardiol. 2013 Jul;60:142-50. PMID:23608604

<sup>7</sup> Am J Physiol Heart Circ Physiol. 2003 Sep;285(3):H1032-9. PMID:12730057

<sup>8</sup> Basic Res Cardiol. 2004 Jan;99(1):29-37. PMID: 14685703

<sup>9</sup> Sheng Li Xue Bao. 2003 Apr 25;55(2):115-20. PMID:12715097



Within the gastrointestinal system, opioids inhibit gastric emptying, increase absorption and decrease secretion in both the large and small intestine, delay small intestinal and colonic transit, and increase internal anal sphincter tone. Consequently, this results in increased gastroesophageal reflux, hard dry stools, incomplete evacuation, straining, and abdominal distension.

Opioid antagonists can reverse opioid receptor stimulation, including peripheral opioid receptors, and therefore represent one therapeutic option to treat OIC. Development of antagonists that are restricted from crossing the blood-brain barrier (CNS) has been intended to achieve the clinical goal of “peripherally-acting” mu-opioid receptor antagonism in tissues, such as the gastrointestinal tract, thereby decreasing the constipating effects of opioids without impacting opioid-mediated analgesia (mediated via the CNS). However, it is important to consider that the restriction to crossing the blood-brain barrier may not be absolute; some “peripherally” acting antagonists may still cross the blood-brain barrier to some extent in ways that may not be completely understood.

#### **1.4    *Currently Available Therapies for OIC***

Non-pharmacologic strategies for managing OIC include dietary changes (e.g., increased fluid intake), manual evacuation, behavioral treatment (e.g., increased activity), and stress/anxiety reduction.

There exist multiple over the counter products (OTC) used for constipation; however, none of these products carry a specific labeled indication for OIC. OTC medications available for treatment of constipation (although not FDA approved for OIC, specifically) include: stool softeners such as docusate; bulk-forming laxatives such as psyllium, methylcellulose, and polycarbophil; stimulant laxatives such as bisacodyl, senna, and castor oil; saline osmotic laxatives such as sodium phosphate, magnesium citrate, and magnesium hydroxide; osmotic laxatives such as lactulose and sorbitol; lubricants such as mineral oil and glycerin, other osmotic agents like polyethylene glycol (PEG) 3350 (MiraLax).

Three prescription drugs are available for the treatment of OIC; two are opioid receptor antagonists that are limited in use to specific populations as discussed previously (Entereg and Relistor). Lubiprostone (Amitiza), which is not an opioid antagonist, is approved for treatment of OIC in adults with chronic non-cancer pain.

#### **1.5    *Efficacy and Safety Evaluation of OIC Therapies***

The design of phase 3 trials to support approval for drugs in OIC for a chronic, non-cancer pain population has evolved as FDA has gained more recent experience with these clinical trials. Patient populations eligible for enrollment typically are not refractory to laxatives at baseline, and have their regular laxative regimen stopped at study entry. Clinical trials assess efficacy on the frequency of spontaneous, or “rescue free” bowel movements (BMs), defined as BMs that occur without taking a laxative. Although Relistor evaluated a primary endpoint defined as the proportion of subjects having a rescue-free BM within 4 hours, presently, FDA requires demonstration of durability of benefit over a longer timeframe. Use of a short term endpoint to support Relistor’s approval in the palliative care OIC setting seemed suitable as the patients in that program had constipation refractory to laxative treatment and took Relistor in conjunction with their established laxative regimen. However, in phase 3 clinical trials evaluating treatments for OIC in patients with chronic non-cancer pain, the recommended

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primary endpoint is based on an *overall* response over the course of 12 weeks of treatment. In this approach, an overall responder would be defined as a subject who responds for at least 9 out of 12 weeks (or  $\frac{3}{4}$  of total weeks). A weekly responder would be defined as having some minimum number of weekly SBMs (e.g.,  $\geq 3$ ) and an increase from baseline of  $\geq 1$  (counting only those BMs not the result of rescue laxatives). However, the duration of the efficacy portion of phase 3 clinical trials has historically ranged from 1 to 3 months.

Not all drugs in a class necessarily have the same safety profile. Nonclinical studies and early clinical trials help inform the decision to proceed with phase 3 clinical trials as well as the extent of safety monitoring that will be incorporated in the trials. In a typical clinical development program, the number of patients exposed to the study drug prior to FDA approval is small relative to the number of patients who will be treated with the drug once approved; therefore, important rare safety events may be detected only after approval, when a substantially larger number of patients have been exposed to the drug<sup>10</sup>.

Because of their short duration and relatively small sample sizes, premarket clinical trials conducted to support the effectiveness of opioid receptor antagonists for OIC preclude the ability to detect an increased risk of relatively uncommon adverse reactions associated with the drug, such as an increased CV risk.

### **1.5.1 Assessment of Opioid Withdrawal in OIC Trials**

Mu opioid receptor antagonists developed to treat OIC are anticipated to lack CNS effects while antagonizing peripheral receptors within the GI tract. Adequate assessment of mu opioid receptor antagonism on analgesia (mediated via the CNS) is considered a key component of development programs. For this reason, sponsors evaluate symptoms of withdrawal and stability of pain control for these drugs within OIC clinical trials.

Physical dependence, tolerance, and withdrawal are biological phenomena of some drugs, including opioids. Physical dependence to a drug is “a state that develops as a result of the adaptation (tolerance) produced by a resetting of homeostatic mechanisms in response to repeated drug use.”<sup>11</sup> Opioid withdrawal can occur following an abrupt reduction in dose, termination of the drug in a physically dependent patient, or administration of an antagonist. The symptoms are due to both absence of the direct effect of the drug and central nervous system hyperarousal due to readaptation to the absence of the drug and are opposite the original effects produced by the drug.<sup>12</sup>

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<sup>10</sup> ICH E1A Guidance: “The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions “ available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073083.pdf> (accessed June 18, 2011)

<sup>13</sup> [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2008/021964s000TOC.cfm](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/021964s000TOC.cfm)

<sup>13</sup> [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2008/021964s000TOC.cfm](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/021964s000TOC.cfm)

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The opioid withdrawal syndrome is defined in the DSM-5 to include the following criteria:

A. Either of the following:

1. cessation of (or reduction in) opioid use that has been heavy and prolonged (several weeks or longer)
2. administration of an opioid antagonist after a period of opioid use

B. Three (or more) of the following, developing within minutes to several days after Criterion A:

1. dysphoric mood
2. nausea or vomiting
3. muscle aches
4. lacrimation or rhinorrhea
5. pupillary dilation, piloerection, or sweating
6. diarrhea
7. yawning
8. fever
9. insomnia

While criteria for the determination of opioid withdrawal may vary among different clinical trials, the following assessments are generally recommended:

- Opioid Withdrawal Scales, conducted at a frequency to provide clinically meaningful information, as follows:
  - Objective scales such as Clinical Opioid Withdrawal Scale (COWS); Objective Opioid Withdrawal Scale (OOWS); or Modified Himmelsbach Scale (mHS).
    - COWS has generally been preferred as the objective opioid scale because of the granularity which provides stratification of mild, moderate and severe degrees of withdrawal.
  - Subjective scales such as the Subjective Opioid Withdrawal Scale (SOWS)
- Pre-defined adverse events potentially related to opioid withdrawal
- Major safety findings including deaths, serious adverse events (SAEs) and discontinuations due to adverse events (DAEs) potentially related to opioid withdrawal
- Standardize MedRA Query (SMQ) of Drug Withdrawal Syndrome

Over the time course during which these various products were developed, DAAAP's criteria for defining opioid withdrawal evolved. In the drug-specific analyses that follow in the sections below, the relevant definition for opioid withdrawal is described. Because these definitions vary, the incidences of opioid withdrawal cannot be compared across drug products.

Opioid withdrawal symptoms, which suggest the mu opioid antagonist effects in OIC may not be limited to peripheral receptors in all patients, have been noted in the review of safety data from OIC clinical trials.

Note that the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) provided Consult Reviews to DGIEP for both the Relistor and Movantik applications. These have been provided in Appendix 4.3 and 4.4, respectively.

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## **1.6 Cardiovascular Safety Signal and Possible Mechanisms**

Entereg (alvimopan), which is indicated to accelerate the time to upper and lower gastrointestinal recovery following surgeries that include partial bowel resection with primary anastomosis, is a mu opioid receptor antagonist that was approved on May 20, 2008, with a Risk Mitigation and Evaluation Strategy (REMS) to mitigate the potential risk of myocardial infarction by, 1.) ensuring that Entereg (alvimopan) is prescribed only for short-term use (no more than 15 doses) in a hospital inpatient setting, and, 2.) informing healthcare providers about the potential risk of myocardial infarction observed with long-term use of Entereg. The trials submitted to support approval of Entereg of the postoperative indication were limited in duration, consistent with the indication. No cardiovascular safety signal was identified in those trials; however, in a 12-month, randomized controlled trial conducted to evaluate Entereg in the setting of OIC associated with chronic, non-cancer pain, more myocardial infarctions were observed in the Entereg arm than in the placebo arm. See Section 3 of this Briefing Document for details regarding strength of the cardiovascular event signal, including limitations of the trial design for detection and evaluation of cardiovascular outcomes such as MACE.

It is important to consider possible mechanisms that could lead to cardiovascular adverse events with exposure to these drugs; however, the role of such mechanisms is uncertain. A summary of these potential mechanisms was discussed in a Division of Cardiovascular and Renal Products (DCRP) consult signed April 15, 2014. The following points are excerpted from that review:

From a mechanistic point of view, CV adverse event observations for these drugs should be interpreted in the context of an understanding of the determinants of myocardial oxygen demand. Opioid withdrawal (be that central or peripheral in the GI tract) induces physiologic stress in some patients. This physiologic stress will increase myocardial work and myocardial oxygen demand. Any drug, device, or procedure that induces physiologic stress has the potential for causing destabilization in patients with tenuous coronary perfusion and/or important stenotic valvular heart disease. Indeed, in the evaluation of safety for such products, patients with these conditions are not “confounders” – they are exactly the patients that would be expected to have difficulties with these physiologic stressors. These are basic principles of medicine that apply to many approved therapies, and for which clinical judgment of the treating physician is important.

In addition to those physiologic stressors that can be associated with opioid withdrawal in some patients, there are at least three other mechanisms by which CV adverse outcomes could theoretically occur with these agents:

- *Syndromes of increased vasomotor tone.* Peripherally, this would include elevations of systemic blood pressure. In the coronary circulation, the concern would be drug-induced epicardial coronary vasospasm with classic Prinzmetal’s angina. This is more than a hypothetical concern. Opioid antagonists (including the more mu-specific molecules) induce contraction of the intestinal smooth muscle (peristalsis). If this same effect were to occur in the smooth muscles of coronary arteries, an important decrease in coronary flow could occur. Indeed, since DCRP’s first consult on these drugs in 2006, immunohistochemical staining has demonstrated that mu-, kappa-, and delta- opioid receptors are present in the human heart (Sabanski et al, Heart Vessels Jan 2014, DOI 10.1007/s00380-013- 0456-5) (<http://link.springer.com/article/10.1007%2Fs00380->

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013-0456-5). While the authors hypothesize a role for these receptors in neural transmission and regulation of myocardial cell function, the clinical consequences of their activation and/or antagonism on the heart are unknown. It is interesting to note that one subject from the open-label MNTX study 3358 experienced the SAE of vasospastic angina. This subject was admitted to the hospital with chest pain and difficulty breathing and subsequently had ergonovine-induced coronary vasospasm in the catheterization laboratory involving the LAD and CFX coronary arteries that was reversed with 1000 mcg of IC nitroglycerin.

- *Drug induced electrical instability / repolarization abnormalities.* No evidence of drug-induced proarrhythmic ECG changes has been demonstrated for any of these drugs.
- *Prothrombotic effects.* These have not been demonstrated for any of these drugs, but for most if not all, this has not been systematically assessed

In ongoing internal discussions regarding strengths and limitations of these potential mechanisms, it has been noted that in a class of drugs that can cause vasospasm, i.e., anti-migraine triptans, angina appears much more common than myocardial infarctions. Increased myocardial demand has been challenged as a potential mechanism for cardiovascular adverse events, particularly myocardial infarctions. The role of factors (beyond thrombosis and sustained hypertension) that might contribute to myocardial infarction has been questioned.

**1.8 Characterizing the Cardiovascular Safety of OIC Therapies: Requests and Comments Provided to Sponsors**

The cardiovascular adverse events observed in the Entereg OIC program and concerns about the interpretability of uncontrolled safety extension studies, including the safety study conducted in the Relistor program, have been the basis for ongoing discussions between the Division of Gastroenterology and Inborn Errors Products and sponsors of opioid antagonists for the treatment of OIC regarding the type and magnitude of a preapproval cardiovascular safety evaluation needed. The Relistor NDA received a Complete Response (CR) on July 27, 2012. In the CR Letter (CRL), the FDA noted that, “[t]here were patients identified in the long-term open-label safety trial (Study 3358) that had cardiovascular adverse events, including myocardial infarction, cerebrovascular accident and death. Some of these patients also had documented signs and symptoms consistent with opioid withdrawal.” Further, because the uncontrolled open-label design of Study 3358 and the uncontrolled portion of Study 3356 do not permit assessment of causality, the FDA stated that Salix will need to conduct a randomized, controlled trial designed and powered to assess the risk of adverse cardiovascular events associated with the use of RELISTOR. During meetings between Salix and FDA subsequent to the CRL, discussions focused on the design and feasibility of the required CV safety trial. In a meeting held on October 5, 2012, there was debate on what the anticipated background CV event rate was in the OIC population (FDA considered a proposed background incidence of 1/1000 as too low) and FDA took a position that a randomized, controlled trial (RCT) designed to rule out an upper bound of a hazard ratio of 2.0 for MACE is feasible.

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Subsequently, Salix requested a Formal Dispute Resolution Appeal (April 02, 2013) for the CR, and FDA later determined that an Advisory Committee meeting would be necessary to resolve the dispute. While consideration and planning for an AC was occurring, FDA held meetings with other sponsors seeking advice for their OIC programs.

FDA met with AstraZeneca on April 23, 2013 to discuss FDA concerns that there may be a class effect of mu-opioid receptor antagonists precipitating opioid withdrawal and related cardiovascular safety concerns (based on a communication sent to AstraZeneca (AZ) on October 8, 2012). At the April 2013 meeting between FDA and AZ, FDA discussed the history of alvimopan with regards to CV safety, postmarketing reports of opioid withdrawal associated with methylnaltrexone, and known presence of opioid receptors within the CV system. Given these concerns and the potential for opioid withdrawal, as well as the elevated baseline risk for CV events in the OIC population (described in the literature), the FDA relayed their concerns about a possible association between withdrawal due to naloxegol and CV events. FDA stated, "Your development program should explore potential mechanisms and the resultant cardiovascular safety concern." FDA provided recommendations for "additional analyses or data presentations we would like to see included in the NDA to further assess the CV risk for naloxegol." FDA also provided detailed recommendations for "additional analyses or data presentations we would like to see included in the NDA to further assess the opioid withdrawal risk for naloxegol."

It was AstraZeneca's position during the April 2013 meeting that a randomized, controlled clinical trial to rule out a specific upper bound of the confidence interval for CV risk associated with opioid withdrawal is neither necessary nor practicable. FDA initially did not agree with this position and stated that it will be necessary to conduct a cardiovascular safety trial given their concerns. However during the meeting, FDA agreed to further discuss internally whether these data will be required to file an NDA submission.



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As a result, after this meeting, it was later determined that the results of a cardiovascular safety trial would not be required to successfully file the naloxegol NDA.

By the Fall of 2013, both Develco and Theravance were made aware of FDA's concern regarding the potential for CV risk associated with their products and were invited to participate in the planning of the AC, which at that time, preparations were ongoing.

In preparation for this AC, sponsors that agreed to present were asked to summarize within their backgrounders CV adverse events observed in their clinical programs and evaluate the occurrence of opioid withdrawal and hemodynamic changes, as well as explore associations between these events.

Biological plausibility of a particular adverse reaction, including CV reactions, may help inform decision making regarding design of a pre-approval development plan to detect a safety signal or to exclude a specific increase in risk. In addition to sample size and duration of treatment, the presence of a control arm and a pre-specified plan to ascertain CV events ideally would be prospectively addressed in the development plan. With regard to assessing the validity of any safety signals, one must be aware that the observed treatment effect is a combination of both the true treatment effect (that is unknown) and random "noise." When few events are observed in a clinical trial or when clinical trials are not enriched with subjects at risk of having specific adverse drug reactions (such as was the case with the Entereg OIC chronic non-cancer pain trial), it might be impossible to detect a real CV effect or determine whether observed small differences are real or due to chance. Consequently, with few observed events there is the potential for either a false positive or false negative conclusion. Adequately powering a clinical trial or development program to observe a sufficient number of adverse drug reactions reduces the risk of making false conclusions on the observed data.

For the assessment of cardiovascular safety, a dedicated, randomized, controlled, cardiovascular (CV) outcomes trial is considered the gold standard in estimating the risk associated with an investigational treatment relative to a control. Such trials are typically designed as event-driven trials with the objective of ruling out an excess risk, measured by an upper bound of the 95% confidence interval around the observed point estimate for the risk measure. Despite being the gold standard in assessing risk of a product, the feasibility of conducting such trials limits their use in many situations.

The feasibility of such trials often revolves around the large size of the trials and the duration of the trials necessary to observe a sufficient number of events to attain a desired level of statistical power. Related to the feasibility of the trial, an adequate control that has an accepted level of cardiovascular risk and an acceptable level of tolerability to permit its use for the duration of the trial must be identified. Other feasibility issues include patient adherence to study medications in long-term trials; low adherence could seriously impact the attribution of CV events to treatment with a particular product.

Section 3.3 of this briefing document displays sample size calculations for considering the design of a CV outcome trial, assuming various hazard ratio margins and various background event rates. In general, a trial not enriched with an at-risk population with a relatively low CV event rate requires more patient-years than a trial in an enriched population in order to observe the same number of events and achieve the same statistical power for a pre-specified hazard ratio margin.

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## **1.7 Summary**

This background package provides an overview of the Entereg cardiovascular safety data available at the time of its approval, in order to provide a framework for understanding the evolving regulatory history of the class of mu opioid antagonists intended to treat OIC in the setting of non-cancer pain. Relevant nonclinical and clinical safety data from several other ongoing OIC development programs for opioid receptor antagonists will be summarized, including data for Relistor (methylnaltrexone), Movantik (naloxegol), TD 1211, and naloxone.

The decision to approve a new drug is based on an assessment of the demonstrated efficacy of a drug for a given indication and patient population, weighed against the potential harms that the drug may present to these patients. For example, in the case of life-threatening diseases, a drug with serious risks may be acceptable if there is a reasonable expectation of a survival benefit. However, for non-life threatening diseases or conditions which are not considered to be serious, the risk/benefit balance is not as straightforward. In cases where the underlying disease is manageable with other drugs or lifestyle modifications, the risk of a serious rare event may be less acceptable. Therefore, it is important to consider the diseases for which the drug is intended.

For the assessment of cardiovascular safety, dedicated, randomized cardiovascular outcomes trials are considered to be the gold standard. Whether a potential serious risk needs to be defined pre- or post-approval must be considered in the context of the patient population, the condition being treated, and the availability of alternative treatments (including their effectiveness and associated risks). If there is a reasonable concern about a potential serious risk, but there is an equally reasonable need to bring a therapy to market, one approach is to initiate the outcomes trial pre-approval, and approve for marketing after a certain pre-specified level of increased risk has been excluded. The trial then continues post-marketing until the number of events is reached that allows for defining the level of risk considered most meaningful to exclude. With regard to defining cardiovascular events of interest, unless there is a reason to be specifically concerned about arrhythmia or congestive heart failure, the Agency has moved toward focusing on major adverse cardiovascular events or MACE (defined as the composite of CV death, non-fatal MI and non-fatal stroke).

When there is an existing concern about a CV safety problem for a drug, it is important to consider the amount of and type of CV data needed to provide some assurance that there is no CV signal associated with a drug in development. A prospective plan to identify and assess MACE events, within the context of a controlled trial, is critical to the proper evaluation of these events. The gold standard dedicated CV outcomes study might be modified for this purpose, i.e., identify a signal, by prespecifying the number of events needed to exclude a relatively high relative risk, which has been selected as indicative of a signal.

The Agency acknowledges that cardiovascular outcomes trials are resource intensive. They may also be impractical for OIC drug programs. For assessment of cardiovascular safety, cardiovascular outcomes trials may be the best way to estimate the risk; however, the sample size and duration of study required could be an obstacle to the development of necessary new drugs. We are asking the Committee now for advice on the extent of the cardiovascular safety assessment that should be available for opioid antagonists in order to make a reasonable risk/benefit assessment to appropriately guide approval decisions. In particular, we are seeking advice regarding the necessity, timing, design and size of

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cardiovascular outcomes trials to support approval of products in the class of opioid receptor antagonists intended to treat opioid induced constipation.

**1.8 *Points for Consideration by the Advisory Committee***

The FDA requests that the Advisory Committee consider a number of potential discussion topics during its review of these (and the Sponsors') briefing documents. These topics are intended to frame the major review issues for more specific questions to be posed to the Committee at the meeting.

1. Discuss whether the totality of data suggests a cardiovascular safety signal associated with the use of peripherally active mu opioid receptor antagonists. Include in your discussion:
  - a. the strength of the signal;
  - b. whether you believe the signal is limited to a certain drug(s) within the class or whether you believe there is a class effect;
  - c. the biologic plausibility of the signal:
    - i. the effect of opioid withdrawal on the autonomic nervous system and the relevance of hemodynamic changes on risk of cardiovascular events.
    - ii. the effect of off-target receptor affinity for opioid receptors on the heart.
    - iii. other effect(s)
2. Discuss the feasibility of conducting a cardiovascular outcomes trial in patients with chronic non-cancer pain who have opioid-induced constipation, in which patients are randomized between the mu opioid receptor antagonist versus a standard of care regimen. As part of this discussion, consider what would be an acceptable degree of risk that would need to be excluded in such a trial; also comment on sample size and trial duration.
3. Discuss whether cardiovascular outcomes trials should be required for all or only specific mu opioid receptor antagonists being developed for the treatment of opioid-induced constipation in non-cancer pain patients. If only selected antagonists should be evaluated in such a trial, specify which ones and what concerns form the basis for such a requirement.
4. If a cardiovascular outcomes trial is required for a peripherally active mu opioid receptor antagonist being developed for the treatment of opioid-induced constipation in patients with non-cancer pain, discuss whether the trial should be required in the pre-approval setting, required in the post-marketing setting, or a combination of both pre-approval and post-marketing settings (as described in Section 1.7 above).
5. If a cardiovascular outcomes trial is not required, discuss whether a longer term controlled clinical trial should be required pre-approval to further assess the safety of peripherally active mu opioid receptor antagonists being developed for the chronic treatment of opioid-induced constipation in patients with non-cancer pain, and describe specific outcomes that should be assessed in such a trial.

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***Administrative Note:***

This background package is organized into separate sections by drug. For Entereg (alvimopan), Relistor (methylnaltrexone) and Movantik (naloxegol), highlights of important information relevant to potential cardiovascular safety issues and withdrawal symptoms are provided. This document also provides a separate section on epidemiological and biostatistical considerations for assessment of cardiovascular safety.

DGIEP invited pharmaceutical firms to present at this advisory committee who either had marketed opioid receptor antagonists or are actively developing opioid receptor antagonists for the treatment of OIC. Of these, Salix, Theravance, Cubist, AstraZeneca and Develco accepted the invitation to present information about opioid antagonists they are developing for opioid induced constipation.

This background package is based upon publically available information or when not publically available, the information was included with permission from the sponsors.

## **2 Individual Drug Products**

This section will provide background with regard to duration of therapy, study design (controlled vs. uncontrolled; blinded vs. open label) and adverse events of interest, in order to highlight the discussions presented in the Pharmaceutical companies' briefing documents. A summary table is available in the Appendix 4.1 which provides side-by-side information on the RCTs conducted in the various programs, including number of trials, sample size, high level design features, and the age and gender distribution of the populations enrolled. The table includes similar summary data for the "long term" safety studies conducted in the programs. An overview of CV outcomes observed can be found at the bottom of the table.

### **2.1 ENTEREG (*alvimopan*)**

Entereg (alvimopan) is a mu opioid receptor antagonist. Approved on May 20, 2008, Entereg is currently indicated to accelerate the time to upper and lower gastrointestinal recovery following surgeries that include partial bowel resection with primary anastomosis. It is available as a 12 mg tablet, prior to surgery and twice daily. It is approved with a Risk Mitigation and Evaluation Strategy (REMS). The goal of the Entereg REMS is to mitigate the potential risk of myocardial infarction by 1.) ensuring that Entereg (alvimopan) is prescribed only for short-term use (no more than 15 doses) in a hospital inpatient setting, and 2.) informing healthcare providers about the potential risk of myocardial infarction observed with long-term use of Entereg.

A GIDAC meeting was held on January 23, 2008 to discuss the safety and efficacy of alvimopan for the postoperative ileus indication (referred to here as POI). The safety review for the short-term use of alvimopan in POI did not reveal a cardiovascular signal. However, a lower dose of alvimopan was concurrently developed for the treatment of OIC in the setting of chronic non-cancer pain. In that program, there were more reports of myocardial infarction in patients treated with alvimopan 0.5 mg twice daily compared with placebo-treated patients in a single 12 -month trial (Study 014), which

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randomized patients 2:1 to alvimopan or placebo. In the trial, the majority of myocardial infarctions occurred between 1 and 4 months after initiation of treatment.

A retrospective analysis of the 12 month trial was conducted and presented at the 2008 Advisory Committee meeting. The assessments of cardiovascular outcomes were not pre-specified and there was no systematic assessment for ascertainment of events. In addition, there was loss to follow-up of patients who dropped out of the trial. The retrospective safety analysis performed at that time reported all potential cardiovascular safety terms. The results from Study 014 presented in the table below were based on adjudicated cases from the retrospective-analysis conducted in 2008, and are not limited to events considered strict MACE (major adverse cardiovascular events), which includes non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death.

**Table 2. Alvimopan: Long term cardiovascular safety results Study 14**

**Table 3**

**Number (%) of Deaths and Cardiovascular Events by Treatment in the Non-Cancer OBD Study SB-767905/014**

		<b>Alvimopan N=538 n (%)</b>	<b>Placebo N=267 n (%)</b>	<b>Relative Risk (asymptotic 95% CI)</b>
All cases	<b>All cause death (total)</b>	<b>2 (0.37)</b>	<b>2 (0.75)</b>	<b>0.50 (0.09, 2.80)</b>
	• Death from cardiovascular events	1 (0.19)	0 (0.0)	- (0.13, -)
	<b>Subjects with cardiovascular events (total)</b>	<b>14 (2.60)</b>	<b>0 (0.0)</b>	<b>- (1.83, -)</b>
	• Ischemic events	11 (2.05)	0 (0.0)	- (1.44, -)
	• <i>Fatal</i>	1 (0.19)	0 (0.0)	- (0.13, -)
	• Other serious cardiovascular events	3 (0.56)	0 (0.0)	- (0.39, -)

Source: Statistical Reviewer's calculation using sponsor Table 2 on page 10 of the OBD CV safety report.

Ischemic events include the following fatal and non-fatal events: MI, Unstable angina, and cerebro-vascular accident.

Other serious cardiovascular events include the following fatal and non-fatal events: congestive heart failure and serious arrhythmia.

Note: Alvimopan group includes the following alvimopan dose and regimen: 0.5 mg BID (N=538).

Source: Memorandum of Statistical Consultation, NDA#21775 (alvimopan), signed 4/16/2008

Note: OBD = Opioid Bowel Dysfunction, referred to in this section as OIC.

However, among the ischemic events (14) listed above, were deemed to be 7 myocardial infarctions, one of which was fatal, among patients receiving alvimopan and compared to no such events in the placebo group (Study 014). According to strict MACE definition applied for this Advisory Committee meeting, the analysis of Study 014 reveals 1 CV death and 6 non-fatal MIs compared to no such events in the placebo group.

This imbalance in myocardial infarctions had not been observed in other shorter term OIC studies of Entereg in patients treated with opioids for chronic pain, nor in studies involving patients treated within the surgical setting, including patients undergoing surgeries that included bowel resection who received Entereg 12 mg twice daily for up to 7 days (Entereg 12 mg, n = 1,142; placebo, n = 1,120). A causal relationship with alvimopan with long- term use has not been established.

There were notable differences in opioid use between the study populations in the POI and OIC trials. The mean duration of opioid use, prior to treatment with alvimopan or placebo in the OIC phase 3 program, ranged from approximately 4 to 8 years with an average total daily dose of 108 to > 240 mg morphine equivalents. These opioid-tolerant patients were more sensitive to the effects of alvimopan, and low alvimopan doses were used in this population (i.e., 0.5 mg BID). In contrast, surgical patients in the POI phase 3 program were opioid naive and their acute postsurgical pain was managed with short-

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term opioid-based IV PCA, with an average total daily dose of 28 mg morphine equivalents (5- to 10-fold lower than the OIC population). Much higher doses of alvimopan (12 mg BID) were required to antagonize opioid effects on bowel motility in the POI setting.

In 2008, the Gastrointestinal Drugs Advisory Committee (GIDAC) recommended approval of alvimopan for short term in-hospital use in patients with postoperative ileus. Entereg was subsequently approved with a Boxed Warning ("For Short-Term Hospital Use Only") and a Risk Evaluation and Mitigation Strategy (REMS) that limits its use to 7 days or 15 doses. The findings in the controlled, long term safety trial in OIC led FDA to discuss the need for additional cardiovascular outcome trials to address the potential cardiovascular safety signal with the sponsor.

In preparation for the current Advisory Committee meeting, DGIEP requested that CUBIST Pharmaceuticals, Inc., the current Entereg sponsor, reanalyze the cardiovascular events according to the strict MACE definition (Study 014 results listed above). Refer to the Cubist 2014 Advisory Committee briefing document for a detailed description of that analysis. In general, the findings are consistent with the previous analysis of cardiovascular adverse events presented in 2008. Cubist also reviewed adverse events potentially related to opioid withdrawal and evaluated whether any preceded the cardiovascular adverse events. The majority of withdrawal events identified were related to the gastrointestinal tract, as expected given the mode of action of alvimopan. Cubist did not identify any events consistent with symptoms of withdrawal that preceded a MACE event.

In summary, there were seven MIs, including one death due to myocardial infarction, among patients treated with alvimopan for OIC compared to none in the placebo group, in a single 12 month safety study in which subjects were randomized 2:1 between alvimopan and placebo. There were no significant differences identified for the presence of risk factors for cardiovascular disease between patients enrolled in the two arms of the trial. The prevalence of cardiovascular risk factors was higher in the study population than in the general U.S. population. In 2008, the GIDAC considered these safety data, and in a 9 to 6 vote recommended approval with a risk management plan to limit its use to 15 total doses for in-patient use prescribed by surgeons performing bowel resections only. It is unclear whether or not the observed imbalance in cardiovascular events was a chance finding; if not, it remains to be shown that the risk is specific and isolated to this particular molecular entity (and not a class effect).

## **2.2 RELISTOR (*methylnaltrexone bromide*)**

Relistor is approved for treatment of OIC in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. It was approved for this indication in 2008 shortly after Entereg was approved with a REMS. Relistor does not have a REMS for the OIC indication. The indicated population has advanced illness, with relatively short life expectancy.

Salix is developing Relistor for the expanded indication of treatment of OIC in patients receiving opioids for chronic non-cancer pain. The phase 3 efficacy trial included a 4 week evaluation comparing Relistor to a placebo control. The 48-week open label safety study did not include a control arm. Cardiovascular events were observed during that uncontrolled study, and it is difficult to assess the relationship of the events to Relistor in the absence of a control arm. The imbalance in cardiovascular events observed with Entereg occurred in a placebo-controlled OIC trial of 12 months duration. Because of the cardiovascular safety signal observed with Entereg, another member of the same drug class, and because of the lack of adequate controlled safety data to assess the cardiovascular safety of Relistor, the

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DGIEP concluded that additional controlled safety data were needed to evaluate the cardiovascular safety of Relistor in this population.

The following sections describe the Relistor clinical safety data from both OIC development programs, including cardiovascular related adverse events, and opioid withdrawal adverse events.

Methylnaltrexone is an antagonist of opioid binding at the mu-opioid receptor. As a quaternary amine, the ability of methylnaltrexone to cross the blood-brain barrier is restricted. Following subcutaneous administration, methylnaltrexone achieves peak concentrations (C<sub>max</sub>) at approximately 0.5 hours. Methylnaltrexone is excreted primarily as the unchanged drug in the urine and feces. The terminal half-life (t<sub>1/2</sub>) is approximately 8 hours.

### **2.2.1 Currently Approved Indication: OIC in patients with advanced illness receiving palliative care**

RELISTOR (methylnaltrexone bromide) Subcutaneous Injection was FDA approved in 2008 for “the treatment of OIC in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. Use of RELISTOR beyond four months has not been studied in the advanced illness population.” The recommended dose of RELISTOR is weight-based, 8 mg subcutaneously in patients weighing 38 kg to less than 62 kg or 12 mg subcutaneously for patients weighing 62 kg to 114 kg. The recommended dose in patients whose weight falls outside of these ranges is 0.15 mg/kg.

The safety and efficacy of RELISTOR for the currently approved indication was evaluated in two double-blind, randomized, placebo-controlled phase 3 trials (MNTX 301 and MNTX 302) and one double-blind, randomized, dose-ranging phase 2 trial (MNTX251), which had no placebo arm. Patients who had inadequate response to their regular laxative regimen, defined as either < 3 bowel movements in the preceding week or no bowel movement for greater than 2 days, were eligible for the trials and they maintained their regular laxative regimen for at least 3 days prior to trial entry and throughout the trial. The phase 3 trials were each followed by a three-month, open-label extension study (MNTX 301EXT and MNTX 302EXT).

MNTX 301 was a phase 3 trial that compared a single, double-blind, subcutaneous (SC) dose of RELISTOR 0.15 mg/kg (n=47), or RELISTOR 0.3 mg/kg (n=55) versus placebo (n=52). The trial included a one day, double-blind, placebo-controlled period followed by a four-week open-label period in which all subjects received RELISTOR. The primary efficacy endpoint was laxation response within 4 hours of double-blind dosing in the first day of dosing. 154 subjects were enrolled and treated.

MNTX 302 was a phase 3, double-blind, placebo-controlled trial in which 134 patients were randomly assigned to receive either SC RELISTOR 0.15 mg/kg (n=63) or SC placebo (n=71) every other day for two weeks. The duration of double-blind treatment was 2 weeks (7 doses). Co-primary efficacy endpoints were: 1) Proportion of patients with laxation within 4 hours after the first dose of study drug 2) Proportion of patients who had a laxation response within 4 hours after at least 2 of the first 4 doses (the first week of treatment).

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MNTX 251 was a phase 2, double-blind, dose-ranging trial in 33 subjects with a duration of treatment of up to four weeks. The duration of double-blind treatment was one week (3 doses).

The duration of the open-label extension period in MNTX 301/301EXT was four months; in MNTX 302/302EXT was three months, and in MNTX 251 was three weeks.

A total of 159 deaths were reported among 321 patients who participated in the clinical trials and received RELISTOR or placebo. Of the 140 RELISTOR-treated patients who died, the reported cause of death was the underlying disease or a complication relating to the underlying disease, except in one case, which is described below:

A 73 year old Caucasian female hospice patient with recurrent Stage IV metastatic breast cancer, was randomized and completed the double-blind, single dose period (0.30mg/kg SC) in study RELISTOR 301 (on 5/27/2004). The following day, she received a single dose of RELISTOR 0.15 mg/kg SC. After this dose was given she experienced gastrointestinal cramping and an episode of two small hard stool "pebbles" about one hour post injection. She subsequently received three doses of RELISTOR 0.30 mg/kg SC from 5/29/2004 until (b) (6). One hour after the (b) (6) dose, the patient complained of mild abdominal pain and had massive diarrhea, nausea and vomiting, and syncope. Vital signs taken during this time revealed a pulse of 60, respirations 18, and BP of 110/60. The following day she was found dead. An autopsy was not performed. In the Investigator's opinion, the events of severe diarrhea, dehydration, and cardiovascular collapse were probably due to study drug.

The 2008 clinical review of RELISTOR for the original NDA (approved) emphasized two combined (pooled) study populations for purposes of evaluating safety: the DBPC Pool (N=288) and the RELISTOR Pool (N=286)<sup>13</sup>.

1. The Double-Blind, Placebo-Controlled Pool (DBPC Pool): Safety data from the double-blind period of the two placebo-controlled studies, MNTX 301 (one double-blind dose) and MNTX 302 (maximum of seven double-blind doses over two weeks) are included in this pool. (N=288, of whom 123 received placebo and 165 received MNTX.)
2. RELISTOR Exposure Pool (RELISTOR Pool): This pool includes all patients who received at least one dose of RELISTOR (N=286) in studies MNTX 301/301EXT, MNTX 302, MNTX 302EXT and MNTX 251.

Table 3 is a side-by-side tabulation of the non-fatal serious adverse events from the DBPC Pool and the RELISTOR Pool.

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<sup>13</sup> [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2008/021964s000TOC.cfm](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/021964s000TOC.cfm)



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**Table 3. Select Non-Fatal Serious Adverse Events with Possible CV Etiologies: DBPC Pool and RELISTOR Pool**

Primary System Organ Class Preferred Term	Placebo-Controlled Pool		RELISTOR Pool
	Placebo (n=123) n (%)	RELISTOR (n=165) n (%)	RELISTOR (n=286) n (%)
Cardiac Disorders			
Cardiac failure congestive	1 (0.8)	0	1 (0.3)
Cyanosis	1 (0.8)	0	0
Myocardial infarction	0	0	1 (0.3)
General Disorders and Administration Site Conditions			
Chest pain	0	0	4 (1.4)
Drug withdrawal syndrome	0	0	2 (0.7)
Edema peripheral	0	0	2 (0.7)
Respiratory, Thoracic and Mediastinal Disorders			
Pulmonary edema	0	0	1 (0.3)
Vascular Disorders			
Hypotension	1 (0.8)	0	1 (0.3)
Peripheral vascular disorder	1 (0.8)	0	0
Hot flush	0	0	1 (0.3)
Thrombosis	0	0	1 (0.3)

Source: Adapted from FDA Clinical Review, NDA 02164, Clinical Review Table 36, approval date 4/24/2008<sup>14</sup>

Cardiac related non-fatal, serious adverse events were reported in 2 patients (0.7%) in the RELISTOR Pool. One 68 year old male (ID: 301-22-0003) with advanced mesothelioma on RELISTOR 0.30 mg/kg developed congestive heart failure and worsening pneumonia not thought to be related to the study drug. A 72 year old Caucasian female (ID: 302-39-0004) on RELISTOR 0.30 mg/kg experienced a non-Q wave myocardial infarction from which she later recovered.

## 2.2.2 Proposed indication: OIC in patients receiving opioids for chronic non-cancer pain

The safety and efficacy of RELISTOR in OIC in patients on chronic opioid treatment (a non-advanced illness, palliative care population) was evaluated in a single double-blind, randomized, placebo-controlled phase 3 trial, Study 3356 (four weeks duration), and one safety trial, Study 3358, which was an open-label, uncontrolled trial conducted to assess the safety of 12 mg SC Relistor administered over 48 weeks. A third trial, Study 2101 contributed additional safety data from 37 subjects with OIC during rehabilitation after orthopedic procedures. A total of 1484 patients received Relistor SC and 177 received placebo SC during the clinical trials (2101, 3356, and 3358) submitted in this supplemental NDA (sNDA). The design features of these trials are summarized in Table 4.

<sup>14</sup> [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2008/021964s000\\_MedR\\_P2.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/021964s000_MedR_P2.pdf)

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**Table 4: Clinical trials submitted to Support the Relistor supplemental NDA for OIC in Chronic Nonmalignant Pain**

Study ID	Number of centers Location	Title	Study Design Objectives	Total N*	Treatment arms No. of pts per arm treated/completed	Duration
3356	91  USA Canada	A Multicenter Randomized, Double-Blind, Placebo-controlled, Parallel-group study of subcutaneous MOA-728 for the treatment of Opioid-induced constipation in subjects with chronic non-malignant pain	Phase 3, R, PG, DB, PC pd followed by OL pd  Efficacy, safety, & tolerability	469	<b>4 wk DB period**</b> • RELISTOR 12 mg QD SC: 150/122 • RELISTOR 12 mg QOD SC: 148/120 • Placebo SC: 162/146 <b>8 wk OL period</b> RELISTOR 12 mg SC prn • 364/303	12 weeks (4 wk DB pd followed by an 8 wk OL pd)
3358	120  6 countries (USA, Australia, Spain, South Korea, Colombia)	An open-label study to evaluate the long term safety of subcutaneous MOA-728 for treatment of Opioid induced constipation in subjects with nonmalignant pain	Phase 3, OL  Long term safety, & tolerability	1040	RELISTOR 12 mg SC q d or prn (but not less than once weekly)  1034/477	48 weeks
2101	19  USA	A Multicenter, Double-Blind, Randomized, Parallel-Group, Placebo Controlled Phase 2 Study of Once-Daily Subcutaneous Methylnaltrexone (RELISTOR) in the Treatment of Opioid-Induced Constipation During Rehabilitation After Orthopedic Procedures	Phase 2, R, DB, PG, PC  Activity, PK/PD, and safety	37	RELISTOR 12 mg SC QD: 18**/15  Placebo SC: 15**/12	Up to 4 or 7 days

\*N=patients who signed informed consent form, met all study criteria, and were allocated to receive study drug

\*\*Modified intent-to-treat population (randomized patients who received at least one dose of study medication)

Source: Reviewer's table adopted from Sponsor's table 1, 5.3.5.3 Integrated summary of efficacy, pages 22-24

During FDA's review of the application, safety concerns emerged from the observation of cardiovascular events and deaths in Study 3358, the uncontrolled, open label safety study. Because of the absence of a control arm, FDA was unable to adequately assess the relationship between the events and the drug. These events were of particular concern in light of the cardiovascular safety signal observed with ENTEREG, another member of the class. The Entereg cardiovascular safety signal was detected only in the context of a placebo-controlled trial of 12 months duration.

The safety data from each trial are described in the sections that follow.

### **2.2.2.1 Relistor Study 3356 (placebo-controlled)**

Study 3356 had a 4 week double-blind, placebo-controlled treatment phase, followed by an 8 week open label phase (in which all subjects took Relistor on an as needed basis). Study 3356 evaluated 2 dosing regimens of Relistor, 12 mg daily (QD) and 12 mg every other day (QOD) versus placebo for the proposed indication of treatment of OIC in patients with chronic non-cancer pain. A total of 469 subjects were randomized to one of the 3 treatment groups (placebo, Relistor 12 mg QD, Relistor 12 mg QOD).

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In Study 3356, on average, patients had a baseline mean duration of OIC of 76 months (over 6 years) and were taking a mean daily dose of 222 mg of morphine equivalents.

### 2.2.2.1.1 Cardiovascular Events

There were no MACE events observed in Study 3356. There were no deaths in Study 3356 (or Study 2101, the small post-op rehab for orthopedic surgery study).

Table 5 presents the adverse events reported by patients in Study 3356 within the Cardiac Disorders System Organ Class (SOC), as identified by the applicant.

**Table 5. Study 3356: Number (%) of Subjects Reporting Adverse Events in Double-blind Period: Safety Population**

System Organ Class [a] Preferred Term	Overall P-value	Number (%) of Subjects Reporting Adverse Events in Double Blind Period Safety Population				Treatment			
		MOA-728 12mg QD n=150	MOA-728 12mg QOD n=148	Placebo n=162	Total n=460	MOA-728 12mg QD n=150	MOA-728 12mg QOD n=148	Placebo n=162	Total n=460
Cardiac disorders	0.273	3 (2.0)	6 (4.1)	2 (1.2)	11 (2.4)	3 (2.0)	6 (4.1)	2 (1.2)	11 (2.4)
Angina pectoris	0.322	0	1 (0.7)	0	1 (0.2)	0	1 (0.7)	0	1 (0.2)
Atrioventricular block first degree	0.770	0	1 (0.7)	1 (0.6)	2 (0.4)	0	1 (0.7)	1 (0.6)	2 (0.4)
Bradycardia	0.770	0	1 (0.7)	1 (0.6)	2 (0.4)	0	1 (0.7)	1 (0.6)	2 (0.4)
Cardiac failure congestive	0.322	0	1 (0.7)	0	1 (0.2)	0	1 (0.7)	0	1 (0.2)
Cardiac flutter	0.648	1 (0.7)	0	0	1 (0.2)	1 (0.7)	0	0	1 (0.2)
Extrasystoles	0.322	0	1 (0.7)	0	1 (0.2)	0	1 (0.7)	0	1 (0.2)
Palpitations	0.211	1 (0.7)	2 (1.4)	0	3 (0.7)	1 (0.7)	2 (1.4)	0	3 (0.7)
Sinus bradycardia	1.000	0	0	1 (0.6)	1 (0.2)	0	0	1 (0.6)	1 (0.2)
Sinus tachycardia	0.322	0	1 (0.7)	0	1 (0.2)	0	1 (0.7)	0	1 (0.2)
Supraventricular extrasystoles	0.648	1 (0.7)	0	0	1 (0.2)	1 (0.7)	0	0	1 (0.2)

Source: Applicant, Study 3356 Study Report, Table 16.121, page 607

In addition, FDA undertook its own review of the clinical trial datasets and narratives for adverse event verbatim and preferred terms that might signal cardiovascular signs and symptoms<sup>15</sup>. In the double blind phase, these events included 2 chest pain events in the Relistor arms (one designated “angina pectoris”) and one “musculoskeletal chest pain” in the placebo arm, 1 congestive heart failure in a Relistor arm, and 3 ECG changes in a Relistor arm (two of which were QT prolongation). During the uncontrolled extension phase, there were two hypertension events, 1 dyspnea, 2 syncopal events, 1 loss of consciousness, 1 chest pain and 1 “chest discomfort”.

Given the small number of events, the short duration of the trial, and the lack of a comparator in the open label phase, FDA was unable to draw any meaningful conclusion regarding the cardiovascular safety of Relistor. Furthermore, the study did not prospectively define standardized criteria for ascertainment of cardiovascular adverse events, and there was no independent adjudication of MACE events.

<sup>15</sup> The following terms were identified as a potential signal for cardiovascular AEs in the datasets: syncope, angina pectoris, chest pain, cardiac failure congestive, musculoskeletal chest pain, loss of consciousness, pulmonary congestion, hypertension, hypotension, non-cardiac chest pain, dyspnea, chest discomfort, breast pain, vision blurred, electrocardiogram QT prolonged, stroke, cardiac arrest, thrombosis, vagal shock, myocardial infarction, nuclear magnetic imaging abnormal, pleural effusion, edema peripheral, troponin increased, blood creatinine phosphokinase increased, coronary artery disease, Prinzmetal angina, dysarthria, dyspnea exertional, sudden death, respiratory distress, angina unstable, acute respiratory failure, in-stent coronary artery restenosis, dyspepsia, palpitations, mental status changes, right leg numbness, pulmonary embolism, electrocardiogram PR prolongation, HR decreased, atrioventricular block second degree, and hypoaesthesia.

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**2.2.2.1.2      *Assessment of Opioid Withdrawal (Study 3356)***

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), conducted a review of specific AE terms based upon DSM IV, Objective Opioid Withdrawal Scale (OOWS), Subjective Opioid Withdrawal Scale (SOWS) and clinical judgment in order to identify cases of opioid withdrawal that occurred in the clinical trial. See Appendix 4.3 for DAAAP's consult review of Relistor. This assessment was of interest in determining whether Relistor had activity on central mu opioid receptors in addition to its primary effect on peripheral mu opioid receptors. Such an effect would be expected to have a negative impact on pain control, and from a safety standpoint, such withdrawal symptoms could pose a serious safety concern, especially if they result in hemodynamic changes that could stress the heart.

DAAAP determined that the most clinically meaningful opioid withdrawal cases would be those which were reported as a serious adverse event or resulted in discontinuation and the review of opioid withdrawal cases was limited to those subjects. Using these parameters, DAAAP's review noted the following:

- Seven subjects treated with RELISTOR discontinued treatment due to AEs possibly related to opioid withdrawal in the double-blind phase. There were no subjects in the placebo-treatment arm that were identified as having a constellation of symptoms consistent with opioid withdrawal that led to study discontinuation.
- In general, treatment emergent adverse event terms potentially related to opioid withdrawal with  $\geq 2\%$  incidence occurred more frequently in the drug treatment group than placebo group (as shown in Table 13 of DAAAP Consult Review).
- Evidence of opioid withdrawal occurring during this study is based primarily upon the specific AEs of hyperhidrosis and piloerection, which occurred more frequently in drug-treated subjects than placebo-treated subjects.
- The most frequently occurring AE consistent with opioid withdrawal was hyperhidrosis.
- Opioid withdrawal symptoms occurred with increased incidence in the QOD treatment group compared to the QD or placebo groups. The significance of this is unclear.
- Individual item objective opiate withdrawal scale (OOWS) scores showed that perspiration occurred more frequently than other individual items on the OOWS in subjects treated with RELISTOR. This most likely correlates with the reported AEs of hyperhidrosis.

As per DAAAP's review, limitations of the study regarding opioid withdrawal assessments include the following:

- Infrequent assessments of withdrawal may not have captured symptoms during clinically relevant times. Specifically, OOWS/subjective opiate withdrawal scale (SOWS) were obtained at pre-dose, one hour post-dose, and not again until days 14 and 28 during the DB period. Although opioid withdrawal may have occurred at any time during treatment, the expectation is that withdrawal would occur early in treatment, likely within the first 7 to 14 days.
- Patients were allowed to increase pain medication throughout study. Although there was no definite evidence of increased analgesic requirements in patients treated with methylnaltrexone, the interpretation of this information is limited by the frequency of assessments of opioid dosage and the use of concomitant medications that could have affected the study subject's pain and need for a change in opioid dosing.
- The Sponsor provided no defined criteria for mild, moderate or severe rating for OOWS scores.

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### **2.2.2.2 Relistor Study 3358**

This was an uncontrolled open label safety study. Mean duration of open-label treatment was 212 days (median 280). Of the 1034 subjects who received Relistor, 477 completed the study. The reader is referred to Appendix 4.2 that contains the Clinical Review Amendment by Helen Sile (dated July 27, 2012), Section 3.2 (starting on page 17). Adverse events within the cardiac disorders SOC that were reported in Study 3358, as well as other CV events of interest identified by the applicant and the FDA, respectively, are presented in Section 2.2.2.2.1 below.

In order to evaluate MACE events, deaths, myocardial infarctions and stroke were also reviewed separately and are presented in Section 2.2.2.2.2 below. However, the assessment/analysis of MACE events was not prespecified, lacked standardized definitions and was not adjudicated independently.

See Table 6 in the next section for a presentation of subjects reporting adverse events that were identified under Cardiac Disorders System Organ Class (SOC) in Study 3358.

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**2.2.2.2.1 Cardiovascular Events**

Table 6 presents subjects reporting adverse events that were identified under Cardiac Disorders System Organ Class (SOC) in Study 3358.

**Table 6. Study 3358: Number (%) of Subjects Reporting Adverse Events for Cardiac Disorders SOC**

<b>System Organ Class [a] Preferred Term</b>	<b>RESLITOR 12mg QD n=1034</b>	<b>(%)</b>
<b>Cardiac disorders</b>	<b>33</b>	<b>(3.2)</b>
Angina pectoris	8	(0.8)
Angina unstable	1	(0.1)
Atrial fibrillation	2	(0.2)
Atrial flutter	1	(0.1)
Atrioventricular block first degree	2	(0.2)
Atrioventricular block second degree	1	(0.1)
Bradycardia	1	(0.1)
Bundle branch block right	1	(0.1)
Cardiac arrest	1	(0.1)
Cardiac failure congestive	1	(0.1)
Coronary artery disease	2	(0.2)
Left ventricular hypertrophy	1	(0.1)
Mitral valve incompetence	1	(0.1)
Myocardial infarction	4	(0.4)
Palpitations	3	(0.3)
Prinzmetal angina	1	(0.1)
Sick sinus syndrome	1	(0.1)
Sinus arrhythmia	1	(0.1)
Sinus bradycardia	1	(0.1)
Supraventricular extrasystoles	2	(0.2)
Supraventricular tachycardia	1	(0.1)
Tachycardia	3	(0.3)
Ventricular extrasystoles	3	(0.3)

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).

- a. Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.

Source: Applicant Study 3358 CSR, Table 15.15 page 373.

The clinical significance of these adverse events are difficult (if not impossible) to interpret given the lack of a control arm; however, the analysis did identify a number of angina and “chest pain” adverse events occurring in this population. Note that any given subject could report multiple events and therefore the percentages do not reflect the proportion of subjects having a given event. Rather, this table is intended to provide an overview of the types of adverse events that were captured as cardiovascular disorders in the original dataset.



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**2.2.2.2.2 Summary of Major Adverse Cardiovascular (MACE) Events in Study 3358**

FDA also conducted an analysis using a strict MACE definition (CV death, non-fatal MI and non-fatal stroke).

Table 7 presents a summary of the 7 reported MACE events in Study 3358 (based on the investigator's reported term).

**Table 7. Summary of Major Adverse Cardiovascular Events (MACE) in Study 3358**

Subject ID	Reporter term / study day	Subject demographics	Clinical History
008-080235	Cerebrovascular accident (fatal) Study day 211	45 y/o female	BMI – 46 kg/m2, hypertension
020-080651	Cardiac arrest (fatal) Study day 63	67 y/o female	Morbid obesity, past smoker
072-081899	Sudden death Study day 257	46 y/o male	ALS Smoker COPD/asthma
095-082943	Myocardial infarction Study day 306	57 y/o female	Dyslipidemia Smoker Rheumatoid arthritis
198-083617	Myocardial infarction Study day 243	81 y/o female	Coronary disease Peripheral vascular disease, coronary risk factors
198-083624	Myocardial infarction Study day 6	59 y/o male	Type 2 diabetes Hypertension Smoker
200-083696	Myocardial infarction (fatal) Study day 278	57 y/o male	Coronary disease, s/p MI and PCI, smoker, hypertensive, dyslipidemic

**Deaths (Study 3358)**

There were 4 deaths reported out of 1034 patients treated in Study 3358 (Table 23). All subjects who died were receiving Relistor 12 mg SC on an as needed basis with permitted dose adjustment of a minimum of one SC injection/week and a maximum of one SC injection/day. According to the investigators, subject 080235 died due to a cerebrovascular accident; subject 080651 died due to cardiac arrest; subject 081899 died due to sudden death; and subject 083696 died due to myocardial infarction. These 4 patients had underlying medical illnesses and confounding events that made it difficult to determine causality.

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**Table 8: Brief Narratives of Deaths in Study 3358**

Study 3358	Probable Cause of Death*	Time interval of RELISTOR dose
<b>Subject 080235:</b> 45 yo F with HTN, back pain, sinus bradycardia, obesity, anxiety disorder was receiving oxycodone hydrochloride for back pain. Patient had OIC and received her last dose of RELISTOR 12 mg Q D the same day she died suddenly. She was taking Lisinopril for HTN, Xanax for Anxiety disorder.	Cerebrovascular Accident	0 days after last dose
<b>Subject 080651:</b> 67 yo F with HTN, obesity, abdominal hernia, and OIC died suddenly while sleeping in a car. The patient had complained of abdominal pain 24 hrs prior to her death. Her daughter reported that she took her to an urgent care center to be evaluated for abdominal pain. Patient reportedly received a prescription for pain medication and the daughter did not think she took any of the pain medications. On the way home, her daughter reported that patient became somnolent. The daughter could not get her mother out of the car and she left her mother in the car to sleep overnight. The daughter checked on her mother periodically throughout the night and she reported that she was snoring and somewhat arousable. However, in the morning hours, she noticed that her mother was not breathing. She took her to the ER where the patient was intubated and CPR was initiated, but the resuscitation efforts failed.	Cardiac Arrest	6 days after last dose
<b>Subject 081899:</b> 46 yo M with ALS, Asthma, Depression, seizure disorder, urinary retention, and muscle spasms was receiving morphine and oxycodone for pain management. He had OIC and had received his last dose of RELISTOR 12 mg Q D 7 days prior to his death suddenly. The patient was taking soma, lexapro, azmacort, combivent inhaler, singular, baclofen, and flomax for muscle spasms, asthma, and depression.	Sudden death	7 days after last dose
<b>Subject 083696:</b> 57 yo M (wt 88 kg, BMI = 29) with CAD with prior MI and stent placement X 2, HTN, hyperlipidemia, cervical herniated disks, tobacco abuse and migraine headaches was receiving fentanyl and hydromorphone for chronic neuropathic pain. The patient was withdrawn (on (b) (6)) from the trial 13 days prior to his death due to non-compliance with protocol. He was taking ramipril, valium, prevacid, domperidone, plavix, tamsulosin, metoprolol, lipitor, gabapentin, and diltiazem. On Jan 23, 2010, the subject was diagnosed with angina pectoris by a local physician and was prescribed nitroglycerin 0.4 mg sublingual as needed. On (b) (6), study day 278 and 13 days after his last dose of Relistor (received Relistor through (b) (6), study day 265), the subject was found dead with "cadaveric rigidity" by a friend who had not heard anything from him for one week. No autopsy was performed. The death report and the ER physician documented "patient with past history of cardiovascular disease, presenting with rigidity and no sign of violence; diagnosis: myocardial infarction".	Myocardial infarction	13 days after last dose

\*Verbatim term per investigator

Source: Reviewer's table created from data in final CSR, Protocol 3200K1-3358-WW pages 69-70 and subject narrative information pages 554, 573, 677, and 788-789.

**Myocardial Infarctions (Study 3358)**

There were 4 myocardial infarctions (MIs) reported by investigators in Study 3358. Their narratives follow below. The single MI associated with death is the same as that described in the death narratives (Subject 083696).



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There is no clear pattern to the clinical presentation of the CV events across these four subjects and it is therefore difficult to make conclusions that the events were actually *caused* by Relistor.

***Subject 083624***

59 yo M w/ OIC, complex regional pain syndrome, HTN, hyperlipidemia, tobacco use, and GERD was taking methadone for pain management. He experienced SAEs of MI on study Day 6, congestive heart failure on study day 43 and worsening HTN on study day 57. The subject experienced severe abdominal cramping, moderate nausea, diarrhea, sweating, rhinorrhea, muscle twitching, hot and cold flashes, and lacrimation after the *first injection* and thereafter, for the first 2 wks. The subject remained on a consistent dose of methadone, 125 mg TID, throughout the 2 week period.

Subject experienced retrosternal chest pain at 2 am on study Day 6, which woke him from sleep. He took ASA and the pain subsided, and he went back to sleep. At 11:30 am on study Day 6 the subject developed retrosternal chest pain lasting approximately 10 min with nausea and cold sweating while walking slowly. In addition, the subject reported dyspnea at rest and with exertion for a 2 week period. However, he did not seek any medical attention.

At a study Day 57 during study visit, he was found to be hypertensive with a sitting BP of 180/108 mmHg. ECG revealed marked T wave inversion consistent with a recent septal MI, and he was admitted to the hospital. Chest x-ray revealed CHF and the patient continued to report dyspnea with exertion. Cardiac catheterization revealed total occlusion of the LAD after the first diagonal, with 90% narrowing of first diagonal, and 70-80% narrowing of the RCA.

The subject continued to take opioid analgesics for the complex regional pain syndrome, but Relistor was discontinued for 4 days on study Day 57, and then restarted. On study Day 62, the subject's BP was 146/73 at 15:35. He received Relistor at 15:40 and experienced "moderate to severe painful abdominal cramps," as he had previously with his other Relistor injections. Between 15:50 and 16:00, he had several large bowel movements. He also reported perspiration and some rhinorrhea. The subject's BP at 16:01 was 165/88 and the abdominal cramping lasted for 90 minutes. The subject did not experience any chest pain and his blood pressure at 17:15 decreased to 133/75 mmHg. By this time, the abdominal cramps were very mild and subsided shortly thereafter.

Per the investigator, despite antihypertensive medications, there had been significant increases in BP associated with the painful abdominal cramps. A myocardial perfusion scan revealed a small to moderate anterior septal infarct, moderate to large apical infarct, and EF of 41%. A cardiac MRI was done for pre-bypass assessment and revealed a moderate sized transmural antero-septal infarct with adjacent subendocardial anterior infarct, transmural inferoapical infarct with subendothelial adjacent inferior infarct, and global hypokinesis more marked to the inferoapical region. Subject ultimately underwent triple coronary bypass surgery. The investigator considered MI and worsening HTN related to study medication. Per the investigator, the subject had preexisting untreated "borderline HTN" by history. He was significantly hypertensive when admitted to the hospital and BP normalized when treated. However, with a Relistor challenge, there was a significant increase of his BP during the time he was experiencing painful abdominal cramps (investigator note: "this SAE is an expected physiological response to pain"). Per the investigator, in the setting of a severe narrowing of the LAD, a significant rise in BP might have contributed to the acute cardiac event (since the subject had taken 5 doses of Relistor and with each dose, the subject experienced severe abdominal cramps).

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**Subject 082943**

57 yo F (wt 64 Kg, BMI = 23) with OIC, rheumatoid arthritis, fibromyalgia, peripheral neuropathy, depression, tobacco abuse, and hyperlipidemia who was taking Percocet for pain management, experienced a SAE of inferior wall MI requiring stent placement. She was taking Cymbalta, Neurontin, Soma, Xanax, and amitriptyline. On (b) (6) (study day 306), the subject was hospitalized with complaints of severe retrosternal chest pain. Troponin level was elevated and ECG revealed an inferior wall ST segment elevation. The same day, she underwent a cardiac catheterization with PTCA and stent placement in the RCA and LAD artery. On (b) (6), she was discharged. Last dose of Relistor prior to the MI was on May 5, 2010. Relistor was temporarily discontinued, and was resumed on May 14, 2010 and continued until study completion (last dose received on study day 333).

**Subject 083617**

81 yo F with OIC, fibromyalgia, back pain, obesity (74 kg, BMI = 32), congenital hiatus hernia, diverticulosis, carotid stenosis s/p right carotid endarterectomy, CVA, hyperlipidemia, hypotension, and depression who was taking Hydromorphone Contin and Emtec (codeine-acetaminophen) for pain management experienced SAEs of partial small bowel obstruction and myocardial infarction. She was taking concomitant Plavix, Nexium, diltiazem, lipitor, temazepam, citalopram, and depomedrol.

On (b) (6) (study day 233), the subject took Relistor in the morning and had a "normal" BM. Several hours later, at approximately 12:30pm, she experienced central upper abdominal pain associated with upper abdominal distension, nausea and vomiting. She went to the ER that same evening and an x-ray of the abdomen revealed partial small bowel obstruction (SBO). A nasogastric tube (NGT) was placed and the etiology of the SBO was attributed to adhesions from previous abdominal surgeries (cholecystectomy). Relistor was discontinued during this time, and she did not have any BMs. Patient remained on narcotic analgesics throughout her hospitalization. CT abdomen and pelvis done on (b) (6) confirmed partial small bowel obstruction.

On (b) (6), subject began passing flatus, and the NGT was removed. The same day the subject experienced retrosternal chest pain radiating to the right shoulder. ECG revealed T wave inversion in the central pre-cordial leads, and her initial troponin level was elevated at 0.07ug/L and further increased to 0.1 ug/L twelve hours later. On (b) (6), the patient underwent cardiac catheterization with left ventricular angiogram, which revealed anteroapical akinesia with ejection fraction of 39%, consistent with recent anterior myocardial infarction, but minimal narrowing of the coronary arteries. Etiology of the infarct was unclear. The patient restarted use of Relistor on April 10, 2010 (study day 248) and continued to administer it 2-3 times per week until study completion on July 12, 2010 (study day 341).

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**Strokes (Study 3358)**

There was one investigator reported fatal stroke (Subject 008-080235). This subject is already discussed separately under the discussion of deaths.

**2.2.2.2.3      *Assessment of Opioid Withdrawal (Study 3358)***

The following is a summary of the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), review of opioid withdrawal symptoms among AEs reported in Study 3358:

- There was evidence of opioid withdrawal symptoms in at least eight patients who received study drug on a prn (12 mg daily minimum) basis and discontinued treatment due to these events.
- Hyperhidrosis was reported as the most frequent AE in the cases of those patients who discontinued due to possible opioid withdrawal symptoms.
- There was no definite evidence of increased use of opioids (MED) or consistent pattern to suggest a change in pain intensity scores related to use of study drug.
- The primary study limitation is that it is open label, in addition to the limitations noted for Study 3356.

**2.2.2.2.4      *Vital Sign Assessments***

Supine and standing blood pressure, pulse rate, and weight were evaluated in Study 3356 and Study 3358.

In Study 3356 supine and standing blood pressure, and pulse rate were evaluated at screening, day 1, days 14 and 28 of the double-blind phase, and days 42, 56, 84, and 98 of the open-label phase. In Study 3358 standing and supine BP and pulse rate were evaluated at screening, baseline, and weeks 4, 8, 12, 16, 24, 32, 40, 48, and follow-up or at early discontinuation.

The sponsor pre-specified the following criteria for determining “potentially clinically important” changes in vital signs:

- Pulse rate: Increase of  $\geq 15$  beats/min to  $\geq 120$  beats/min or decrease of  $\geq 15$  beats/min to  $\leq 50$  beats/min
- Systolic blood pressure: Increase of  $\geq 20$  mm Hg to  $\geq 180$  mm Hg or decrease of  $\geq 20$  mm Hg to  $\leq 90$  mm Hg
- Diastolic blood pressure: Increase of  $\geq 15$  mm Hg to  $\geq 105$  mm Hg or decrease of  $\geq 15$  mm Hg to  $\leq 50$  mm Hg

Outlier analyses using various cutoffs for changes in blood pressure or pulse (for individual subjects) were not provided in the application. The vital sign analyses presented in the NDA do not assess for imbalances in outliers between arms in individuals that experienced intermediate changes in blood

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pressure that were not as extreme as the changes pre-specified as clinically important. For example, a patient whose baseline systolic was 140 mm Hg, who shifted to 170 mm Hg, would not be considered clinically important by the pre-specified definition. Similarly, a patient with a baseline systolic BP of 120 mm Hg that shifted to 170 mm Hg, would also not meet criteria for a clinically important change.

However, no meaningful differences in mean or median changes from baseline were observed across assessment time points in Study 3356 and 3358. The total number of subjects who had “potentially clinically important” changes in vital sign measurements did not appear to be different between the treatment groups.

Datasets containing supine and standing blood pressure measurements in both the double blind and open label phase of Study 3356 were analyzed to evaluate for potential increases in blood pressure (from baseline) across treatment arms. In this analysis, the proportion of subjects who had increases in blood pressure (supine/standing and diastolic/systolic) compared to baseline at any study visit did not appear to differ between treatment arms. This suggests that blood pressure effects were neither of a magnitude nor sustained to an extent that was detectable given the BP assessments that were performed. Whether or not more detailed assessments of sitting blood pressure at each study visit both pre and post dose would have detected increases in BP across treatment arms is unknown. It is also not clear what the timing of vital sign assessment relative to Relistor dosing was after Day 1 (only visit when pre and post dose vital sign assessment was performed).

## **2.3    *MOVANTIK (naloxegol oxalate)***

### **2.3.1    NDA currently under review for the proposed indication of treatment of OIC in adult patients with chronic non-cancer pain**

Two identical placebo-controlled efficacy trials (04 and 05) were submitted in support of the efficacy of naloxegol for the proposed indication. Adult patients were eligible for enrollment if they had a confirmed diagnosis of OIC, were receiving a stable maintenance opioid regimen of 30 mg to 1000 mg per day of oral morphine or equianalgesic amount(s) of 1 or more opioid therapies for a minimum of 4 weeks prior to screening for non-cancer-related pain, and reported a history of fewer than 3 spontaneous bowel movements/week and at least 1 OIC-associated symptom at screening (hard/lumpy stools, straining, or sensation of incomplete evacuation/anorectal obstruction in at least 25% of BMs). Studies 04 and 05 were phase 3, randomized, multicenter, double-blind, placebo-controlled, parallel group trials using two doses (12.5 mg and 25 mg) of naloxegol for the treatment of OIC. The study durations were up to 18 weeks consisting of the following periods:

- initial screening period to review inclusion/exclusion criteria and perform baseline screening tests
- 2-week OIC confirmation period to confirm the diagnosis of OIC and stability of the opioid regimen (patients were only allowed to take laxatives for rescue therapy if no BM in previous 72 hours)
- 12-week treatment period
- follow-up visit 2 weeks after the last dose of study drug

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Patients who successfully completed the 12-week treatment period (for Study 04 only) were eligible to participate in a separate 12-week safety extension study (Study 07) during which each patient continued the same study treatment from Study 04 (including placebo). The mean duration of exposure to naloxegol during the placebo-controlled trials was 93.0 days (12.5 mg) and 90.3 days (25 mg).

Study 08 was a 52-week safety study. Patients in Study 08 were randomized, in a 1:2 ratio, to receive usual care (any laxative regimen prescribed by the investigator) or naloxegol 25 mg, respectively, in an open-label fashion. The mean duration of exposure to naloxegol 25 mg was 268.1 days compared with a mean of 296.7 days for usual care patients.

There are three primary analysis sets for the review of safety: the 12-week pool (Studies 04 and 05), the placebo-controlled safety pool (Studies 04, 05, and 07), and the 52-week pool (Study 08). For each safety analysis in the review, the most appropriate pool will be presented and discussed.

### **2.3.2 Cardiovascular-related Adverse Events**

Cardiovascular events were identified as a topic of special interest in the naloxegol phase 3 program for two main reasons: First, there were findings in a phase 1 dog telemetry study of decreased blood pressure and heart contractility associated with the use of naloxegol. Second, a potential CV safety signal (myocardial infarction) was observed in a long-term safety study of Entereg, a drug in the same class as naloxegol. Therefore, the Applicant used a prospective adjudication process and convened a 4-member CV-event adjudication committee (CV-EAC). The CV-EAC was to be an independent and unbiased group of experts responsible for adjudicating pre-specified clinical events. According to the CV-EAC charter, all deaths and non-fatal cardiovascular events (see Table below) were to be adjudicated. In addition, investigators were allowed to select any CV-type SAE/AE for adjudication that they felt were appropriate, and all SAEs that were clearly CV in nature were to be adjudicated. In addition, non-SAE events could also be adjudicated based on either investigator selection or by AstraZeneca medical review.

The CV-EAC was to review and adjudicate the following reported non-fatal cardiovascular events:

- Acute myocardial infarction
- Hospitalization for unstable angina/other angina/chest pain
- Stroke/TIA/Other cerebrovascular events (i.e. subdural/extradural hemorrhage)
- Heart failure requiring hospitalization
- Coronary revascularization procedures (i.e. percutaneous coronary intervention, coronary artery bypass grafting)

In light of the nonclinical findings of decreased heart contractility, extending the event list for adjudication beyond a strict MACE case list to include heart failure might be justified.

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**Table 9. Number (%) of patients with  $\geq 1$  CV outcomes event during the treatment period or post-treatment follow-up as determined by the independent CV-EAC (placebo-controlled pool and Study 08)**

Category	Placebo-controlled pool (Studies 04/07 and 05)			52-week safety study (Study 08)	
	Placebo (N=444)	NGL 12.5 mg (N=441)	NGL 25 mg (N=446)	Usual care (N=270)	NGL 25 mg (N=534)
Patients with any AE submitted to the CV-EAC <sup>a</sup>	7 (1.6)	12 (2.7)	13 (2.9)	11 (4.1)	11 (2.1)
Number of AEs submitted <sup>a</sup>	11	17	15	12	13
Any MACE per CV-EAC	2 (0.5)	2 (0.5)	1 (0.2)	2 (0.7)	2 (0.4)
CV death	0	2 (0.5)	0	1 (0.4)	1 (0.2)
Acute MI	2 (0.5)	1 (0.2)	1 (0.2) <sup>b</sup>	0	1 (0.2)
Stroke	0	0	0	1 (0.4)	0
<b>Other CV events of interest per CV-EAC</b>					
Hospitalization for unstable angina	0	0	0	0	0
Hospitalization for heart failure	0	0	1 (0.2)	1 (0.4)	0

<sup>a</sup> Deaths due to any cause, serious CV AEs, and selected non-serious CV AEs were adjudicated by the independent external CV-EAC, as described in Section 1.1.4.1.

<sup>b</sup> Patient E4010003 (naloxegol 25 mg), a 40-year-old male with a medical history of multiple CV risk factors, had a severe MI on study Day 1, and study drug was discontinued. The MI was reported as resolved on Day 3. The CV-EAC asked for additional information regarding this patient and received the following information from the study site: The patient died approximately 16 months after the MI, presumably due to aortic dissection, hypoxic respiratory failure, and renal failure. This death is not captured in the clinical database and is therefore not included in either Study 04 or pooled data presentations.

AE Adverse event; CV Cardiovascular; CV-EAC Cardiovascular Event Adjudication Committee; MACE Major adverse cardiovascular event; MI Myocardial infarction; NGL Naloxegol.

Electronically copied and reproduced from the naloxegol NDA, Summary of Clinical Safety, p 63

The adjudicated events in Table 9 do not represent unique patients; however, only one patient experienced two events. A 73 y/o male had an MI on day 16 and CV death on day 19 in the 12.5 naloxegol group of the placebo-controlled pool. All other events in the table represent unique patients.

In the placebo-controlled 12-week pool, the incidence rate of MACE was 0.5% in both the placebo and naloxegol 12.5 mg treatment groups (2 patients in each group). The incidence of MACE was 0.2% (one patient) in the naloxegol 25 mg group. In the 52 week safety study, the incidence of MACE events was 0.7% in the usual care arm compared with 0.4% in the naloxegol 25 mg arm.

### **Narratives of MACE in the naloxegol clinical program:**

#### Narratives of patients with CV death

- Study 04 Patient E4068050 was a 73-year-old male in the naloxegol 12.5 mg group with multiple CV risk factors. He had a SAE of acute MI on Day 16 that led to surgery for aortic valve replacement and a coronary artery bypass graft, which was complicated by pneumonia, sepsis, and renal failure. The SAE of cardiac valve replacement on Day 19 resulted in the patient's death on Day 49. This event was adjudicated as a CV death.
- Study 07 Patient E4073006 was a 54-year-old male in the naloxegol 12.5 mg group with diabetes. He was in a serious traffic accident on Day 146 (Day 60 of Study 07), after a "blackout"

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attributed to hyperglycemia. The patient refused to be admitted to the hospital and left the hospital against medical advice. On Day 147, the patient was found dead. The autopsy listed the cause of death as ischemic heart disease secondary to coronary artery disease. This event was adjudicated as a CV death.

- Study 08 Patient E5228010 was a 30-year-old female in the Usual Care group. She was a rollover patient who had been taking naloxegol 12.5 mg before entering Study 08. On Day 95 of Usual Care treatment in Study 08, the patient died in her sleep, cause of death unknown, and no additional details were available. This event was adjudicated as a CV death.
- Study 08 Patient E8843004 was a 39-year-old female in the naloxegol 25 mg group. She was reported to have a SAE of idiopathic generalized epilepsy on Day 111 that resulted in death. There was no previous history of epilepsy and she was not taking anti-epileptic medication. A brain biopsy is pending. Given the unusual circumstances, a police investigation was to be launched. This event occurred 20 days after she stopped taking study drug on Day 92; reason for study drug discontinuation couldn't be determined. The event was adjudicated as a CV death.
- Patient E4010003 (naloxegol 25 mg), a 40-year-old male with a medical history of multiple CV risk factors, had a severe MI on study Day 1, and study drug was discontinued. The MI was reported as resolved on Day 3. The CV-EAC asked for additional information regarding this patient and received the following from the study site: The patient died approximately 16 months after the MI, presumably due to aortic dissection, hypoxic respiratory failure, and renal failure. This death is not captured in the clinical database and is therefore not included in either Study 04 or pooled data presentations. (\*This case is not included in the Table above.)
- There was 1 death in the Phase I studies of naloxegol. In Study 09, Subject E0001005 (severe renal impairment group), a 61-year old, White male, experienced a post-study SAE of MI that led to death. The patient received a single dose of naloxegol 25 mg on Day 1, had the MI on Day 18, and died on Day 35. While hospitalized, the subject's evaluation revealed multi-vessel coronary artery disease, and a 5-vessel coronary bypass was performed on Day 25. Complications during hospitalization included pericarditis, atrial fibrillation, and pneumonia. Hemodialysis was started during hospitalization. The subject was discharged 14 days after being admitted to the hospital and died of sudden cardiac death in his sleep on Day 35. Other AEs during the study included ecchymosis. Notable medical history included congestive heart failure; Grade 1/6 systolic murmur, right base; Type 2 diabetes, kidney impairment, and hypertension. (Phase 1 studies were not adjudicated and this death occurred after completion of the study).

Narratives of patients with Acute MI

- Study 08 Patient E8732012 was a 64-year-old woman in the usual care group. The patient's relevant medical history included a myocardial infarction, hypertension, anxiety, high cholesterol, coronary artery disease, angina pectoris, gastroesophageal reflux disease, a coronary stent placement in 2003 and 2006 and smoking (quit in 2004). She had a SAE of cardiac peri-infarction ischemia, surrounding apical scar on Day 8 of randomized treatment. The event was considered resolved on Day 99, and was adjudicated as a myocardial infarction.

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- Study 04 Patient E4010003 was a 40-year-old white man randomized to the naloxegol 25 mg group. Past medical history was significant for uncontrolled hypertension, 2ppd smoking history, limited activity level, obesity and hyperlipidemia with “dysmetabolic syndrome” (the patient had a body mass index of 36.4), and “excessive” consumption of energy drinks. The patient had a SAE of myocardial infarction on Day 1 of randomized treatment. The patient subsequently withdrew from the study. The event was adjudicated as a myocardial infarction.
- Study 05 Patient E5237018 was a 60-year-old American Indian or Alaska Native man randomized to the placebo group. Past medical history was significant for hypertension, coronary artery disease, left bundle branch block, diseases of tricuspid valve, peripheral vascular disease, 5 vessel coronary artery bypass graft (CABG) in 2008, tobacco use, dyslipidemia, and stable angina. The patient had a SAE of chest pain with shortness of breath and sweating. The event was adjudicated as an acute myocardial infarction.
- Study 05 Patient E5265013 was a 42-year-old white man randomized to the placebo group. Past medical history included hypercholesterolemia and depression. He had a SAE of non-ST elevated myocardial infarction on Day 34 of randomized treatment. He was found lying in bed semi-conscious and unable to be fully aroused. Stool was noted, but there was no report of blood. Upon paramedics’ arrival, the patient was confused and was taken to the emergency room (ER). He was admitted to hospital for non-responsiveness. Final diagnosis was non ST elevated myocardial infarction. The event was adjudicated as an acute myocardial infarction.

Narrative of patient with Stroke

Study 08 Patient E8873013 (usual care group) was a 48-year-old white woman who had a serious adverse event of frontal lobe infarction (MedDRA: ischaemic cerebral infarction) on Day 74 of randomized treatment. The adverse event required treatment: atorvastatin and warfarin. The event was continuing at the time of study withdrawal. Relevant medical history included hypertension, smoking half a ppd and bilateral carotid artery obstruction. Relevant concomitant medications included aspirin, lisinopril and hydrochlorothiazide. She had no history of a transient ischemic attack or stroke.

The patient presented after a fall at home while sitting at the kitchen table in what appeared to be a postictal state. She clearly demonstrated significant left-sided weakness and numbness. She was also unresponsive to noxious stimuli. A computerized tomography and MRI of the brain were performed. The MRI revealed a right frontal lobe infarction. However, a neurologist felt that the MRI finding did not correlate with her symptoms of left lower limb weakness and numbness, raising the question of possible conversion reaction/stress response. She had a significant psychiatric history with bipolar affective disorder. The neurosurgeon also considered the findings on spinal imaging inconsistent with the patient’s left lower extremity weakness and numbness. On the day of discharge, the patient was noted to have spontaneous use of her left lower limb. The event was adjudicated as an ischemic (non-hemorrhagic) stroke.

The total number of events was low; therefore, it is difficult to make specific conclusions regarding the association of naloxegol with MACE events.



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### **2.3.3 Blood pressure-related Adverse Events**

Changes in blood pressure were regarded as AEs of special interest given the changes in BP seen in dog telemetry studies. Changes in BP were not adjudicated because, according to the Applicant, there are no established adjudication criteria for changes in BP. The specific AEs related to BP were categorized as decreased BP, syncope, and increased BP. In addition, "increased BP" was further analyzed as the following: systolic  $\geq 160$  mm Hg and  $\geq 20$  mm Hg increase or systolic  $\geq 180$  mm Hg; diastolic  $\geq 95$  mm Hg and  $\geq 10$  mm Hg increase or diastolic  $\geq 120$  mm Hg. Decreased BP was analyzed as the following: systolic  $\leq 100$  mm Hg and  $\geq 20$  mm Hg or systolic  $\leq 80$  mm Hg; diastolic  $\leq 50$  mm Hg and  $\geq 10$  mm Hg decrease or diastolic  $\leq 45$  mm Hg. "Hypertension" was defined as BP greater than 140/90.

Blood pressure and pulse were to be measured at screening and then at each visit (measurement could happen at any time during the visit). At Visit 1 and Visit 3, patients were to have blood pressure measured pre-dose and one hour post-dose.

There was a small numerical imbalance, not favoring naloxegol, in the incidence of high blood pressure, low blood pressure, and syncope in the phase 3 trials (in favor of placebo). See Table 10 below.

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**Table 10. Number (%) of patients with  $\geq 1$  AE related to BP changes during the treatment period (placebo-controlled pool and Study 08)**

<u>Topic/ Preferred term</u>	<u>Placebo-controlled pool (Studies 04/07 and 05)</u>			<u>52-week safety study (Study 08)</u>	
	<u>Placebo (N=444)</u>	<u>NGL 12.5 mg (N=441)</u>	<u>NGL 25 mg (N=446)</u>	<u>Usual care (N=270)</u>	<u>NGL 25 mg (N=534)</u>
<b>Decreased BP</b>	<b>3 (0.7)</b>	<b>2 (0.5)</b>	<b>6 (1.3)</b>	<b>5 (1.9)</b>	<b>5 (0.9)</b>
Hypotension	1 (0.2)	2 (0.5)	3 (0.7)	1 (0.4)	1 (0.2)
BP decreased	2 (0.5)	0	2 (0.4)	3 (1.1)	3 (0.6)
Orthostatic hypotension	0	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)
<b>Syncope</b>	<b>0</b>	<b>2 (0.5)</b>	<b>2 (0.4)</b>	<b>0</b>	<b>3 (0.6)</b>
Syncope	0	2 (0.5)	1 (0.2)	0	3 (0.6)
Presyncope	0	0	1 (0.2)	0	0
<b>Increased BP</b>	<b>5 (1.1)</b>	<b>10 (2.3)</b>	<b>13 (2.9)</b>	<b>12 (4.4)</b>	<b>21 (3.9)</b>
Hypertension	3 (0.7)	6 (1.4)	8 (1.8)	9 (3.3)	13 (2.4)
BP increased	2 (0.5)	4 (0.9)	3 (0.7)	3 (1.1)	7 (1.3)
Accelerated hypertension	0	0	1 (0.2)	0	0
Malignant hypertension	0	0	1 (0.2)	0	0
BP diastolic increased	0	0	0	0	1 (0.2)

AE Adverse event; BP Blood pressure; MedDRA Medical Dictionary for Regulatory Activities; NGL Naloxegol;  
SOC System organ class.

Source: Module 5.3.5.3, Appendix 2.7.4.7, Table 4.3.3.4; and Module 5.3.5.2, Study 08 clinical study report,  
Table 11.3.6.3.1.

Source: Electronically copied and reproduced from the Naloxegol NDA, Summary of Clinical Safety, p 64/109

In the placebo-controlled 12 week pool, 2 (0.5%) naloxegol 12.5 mg patients and 6 (1.3%) naloxegol 25 mg patients reported decreased BP compared with 3 (0.7%) placebo patients. During the 52 week safety study, the incidence of decreased BP was lower in the Naloxegol 25 mg group than the usual care group, 0.9% and 1.9%, respectively.

Syncope was not reported by any placebo patients in the placebo-controlled pool. Similarly, none of the usual care patients in the 52-week study reported syncope. In contrast, four Naloxegol patients reported syncope during placebo controlled studies (one of these was reported as pre-syncope) and 3 Naloxegol patients reported syncope during the 52-week safety study. No patient reporting a syncopal event also reported a CV AE or a potentially clinically important ECG event near the time of the syncopal event. All patients who reported a syncopal event were on concomitant medication known to be associated with syncope and/or had a medical history of syncope or a diagnosis to which a syncopal event could be reasonably attributed. The patient who reported pre-syncope also reported a concurrent AE of "infection".

Increased BP was observed in more patients taking Naloxegol than placebo patients in the placebo-controlled pool. Specifically, 5 patients (1.1%) taking placebo had increased BP compared with 10 patients (2.3%) taking 12.5 mg Naloxegol and 13 patients (2.9%) taking Naloxegol 25 mg. In the 52 week study, the incidence of increased BP was slightly higher in the usual care group. A total of 12 patients (4.4%) in the usual care group had increased BP compared with 21 patients (3.9%) taking Naloxegol 25 mg. See Table 10 above.

The incidence of hypertension was slightly higher in patients taking naloxegol in the placebo-controlled pool. Specifically, hypertension was observed in 3 patients (0.7%) taking placebo in the placebo-controlled pool, compared with 6 patients (1.4%) taking Naloxegol 12.5 mg and 8 patients (1.8%) taking Naloxegol 25 mg. Additionally, there was one patient in the post-treatment period (randomized to 25

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mg Naloxegol) that had an AE of hypertension. Of the 9 patients randomized to the Naloxegol 25 mg group who had an AE of hypertension, 7 had either a documented history of hypertension or were taking a blood pressure medication, in addition to having at least 1 other CV risk factor. Additionally, 7 of the 9 patients had elevated blood pressure at baseline. None of the 9 hypertension AEs was associated with an AE related to opioid withdrawal or was adjudicated as a CV event of interest. Two of the 9 events in the Naloxegol 25 mg group were SAEs:

- Patient E5212025- 58 year old black female with AE of malignant hypertension. Baseline BP was 169/82. She had multiple CV risk factors, and possible noncompliance with cardiac medications.
- Patient E524006- 69 year old white female with AE of accelerated hypertension. Baseline BP was 185/96. She had a history of diabetes and noncompliance with BP medication.

During the 52-week safety study, the incidence of hypertension was slightly lower in the Naloxegol 25 mg group than in the usual care group. Specifically, 13 patients (2.4%) in the naloxegol 25 mg group and 9 patients (3.3%) in the usual care group had an adverse event of hypertension.

#### **2.3.4 Opioid withdrawal-related Adverse Events**

For a more detailed discussion of the association of opioid-withdrawal events with the use of naloxegol, please see the full consult review (29 January 2014) by Dr. Elizabeth Kilgore, Division of Analgesia, Anesthesia, and Addiction Production (DAAAP). This review can be found in Appendix 4.4. A brief summary of the review is provided below.

DAAAP reviewed the key phase 3 trials in the naloxegol NDA to determine whether there was evidence of opioid withdrawal in subjects receiving naloxegol compared to placebo, and whether naloxegol appears to have an effect on analgesia.

In all analyses, there was an imbalance between study drug and placebo in the 12-week placebo controlled studies, with more patients in the naloxegol-treated arm identified as having possible drug withdrawal syndrome (DWS) or at least three preferred terms (PTs) potentially related to DWS compared to placebo.

- In the clinical trials, there was evidence that symptoms of possible opioid withdrawal may be associated with the use of naloxegol in a small number of patients receiving chronic opioid treatment, with an incidence in study drug arms greater than that in placebo, using the following criteria and analyses:
  - Using the Applicant's analysis of patients identified with the Standardized MedDRA Query (SMQ) term of possible DWS, in the 12-week, placebo- controlled studies (04 and 05) there was one patient in the placebo group (0.2%) compared to 2 (0.5%) in the NG 12.5 mg group and 5 (1.1%) in the NG 25mg group identified by the investigator as experiencing possible DWS.
  - Using broader criteria (based upon Agency advice) for determining potential opioid withdrawal syndrome, defined by the presence of  $\geq 3$  preferred terms (PTs) potentially related to opioid withdrawal, the following incidences of potential opioid withdrawal were observed:

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- In Study 04 the incidence of  $\geq 3$  PTs potentially related to DWS in placebo, NG 12.5 mg, and NG 25 mg groups was 5 (2%), 4 (2%), and 10 (5%), respectively.
- In Study 05 the incidence of  $\geq 3$  PTs potentially related to DWS in placebo, NG 12.5 mg and NG 25mg was 3 (1%), 7 (3%) and 20 (9%), respectively.

The above criterion is sensitive but not specific for identifying possible clinical DWS, in that many patients experienced  $\geq 3$  PTs potentially related to DWS but all of the terms did not occur on the same day or they were gastrointestinal terms only.

- Using narrower criteria that may be more clinically relevant (as determined by the DAAAP reviewer) patients who experienced  $\geq 3$  PTs potentially related to opioid withdrawal occurring on the same day and that were not all GI PTs (i.e., GI+ non-GI or all non-GI terms), the total cases identified in the pooled 12-week, controlled studies were 1 (<1%), 5 (1%) and 14 (3%) for the placebo, NG 12.5mg, and NG 25mg groups, respectively.
- In Study 07, the incidence of  $\geq 3$  PTs potentially related to opioid withdrawal using these clinically relevant criteria was 0, 1 (1%), and 1 (1%) in placebo, NG 12.5mg, and NG 25mg groups, respectively.
- In the open label study (08) the incidence of possible opioid withdrawal syndrome was 3/270 (<1%) in the Usual Care group and 10/534 (2%) in the naloxegol 25 mg group.
- Naloxegol does not appear to have an effect on analgesia, based on analyses of opioid dose and pain scores during the trials. However, these analyses were descriptive in nature as the studies were not designed to assess these endpoints in a statistical manner.

Six patients in the 12-week placebo-controlled trials 04 and 05 had possible opioid withdrawal syndrome ( $\geq 3$  potential opioid withdrawal PTs occurring in the same day with not all 3 terms being GI-related) and at least one CV PT. However, only one patient who met the criteria for possible opioid withdrawal syndrome also met adjudication diagnostic criteria for a CV event. The event was adjudicated as “other chest pain”. The CV PTs in these 6 patients included palpitations (n=3), increased heart rate and orthostatic hypotension. In these trials, there were no patients with MACE events that also experienced possible opioid withdrawal syndrome on the same day.

## **2.4 Other Opioid Antagonists for OIC**

The sponsors of TD-1211 (Theravance, Inc.) and naloxone (Develco) have agreed to present nonclinical and limited clinical data for their respective products. This information has been provided to the committee to describe any pertinent differences in the pharmacological activity of these drugs, as well as to contribute data relevant to discussions surrounding the safety of this class. FDA has not had an opportunity to fully evaluate these data.

## **3 Assessment of Cardiovascular Safety**

### **3.1 General Considerations**

The evaluation of safety is generally based upon the totality of the data available in the NDA, including *in vitro* data, non-clinical data, and pharmacokinetic data, and clinical data. Safety assessments in phase 3 trials may include assessments that target specific organ systems if there is an anticipated safety

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concern, based on information known about the drug from nonclinical data and early phase clinical trials, and/or information known about other drugs in the class. All of the potential safety concerns may not be known prior to the conduct of phase 3 trials, and sometimes not until after a product is marketed.

The size, duration, and design of efficacy trials conducted to support NDA submission may be inadequate to identify a meaningful “signal”. Biological plausibility of a particular adverse reaction may help inform decision making regarding design of a pre-approval development plan to detect both a signal and to exclude a specific increase in risk. In addition to sample size and duration of treatment, the presence of a control arm and a pre-specified plan to ascertain events would ideally be prospectively addressed in the development plan.

When there is an interest in understanding the effects of treatment on specific adverse drug reactions (e.g., CV events), one must be aware that the observed treatment effect is a combination of both the true treatment effect and random noise. When few events are observed in a clinical trial, because the events are relatively uncommon in the patient population (as was the case with the Entereg OIC chronic non-cancer pain trial), or because the trial is short in duration, there will be too few events to draw meaningful conclusions on causality. When there is no concurrent control group, causality is extremely difficult to establish, unless the events would be exceedingly rare in the patient population. Powering a clinical trial or development program to observe a sufficient number of adverse drug reactions reduces the risk of making false conclusions on the observed data but can be difficult or infeasible if the event rate in the patient population is low.

As mentioned previously, efficacy trials for treatments of OIC as currently designed are relatively small in size and treatment duration (ranging from 400-700 subjects treated for up to 3 months). Efficacy trials have not always included a prospective plan to assess for, identify and evaluate MACE. In the case of Entereg, a retrospective analysis that utilized an adjudication committee was performed. The usefulness of such an analysis to rule out a CV safety signal is limited due to missing data and the retrospective nature of the assessment. There are limited clinical data available for mu opioid receptor antagonists for treatment of OIC upon which to judge whether or not the signal detected in the Entereg OIC program was a true signal, or simply due to chance.

Currently, DGIEP recommends that sponsors developing mu opioid receptor antagonists for OIC prospectively define and collect information relevant to the assessment of MACE events. In addition, DGIEP recommends a pre-specified plan for use of external adjudication committees. However, even with a pre-specified plan for ascertainment of CV events, given the typically limited sample size and duration of the controlled studies that are conducted to support approval, it is difficult to make valid conclusions regarding the significance of rare events, even if numerical imbalances among treatment arms are observed.

An approach to excluding a specific incremental increase in CV risk associated with a drug would be to increase the sample size in the intended study population and follow them for a sufficient amount of time in order to observe a sufficient number of CV events. The size of the incremental increase in CV risk of interest to rule out may vary depending on whether the goal is to detect a signal vs. describe the risk, the amount of risk that can be accepted based on the underlying condition being treated by the drug, and by feasibility. Significant resource constraints (e.g., time, financial concerns, limited patient population) may make such trials impractical prior to marketing a drug. Smaller study sample sizes, resulting from enriching the patient population with subjects who have a greater baseline CV risk, such

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as older patients or those with existing CV disease or known CV risk factors (e.g., diabetes or hypertension), could provide sufficient CV events to evaluate increased CV event rate associated with the drug (using an appropriate control or placebo). In considering the baseline cardiovascular risk of the population, it should be noted that in OIC development programs for a chronic non-cancer pain population, historically the majority of patients that enter the trials are female (~ 60%), with a median age of approximately 50- 53 years. (Refer to the table in Appendix 4.1 for a summary of the phase 3 study populations across various drugs evaluated in the setting of OIC associated with chronic non-cancer pain.) However, the patients who have enrolled in OIC programs that will be presented at this meeting had prevalent co-morbid conditions associated with increased cardiovascular risk, including obesity (BMI >30), diabetes, smoking, hypertension and/or lipid disorders (see individual sponsors' briefing packages).

### **3.2 *Approaches to Assessing the Cardiovascular Safety of Drugs***

The following sections will consider how postmarketing surveillance, epidemiologic studies and prospective randomized clinical trials (RCTs) can contribute to our understanding of particular safety signals. In addition, specific considerations for sample size calculations for a Cardiovascular Outcomes Trial (CVOT) are presented.

#### **3.2.1 FAERS**

The FDA Adverse Event Reporting System (FAERS) is a large post-marketing safety reporting database. FAERS contains over 7 million adverse event reported to the FDA by healthcare providers, manufacturers, and consumers.<sup>16</sup> Although the quality of FAERS reports varies, many case reports contain information that suggests causal associations between drugs and adverse events. The utility of FAERS to investigate causal associations differs by the type of medication and adverse event. In general, FAERS case reports might generate drug-event hypotheses that can be tested in other data sources. Major limitations of FAERS with respect to investigating major cardiovascular events associated with mu-opioid receptor antagonists include the voluntary reporting of events to FAERS, the possibility that sudden cardiac death may be underreported in FAERS, the potential for confounding by other medications or comorbidities, and lack of a defined numerator and denominator. Thus, FAERS should be used neither to estimate the risk of cardiovascular events nor to compare the risk of cardiovascular events between mu-opioid receptor antagonist products.

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<sup>16</sup>

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070093.htm>

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### **3.2.2 Mini-Sentinel**

Mini-Sentinel is a five-year contract that is a pilot of the Sentinel Initiative. It involves electronic health data from 18 partners including Aetna, HealthCore, Humana, Optum, several members of the HMORN, several Kaisers, and Medicaid data from Washington and Tennessee held by Vanderbilt University. It includes data on more than 150 million lives for varying periods of time. There are data available from 2000 to the present, although all partners do not have data for all time periods. The Mini-Sentinel web site<sup>17</sup> provides a great deal of relevant information.

Mini-Sentinel has excellent data on dispensing of outpatient oral medications and outpatient and inpatient diagnoses and procedures. It does not have data on inpatient dispensing of oral medications. Thus, if oral mu-opioid receptor antagonists were given in the inpatient setting, Mini-Sentinel would not capture their use. Some outpatient laboratory and vital sign data are available. However, this is only available for some enrollees so it should not be assumed to be available for populations of interest without checking. If administrative data (such as an insurance claim) exist for an individual dispensing, diagnosis, or procedure, the information will be in the Mini-Sentinel Distributed Database. The data can be queried in a number of ways:

- Protocol based assessments are essentially complete epidemiologic studies that allow for adjustment for measured confounding, complex design and statistical approaches.
- PROMPT tools allow for partial adjustment for confounding and complex outcomes algorithms. These tools focus on sequential evaluation of safety endpoints for NMEs and are currently being used for the first time.
- Modular Programs are similar to SAS Procs in terms of being fixed analytic tools that require input parameters. These have very limited adjustment for confounding, but do include stratification by age, sex and year, and provide reasonably rapid results, generally within about three weeks. They can be useful if there are not enough exposed individuals, or enough exposure time, to benefit from a protocol based assessment
- Summary tables provide limited data from pre-calculated tables. Each table relates to one variable type – drug use, diagnosis, or procedure. Information from tables cannot be linked.

The definition of strict MACE includes non-fatal stroke, non-fatal MI, and CV death. CV death may occur in-hospital or out-of-hospital. Mini-Sentinel is currently assessing outcomes of MI, stroke, and heart failure in protocol-based assessments. Mini-Sentinel does not currently have the ability to assess deaths in the absence of associated claims billing or administrative data. However, a project that will develop a link with the National Death Index (NDI) to generate an algorithm for Sudden Cardiac Death (SCD) is in the early planning stage. Another potential limitation to Mini-Sentinel data is the possibility of that claims from elderly patients given mu-opioid antagonists may be incompletely captured in the data since these data sources are not linked to Medicare, the primary payer among this population. In summary, although Mini-Sentinel generally benefits from large sample sizes, it is difficult to produce interpretable results where, 1) the study drug is primarily administered in-patient, 2) out-of-hospital cardiac death is a critical outcome, and 3) elderly patients are the primary users. Therefore assessing the association between mu-opioid antagonists and MACE would be very difficult in Mini-Sentinel.

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<sup>17</sup> <http://www.minisentinel.org>

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### **3.2.3 Post-marketing observational studies**

Observational studies provide a method to assess cardiovascular risk using non-randomized data, typically in the form of electronic healthcare data (EHD). EHD come from large insurance companies (e.g. Humana, Aetna), local/regional health systems (e.g. Kaiser Permanente, Harvard Pilgrim), or government-sponsored health care systems (e.g., Medicare, Clinical Practice Research Datalink [data from United Kingdom's National Health Service]). EHD sources are available in the United States and abroad. These data usually consist of either administrative claims data, which reflect only billable care, or electronic medical records, which support clinical care and often contain more complete information than administrative claims data. Some EHD sources, including data from the U.S. Veterans Administration, are claims-based data with the capability to access medical records. Both forms of EHD generally contain information on healthcare-related encounters as well as prescription records, while electronic medical record data more often contains test results, radiology results, physician notes, and patient lifestyle factors (e.g., smoking). However, quality and size of these data vary significantly between data sources. For example, one data source might contain a large enough number of exposed individuals to statistically detect a MACE relative risk of 2.0 but lack important information such as troponin test results, BMI, or smoking, which would render the findings (from a numerical standpoint) difficult to interpret. Conversely, another data source might contain the data necessary to reliably and accurately assess MACE events but have limited statistical power to detect an increased relative risk for MACE events.

Use of EHD to conduct post-marketing observational studies of increased cardiovascular risk is advantageous in several aspects. First, many EHD sources contain large numbers of individuals (>1,000,000) for analysis. Large databases increase the likelihood of observing more individuals exposed to the drug(s) of interest, thereby increasing the ability to detect rare events and smaller increases in cardiovascular risk. Second, relative to pharmacovigilance methods, EHD allows the investigator to design, initiate, conduct or modify analyses. For example, the investigator might wish to evaluate confounding by specific variables, modify the scale of key variables (e.g., binary, continuous, etc.), vary regression and/or patient matching techniques, conduct sensitivity analyses with important exclusion criteria, and stratify analyses on derived variables such as number of cardiovascular risk factors. Finally, EHD sources consisting of electronic medical records might contain important information on confounding variables, such as BMI and smoking. Adjustment for or stratification on these variables might reduce the possibility of confounding, resulting in more valid risk estimates.

Advantages notwithstanding, EHD also present several significant limitations/disadvantages for investigating associations between mu-opioid receptor antagonists and major adverse cardiac events. The number of patients available for analysis varies by database. Even in large databases, a newly-approved drug and/or a drug indicated for use in a very specific population might not contain enough exposed individuals to analyze rare cardiovascular events. Similarly, to accrue sufficient patient exposure might take several years post-marketing before analyses are feasible. EHD sources consist of non-randomized observational data. Thus, confounding by drug indication, disease severity, or other important variables might result in invalid risk estimates since patients given one treatment might differ significantly with respect to these important variables than patients given a comparator treatment. Statistical techniques such as multivariate regression or propensity score matching can help minimize differences between treatment cohorts; however, the investigator is limited by the data available in the EHD sources. Administrative claims data sources usually lack information on important cardiovascular risk factors such as BMI and smoking, and lack information on over-the-counter medication use, such as



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aspirin. Electronic medical record sources are more likely to contain data on BMI and smoking, but may not be readily accessible or complete. Additionally, only EHD sources with access to a patient medical charts or linkages to disease registries would allow for validation of outcomes diagnosis, a necessary step to prevent outcomes misclassification. Some MACE outcomes (e.g., acute myocardial infarction) may have been previously validated in a particular database, potentially obviating chart review for these outcomes. However, given the lag time that exists in obtaining death certificates to validate death in claims data, EHD is limited in its ability to study newly approved mu-opioid antagonists and cardiovascular death in a timely manner. Finally, while observational post-marketing studies are generally less expensive and quicker to conduct than clinical trials, it might take several years to complete an observational study given the time required to develop a protocol, receive data access and IRB approval, accrue sufficient data, conduct analyses, and interpret study findings.

In some circumstances, post-marketing observational studies using EHD might represent a reasonable alternative to RCTs in conducting analyses of cardiovascular risk, especially if the events are rare and required exposure duration is long. However, it is imperative to select a database that is 1) large enough to provide adequate statistical power to detect rare cardiovascular events, 2) provides complete information on cardiovascular risk factors, and 3) allows for validation of cardiovascular outcomes. Another post-marketing observational risk-assessment design method is a prospective clinical cohort study. These studies use clinical and interview data collected directly from the subject rather than EHD. An investigator might identify and recruit a cohort of patients initiating the drug of interest and a cohort of patients taking a comparator drug. All baseline and medical history data collection occurs at enrollment. Subjects regularly follow up with investigators throughout the study period to assess any changes in treatment, comorbidity, or the development of the study outcomes. This design is similar to a randomized clinical trial (RCT) with respect to the collection of subject information, subject follow up, and the significant resources required to complete such a study. However, unlike an RCT, subjects in a prospective cohort study are not randomized to treatment. Thus, the drug's efficacy or perceived safety might influence the subjects' choice of treatment versus comparator. As a result, an appropriate comparator might be difficult to identify if most subjects with the indication have switched to the more effective treatment. Likewise, if a safety concern with the treatment exists, patients at higher risk of the event preferentially select other treatments.

Losses to follow-up are another potential limitation of the prospective cohort design. If losses to follow-up are differential between cohorts, selection bias might result. While EHD studies also face the potential for losses to follow-up, more complete capture of health-related claims during follow-up that do not require regular investigator contact mitigate the possibility of differential loss to follow-up or fewer total person-years of follow-up.

Finally, recruitment of enough subjects to detect small increases in relative risk of rare cardiovascular adverse events is another limitation of the prospective cohort design. Taken together, a prospective cohort study provides an opportunity to collect important clinical and lifestyle information on subjects that EHD studies often do not permit. However, this gain in important clinical information might come at the expense of much smaller cohort sizes resulting in inadequate statistical power to detect rare cardiovascular events.

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### **3.2.4 Randomized, Controlled Trials**

Randomized controlled clinical trials (RCTs) can provide the best evidence regarding the association between mu-opioid receptor antagonists and major adverse cardiovascular events. Randomization typically achieves cohort balance, thereby minimizing confounding by both measured and unmeasured covariates. As a result, RCTs are more interpretable than observational studies for small risk increases, where unmeasured confounding may account for the observed increases. Moreover, investigators can prospectively collect all data on cardiovascular risk factors and readily ascertain and adjudicate all adverse cardiovascular endpoints. However, significant disadvantages to RCTs make them less feasible under some circumstances. First, the challenge of recruiting enough participants in a safety trial to detect rare cardiovascular events may be difficult. This problem is exacerbated if the treatment is tested in a population with overall lower cardiovascular risk, including those less than 65 years of age or those with few cardiovascular risk factors. Second, the time to complete the trial from protocol development through patient follow-up and obtaining study results takes significantly longer relative to a retrospective observational post-marketing study using EHD. Third, as with prospective cohort studies, differential losses to follow-up may introduce bias that must be addressed. Fourth, retrospective observational studies using EHD use existing administrative claims or electronic medical records data and require no additional patient visits. In comparison, the significant additional resources required to conduct a trial may pose a greater challenge. Finally, if clinical equipoise is not present, treatment randomization may be difficult or unethical.

Thus, RCTs are the most methodologically appropriate design for investigating major cardiovascular risks associated with mu-opioid antagonists. However, challenges to achieving adequate statistical power to detect rare events coupled with the immense resources required to perform such trials serve as barriers to using RCTs in this setting.

### **3.3 *Design of Randomized, Controlled Cardiovascular Outcomes Trials and Statistical Considerations***

For the assessment of cardiovascular safety, dedicated, randomized controlled cardiovascular outcomes trials (CVOT) are considered to be the gold standard in estimating the risk of an investigational treatment relative to an appropriate comparator. Such trials are typically designed as event-driven trials with the objective of ruling out an excess risk measured by an upper bound of a 95% confidence interval for the risk measure. Despite being the gold standard in assessing risk of a product, the feasibility of conducting such trials limits their use in many situations.

The feasibility of such trials often revolves around the large size and the long duration of the trials needed to accrue a sufficient number of events to attain a desired level of statistical power. Related to the feasibility of the trial, an appropriate control needs to be identified that has an accepted level of cardiovascular risk as well as an acceptable level of tolerability to permit its use for the duration of the trial. Moreover, long-term compliance with a product can be an issue if the need for the product changes or if patients discontinue the assigned drug because of side effects. The following sections discuss these issues in more detail, and illustrate FDA's experience in CVOT in drugs being developed for the treatment of Type 2 Diabetes Mellitus, where new therapies are required to exclude evidence of a prescribed level of CV risk.

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Sample size calculation

Dedicated cardiovascular safety trials are commonly designed as event-driven trials which are a type of information-based clinical trial design. A feature of information-based designs is that the statistical information is fixed in advance rather than using the number of subjects to determine the size of trial. The sample size of an outcomes-driven trial depends on several elements:

- A risk margin to rule out (e.g. hazard ratio risk margin),
- The assumed true risk of the treatment related to the control (e.g. the true relative risk of treatment relative to control), and
- The desired level of power (typically 90% power for CV safety outcomes trials as effect sizes for CV safety are generated from a single trial).

In order to observe the desired number of events,  $N$  subjects are followed for a planned amount of time, say  $t$  years. Thus, the study is powered around the number of events and the amount of patient-years to observe these events and can be estimated by  $N*t$ .

Figure 1 below presents sample size calculations in the form of patient years based on using HR risk margins ranging from 1.5 to 4.0, and event rates ranging from 1.0 to 2.5 per 100 patient-years of exposure, with 90% power. Figure 1 shows that as the number of events needed to rule out a HR increases, the HR risk margin decreases. The expected number of patient-years is proportional to the number of events needed, and is a function of the background rate of events; a lower background rate implies that more patient years are needed to observe events.

As an example, consider the RELISTOR OIC program. The seven potential MACE events in Study 3358 occurred in a total exposure of 667 patient years. This provides a background MACE rate of 7 per 667 patient years, or approximately 1 per 100 patient-years. Therefore, a total of 8,800 patient years would be needed to observe 88 events required to rule out a HR risk margin of 2.0 with 90% power.

Because clinical trials depend on the number of observed events to be adequately powered, when possible, it is desirable to “enrich” the study population with subjects who are most likely to have MACE events, such as subjects with known cardiac risk factors, e.g., hypertension, diabetes and/or elevated cholesterol. Enriching study populations can be challenging when scant data is provided on the cardiac risk factors within the indicated population; estimating the “background” MACE event rate can be a challenge.

The literature provides some limited data for estimating the background MACE rate in chronic opioid users. Carman et al<sup>18</sup> estimated the incidence of myocardial infarction (MI) among chronic users of opioid therapy for non-malignant pain. In this claims based analysis, 1067 MIs occurred in 176,732 person-years, providing a background MI rate of 0.6 / 100 person-years. Note that this would result in 4 MIs in the 667 person-years in RELISTOR OIC program, which matches the number of MIs observed (4). Since strict MACE includes MI, stroke and CV death, the study by Carman et al would appear to support an apparent background MACE rate of approximately of 1 / 100 person-years.

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<sup>18</sup> Pharmacoepidemiology and Drug Safety, 2011; 20: 754–762

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**Figure 1. Patient years needed to rule out a hazard ratio with 90% power**

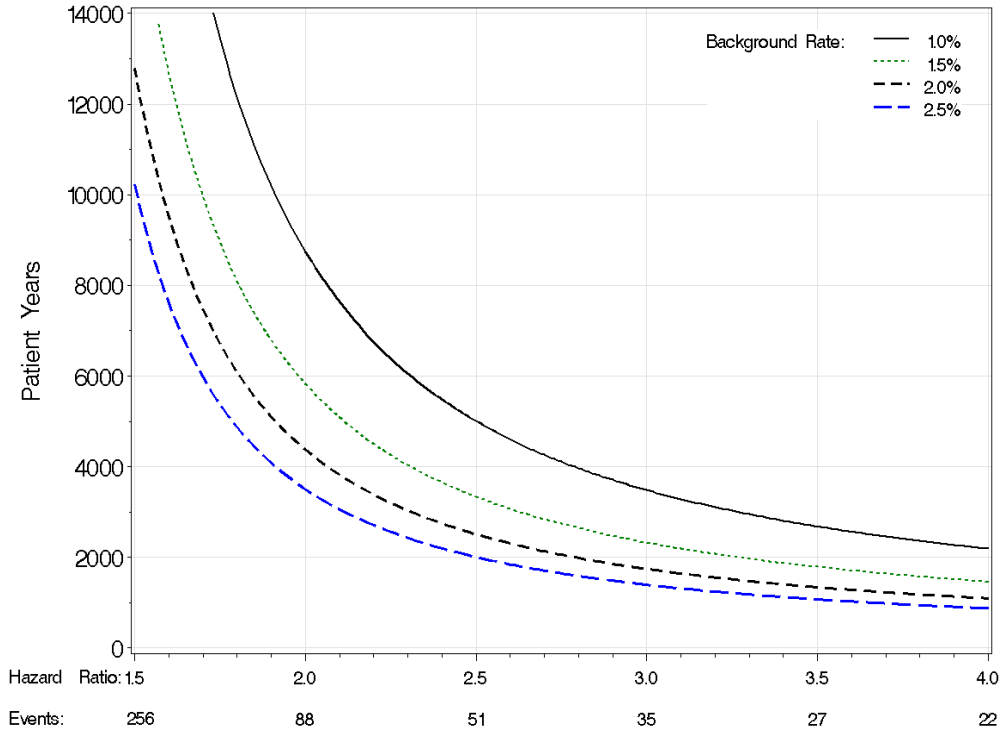


Table 11 presents additional information regarding sample size calculations from those shown in Figure 1. It shows how a combination of HR margins and MACE control (background) rates translates into a risk difference. Table 11 also shows the maximum point estimate for the HR that would need to be observed such that the upper bound of the 95% confidence interval around the HR point estimate is less than or equal to the HR margin. To coincide with the previous example, the shaded cells in Table 11 show that an event rate of 1.0 per 100 patient years and a HR margin of 2.0 translate into a risk difference of 1.0%. The shaded cells also show that the point estimate of the HR of MACE between treatment and control needs to be 1.32 or lower in order for the upper bound of the 95% confidence interval of the HR to be smaller than the HR margin of 2.0.

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**Table 11. Sample size calculations using 90% power when event rate ranges from 1–2.5 per 100 patients years**

Event Rate in Control (per 100 subject years)		Hazard Ratio margin (Treatment / Control)					
		1.5	2.0	2.5	3.0	3.5	4.0
<b>1</b>	Risk Difference	0.5%	1%	1.5%	2%	2.5%	3%
	Total events needed for 90% Power	256	88	51	35	27	22
	Total patient years for 90% Power	25600	8800	5100	3500	2700	2200
	Maximum point estimate to rule out HR	1.17	1.32	1.44	1.55	1.65	1.73
<b>1.5</b>	Risk Difference	0.75%	1.5%	2.25%	3%	3.75%	4.5%
	Total events needed for 90% Power	256	88	51	35	27	22
	Total patient years for 90% Power	17067	5867	3400	2333	1800	1467
	Maximum point estimate to rule out HR	1.17	1.32	1.44	1.55	1.65	1.73
<b>2</b>	Risk Difference	1%	2%	3%	4%	5%	6%
	Total events needed for 90% Power	256	88	51	35	27	22
	Total patient years for 90% Power	12800	4400	2550	1750	1350	1100
	Maximum point estimate to rule out HR	1.17	1.32	1.44	1.55	1.65	1.73
<b>2.5</b>	Risk Difference	1.25%	2.5%	3.75%	5%	6.25%	7.5%
	Total events needed for 90% Power	256	88	51	35	27	22
	Total patient years for 90% Power	10240	3520	2040	1400	1080	880
	Maximum point estimate to rule out HR	1.17	1.32	1.44	1.55	1.65	1.73

### Choice of Control

As illustrated in the preceding section, cardiovascular outcomes trials require substantially more subjects studied for extended periods of time compared to trials designed to establish the efficacy of a new product intended to treat OIC. Suitability of the control arm studied under such a setting should consider, at a minimum, the following factors:

- Ethics (it may not always be ethical to incorporate a placebo control for a study that is planned to be studied for multiple years),
- Knowledge of the background risk of the control (comparison to a control that has a history of CV risk would not be an appropriate control), and
- Tolerability of the control, as it will be studied over an extended period of time. (In general, if the control arm cannot be studied for an extended period of time, the patient-years required to observe the planned number of events would then require an increase in the number of subjects ( $N$ ) with a shorter trial duration ( $t$ ).)

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Attributability of CV events to randomized treatment

Another concern when evaluating the outcomes of a cardiovascular trial for safety is whether one can attribute the CV event to the randomized treatment. CV events experienced by patients who received rescue therapy, regardless of treatment assignment, might not be attributable to the randomized treatment.

When assessing cardiovascular safety, the analysis population should be defined according to the time the safety outcomes occur in comparison to the exposure. In the total-time analysis population, a subject will be censored at the time of loss to follow-up, regardless of whether that subject was on or off treatment. An important consideration in such an analysis is that all subjects should be followed for the full duration of the trial, regardless of whether they are on or off treatment to capture all CV events of interest; whereas, in the on-treatment analysis population, a subject will be censored at the time of treatment discontinuation. These two populations differ in how they count events and define exposure time. Compared to an on-treatment analysis population, total-time analysis population provides more power. However, safety events might not be attributable to the assigned treatment if a large number of subjects discontinue treatment early in the study.

Example: Evaluation of Cardiovascular Risk in Type 2 Diabetes Mellitus

The *FDA Guidance: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* (2008)<sup>19</sup> requires new antidiabetic therapies to demonstrate the relative increase in cardiovascular (CV) risk is no greater than 80% pre-approval and the relative increase in CV risk is no greater than 30% post-approval. While various approaches are used to satisfy the pre-market risk margin of 1.8 (e.g., meta-analyses of phase 2 and 3 clinical trials), cardiovascular outcomes trials are typically used for evaluating the post-market risk margin of 1.3. While designs may vary, the following commonalities are shared.

- Trials are designed as outcomes-driven trials which are typically in excess of 1 year
- Control group: Placebo controlled with standard of care as background therapy
- Study power: All trials are powered at 90% to rule out a relative increase of 30% in CV risk
- The primary analysis population is based on the total-time with supportive analysis from the on-treatment analysis population due to expected similarities in treatment discontinuation across the active and control treatment arms

DGIEP has considered using a similar approach as that outlined in *The FDA Guidance: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* (2008) with sponsors who are developing mu opioid receptor antagonists for OIC. However, DGIEP has not specifically recommended a pre-market risk margin (i.e., upper bound of the 95% confidence interval) of 1.8 to be ruled out. DGIEP has considered a larger pre-market risk margin; however, the acceptability of the magnitude would ultimately be subject to Advisory Committee assessment and comment. In this meeting, we are seeking the Committee's advice on the acceptable pre-market risk margin.

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<sup>19</sup> <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf>

## 4 APPENDICES

### 4.1 Tabulation of Design Features and Population Demographics of Phase 3 Efficacy Trials and “Long Term” Safety Trials for Entereg, Relistor, and Movantik; Including Summary of CV Outcomes

Drug		Entereg	Relistor	Movantik
<b>RCT Efficacy (phase 3)</b>				
STUDY		Study 012	Study 3356	Study 04
	<b>N (#treated)</b>	522 172 P 174 E (0.5 QD) 172 E (0.5 BID)	469	652 217-PL 217-NGL 12.5 218- NGL 25
	<b>Duration</b>	12 weeks	4 week controlled; followed by 8 week open label, uncontrolled	12 weeks
	<b>%Female</b>	60%	65%	61%
	<b>Median Age</b>	52**	52	53
STUDY		Study 013		Study 05
	<b>N (#treated)</b>	485 164 P 161 (0.5 QD) 160 (0.5 BID)		700 233-PL 233- NGL 12.5 234-NGL 25
	<b>Duration</b>	12 weeks		12 weeks
	<b>%Female</b>	65%		63%
	<b>Median Age</b>	52**		53

“Long Term” Safety Trial				
STUDY		Study 014	Study 3358	Study 08
	<b>Randomized, Controlled</b>	Yes	No	Yes Control-usual care
	<b>N</b>	805 267 P 539 E	1040 (1034 treated)	840 559- NGL 25 281- UC
	<b>Duration</b>	52 weeks	48 weeks	52 weeks
	<b>% Female</b>	65%	65%	66%
	<b>Median age</b>	54**	52	53
SUMMARY STATISTICS: CV OUTCOMES				
<b>Deaths (any cause)</b>		5 (012, 014) 4 (014: 2 P, 2E)	4 (all in safety trial)	7 (all phases) 5 (Phase 3)
<b>Nonfatal CV SAEs</b>		28 (012,013,014) (6 P, 22E)  16 (014) (1 P,15 E)	6 (cardiac disorders SOC)	12 week trial (1-NGL; 0-PL) 52 week trial (0-NGL; 1-UC)
<b>Nonfatal CV SAEs MACE</b>		7 (012,013,014) MIs  6 (014: 0 p, 6 E) MIs  (One additional MI was fatal, 014))	3 (MIs)	12 week trial (2- NGL; 2- PL) 52 wk trial (1-NGL; 1-PL)

\* Non-mu opioid receptor antagonist



**4.2 Relistor sNDA: DGIEP Medical Officer Review Addendum (Focus on CV and Opioid Withdrawal Events)**

## CLINICAL REVIEW AMENDMENT

Application Type	sNDA
Application Number(s)	21-964
Priority or Standard	Standard
Submit Date(s)	June 27, 2011
Received Date(s)	June 27, 2011
PDUFA Goal Date	initial April 27, 2012 but extended 3 months, new date July 27, 2012
Division / Office	DGIEP/OD3
Reviewer Name(s)	Helen Sile, M.D.
Review Completion Date	July 27, 2012
Established Name	methylnaltrexone bromide
(Proposed) Trade Name	Relistor
Therapeutic Class	$\mu$ -opioid receptor antagonist
Applicant	Progenics Pharmaceuticals, Inc. and Salix Pharmaceuticals, Inc.
Formulation(s)	Subcutaneous
Dosing Regimen	12 mg
Indication(s)	Opioid induced constipation
Intended Population(s)	adult patients with non-cancer pain

Template Version: March 6, 2009

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## 1 Explanation of need for clinical review amendment

This document is an amendment to a clinical review completed on March 26, 2012 and finalized in DARRTS on April 1, 2012.

In re-evaluating the data and regulatory history of products in the same class (i.e. Entereg), it became apparent that the cardiovascular safety of Relistor should be adequately assessed prior to approval for *chronic* administration. When Adolor (the Sponsor for Entereg) was considering developing Alvimopan ( $\mu$  opioid antagonist) for opioid induced constipation, a SPA was submitted under IND 56,553 (see medical officer review dated December 29, 2008). Due to the numeric imbalance in cardiovascular events observed in study 014 (randomized, double-blind, placebo-controlled, parallel-group, multi-centered, phase 3, one-year, safety study of alvimopan in non-cancer patients with OIC), an advice letter dated March 23, 2009 was sent to the Sponsor providing recommendations to conduct another efficacy and safety trial to support the indication of OIC and address the potential cardiovascular signal. In the SPA advice letter, the Sponsor was informed that a placebo controlled trial that is adequately designed and powered would be required to evaluate the cardiovascular safety of alvimopan in the OIC population.

Reviewer comments: *Since alvimopan and methylnaltrexone belong to the same class ("peripherally" acting  $\mu$  opioid antagonist), this reviewer deems it necessary to re-evaluate the safety data in the sNDA with a focus on cardiovascular safety. This clinical review amendment is to address the CV safety of Relistor.*

## 2 Recommendations/Risk Benefit Assessment

### 2.1 Recommendation on Regulatory Action

Based on the unfavorable risk/benefit ratio (see 2.2 Risk Benefit Assessment), this reviewer does not recommend the approval of Relistor 12 mg SC Q D for the treatment of opioid induced constipation in patients with **chronic** non-cancer pain. For discussion on the approval of Relistor 12 mg SC Q O D dose, please see Relistor clinical review dated March 26, 2012.

In light of the plausible mechanisms, the questionable receptor specificity and the uncertainty of the limited penetration into the blood brain barrier of  $\mu$  opioid antagonists such as Relistor, there are several limitations and potential serious safety concerns detected in the trials (study 3356 and study 3358):

- A major limitation of the data submitted in the sNDA for the proposed indication of OIC in patients with chronic non-cancer pain is the availability of only 4 weeks of controlled data (double blind, placebo controlled). Study 3358, the long term safety trial lacked a comparator arm.
- Events such as myocardial infarction, sudden death and cardiac arrest occurred in the OL safety trial (study 3358). Without a comparator arm and the presence of multiple confounding factors (i.e. opioids, baseline cardiac risk factors), it is difficult to determine the causality of these cardiovascular events
- Events such as angina, unstable angina, chest pain and chest discomfort were not adequately assessed in patients that experienced these events during the trials. The failure to collect data such as troponin values, echocardiogram, and cardiac stress testing in high CV risk patients complaining of symptoms that potentially could signal an acute coronary syndrome has resulted in the absence of necessary information for assessment of risk/benefit.
- Infrequent administration of opioid withdrawal symptoms scales (Objective Opioid Withdrawal Scale and Subjective Opioid Withdrawal Scale) in study 3358 made it challenging to detect opioid withdrawal symptoms affecting other organ systems besides gastrointestinal. However, there were several patients in study 3358 that reported symptoms and exhibited signs consistent with opioid withdrawal +/- catecholamine surges (autonomic hyperactivity) during these episodes.
- Pain scores were not collected prior to every adjustment of prn opioid pain medications in studies 3356 and 3358. This lack of data on pain scores made it challenging to assess the effect of treatment with Relistor on analgesia and potential increase in opioid requirements.
- The interaction of Relistor with commonly used opioids on efficacy and safety was not adequately explored. Essential data are missing to mitigate safety concerns for concomitant use of Relistor in patients who have chronic non-cancer pain and OIC who will continue to receive multiple and various types and doses of opioids while being treated with Relistor chronically. The Sponsor should explore whether subjects using higher morphine equivalent doses might need a lower dose of Relistor for treatment of OIC.

The major safety concerns regarding the use of Relistor is the potential for off target effects observed in the trials (studies 3356 and 3358). Although the Sponsor contends that Relistor is a "peripherally" acting  $\mu$  opioid receptor antagonist, administration of Relistor has the potential to cause physiological effects of opioid withdrawal such as hyperthermia, hypertension, and tachycardia. In patients with coronary disease, the abrupt surges in catecholamines may not be well tolerated and could lead to hemodynamic instability and possibly CV events (i.e. myocardial infarction). In this

reviewer's opinion, adequate labeling will not address the potential serious CV adverse events. Thus, the Sponsor should conduct a well-controlled and adequately powered trial to evaluate the CV safety profile of treatment with Relistor in patients with OIC and chronic non-cancer pain.



## 2.2 Risk Benefit Assessment

**Table 1: Benefit-Risk Assessment Framework**

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<p><b>Summary of evidence:</b> Opioid induced constipation (OIC) is a persistent and common side effect of treatment with opioids and has been reported in 80% of patients taking opioids for cancer and non-cancer pain.<sup>1</sup> OIC does not improve with continued opioid therapy. Symptoms of OIC may impair a patient's quality of life.</p> <p>There are no standard guidelines for treatment of OIC; however, clinicians utilize many strategies to manage OIC: lifestyle changes (increase mobility, increase fiber-rich meals) and laxatives (over-the-counter, "off label" use), see Appendix 5.1 Laxatives used to treat Opioid induced constipation for available laxatives.<sup>2</sup></p>	<p><b>Conclusions (implications for decision):</b> OIC does not cause mortality but can cause complications such as pseudo-obstruction and impaction (a solid immobile bulk of feces in the rectum).</p> <p>When patients present with symptoms consistent with impaction, manual disimpaction and bowel cleansing with enema are the standard of care. For patients that present with signs and symptoms of pseudo-obstruction (i.e. vomiting, abdominal pain, abdominal distention), opioid analgesia might be decreased, suppositories may be used to liquefy the stool and overcome the obstruction, and nasogastric tube might be inserted to decompress the stomach and alleviate symptoms of obstruction (i.e. vomiting).</p>

<sup>1</sup> Tuteja, AK et al. Opioid-induced bowel disorders and narcotic bowel syndrome in patients with chronic non-cancer pain. *Neurogastroenterol Motil* 2010; 22: 424-e96.

<sup>2</sup> Stolbach, A. and Hoffman, Robert S. Opioid withdrawal in the emergency setting. [www.uptodate.com](http://www.uptodate.com) Last accessed 7/20/2012

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
<b>Unmet Medical Need</b>	<p><b>Summary of evidence:</b> There are no FDA approved products for the treatment of OIC in chronic non-cancer pain patient population. However, there are many available products (OTC and "off label") that are currently used to treat the condition. Relistor has not demonstrated efficacy in a "refractory" patient population with OIC. The subjects that participated in the phase 3 trial (3356) were required to discontinue all their laxatives and use only the permitted rescue laxative medication throughout the screening, treatment, and follow-up periods of the trial</p>	<p><b>Conclusions (implications for decision):</b> There may be a need for alternative options for treatment of OIC in the chronic non-cancer patient populations, especially if the drug has been evaluated and found to have demonstrated efficacy in the target population. However, as stated in the Relistor clinical review dated March 26, 2012, the efficacy of Relistor 12 mg SC Q D has not been established beyond 4 weeks.</p>
<b>Clinical Benefit</b>	<p><b>Summary of evidence:</b> Study 3356 was a phase 3 trial that had a 4 week double-blind treatment phase followed by an 8 week open label phase for a total treatment duration of 12 weeks. Two dosing regimens of Relistor (12 mg Q D and 12 mg Q O D) versus placebo were evaluated in the double blind treatment phase for the proposed indication of OIC in patients with chronic non-cancer pain. The 12 mg Q D Relistor dose demonstrated a statistically and clinically meaningful treatment difference versus placebo (primary endpoint: proportion of patients with <math>\geq 3</math> RFBM/wk during the 4 wk DB period), see pages 13-18 of Relistor clinical review dated March 26, 2012.</p> <p>Subjects who have higher baseline daily opioid use (<math>\geq 160</math> mg/day) appeared to have a greater laxation response rate when Relistor 12 mg was administered, see pages 63 to 67 of Relistor clinical review dated March 26, 2012. As is noted in uptodate, a person tolerant to 200 mg/day of methadone who received 2 mg of naloxone IV would probably experience much more severe symptoms than a patient taking 10 mg of methadone/day who stopped the opioid therapy abruptly.<sup>3</sup> The sensitivity to the effects of <math>\mu</math> receptor antagonists in subjects recently exposed to opioids are also noted in the Entereg (alvimopan) label dated 2009. The treatment of Relistor is aimed at specifically reversing the gastrointestinal side effects of opioid therapy, and it appears that subjects at higher doses of opioids seem to have a greater benefit.</p>	<p><b>Conclusions (implications for decision):</b> The ability of Relistor 12 mg Q D to produce a laxation response has been demonstrated in a 4 week double blind phase in patients with OIC receiving opioids for chronic non-cancer pain.</p> <p>In addition, Relistor is approved for treatment of OIC in patients with advanced illness receiving palliative care when responses to laxatives have not been adequate. In the palliative care trials, Relistor was evaluated as add on therapy in a setting where subjects were receiving at least 2 other laxatives.</p>

3 Stolbach, A. and Hoffman, Robert S. Opioid withdrawal in the emergency setting. [www.uptodate.com](http://www.uptodate.com) Last accessed 7/20/2012.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons																																				
Risk	<p><b>Summary of evidence:</b> The CV and opioid withdrawal risks are the safety concerns that will be addressed in this amendment. For detailed discussion of safety, see pages 18-20 of the Relistor clinical review dated March 26, 2012.</p> <p>Relistor is in the same class as Entereg, another <math>\mu</math> receptor antagonist currently approved for post-operative ileus with a REMS that limits its use to short term (7 days or 15 doses). The REMS was implemented to ensure safe use in the target population because a numeric imbalance in cardiovascular events was observed in a placebo-controlled trial of alvimopan in non-cancer patients with OIC (see table below).</p> <p>Number (%) of deaths and CV events by treatment in the non-cancer opioid bowel dysfunction study SB-767907/014</p> <table><tr><th>All cases</th><th>Alvimopan N = 538 n (%)</th><th>Placebo N = 267 n (%)</th><th>Relative Risk (asymptomatic 95% CI)</th></tr><tr><td>All cause death (total)</td><td>2 (0.37)</td><td>2 (0.75)</td><td>0.50 (0.09, 2.80)</td></tr><tr><td>Death from CV events</td><td>1 (0.19)</td><td>0 (0.0)</td><td>- (0.13, -)</td></tr><tr><td></td><td></td><td></td><td></td></tr><tr><td></td><td>Subjects with CV events (total)</td><td>14 (2.60)</td><td>0 (0.0)</td><td>- (1.83, -)</td></tr><tr><td></td><td>Ischemic events</td><td>11 (2.05)</td><td>0 (0.0)</td><td>- 1.44, -)</td></tr><tr><td></td><td>Fatal</td><td>1 (0.19)</td><td>0 (0.0)</td><td>- (0.13, -)</td></tr><tr><td></td><td>Other serious CV events</td><td>3 (0.56)</td><td>0 (0.0)</td><td>- (0.39, -)</td></tr></table> <p>Source: Statistical Reviewer's calculation in Memorandum of statistical consultation for NDA 21-775, dated 4/15/2008, Table 3 page 3, using Sponsor Table 2 on page 10 of the OBD CV safety report</p>	All cases	Alvimopan N = 538 n (%)	Placebo N = 267 n (%)	Relative Risk (asymptomatic 95% CI)	All cause death (total)	2 (0.37)	2 (0.75)	0.50 (0.09, 2.80)	Death from CV events	1 (0.19)	0 (0.0)	- (0.13, -)						Subjects with CV events (total)	14 (2.60)	0 (0.0)	- (1.83, -)		Ischemic events	11 (2.05)	0 (0.0)	- 1.44, -)		Fatal	1 (0.19)	0 (0.0)	- (0.13, -)		Other serious CV events	3 (0.56)	0 (0.0)	- (0.39, -)	<p><b>Conclusions (implications for decision):</b> The overall safety of Relistor is not acceptable due to the occurrence of CV events in an uncontrolled safety trial (study 3358), which raises questions about causality in light of a plausible mechanism of action. Despite the assertion from the Sponsor that receptor selectivity and limited penetration of Relistor into the blood brain barrier limits its off target effects (i.e. opioid withdrawal), there are several subjects that have experienced opioid withdrawal symptoms affecting other organ systems. In addition, few subjects have manifested tachycardia and hypertension, which are signs that result from the catecholamine surge associated with opioid withdrawal (see Table 5 and Table 6). In subjects who are already considered to have higher cardiovascular risk (see narratives within amendment) than the general population, episodes of hypertensive urgency and tachycardia have the potential to result in a CV event (i.e. myocardial infarction).<sup>4</sup></p>
	All cases	Alvimopan N = 538 n (%)	Placebo N = 267 n (%)	Relative Risk (asymptomatic 95% CI)																																		
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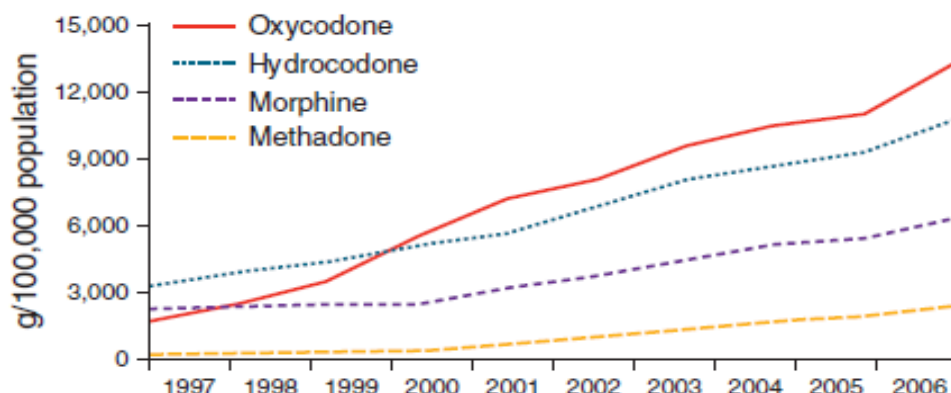
4 Solomon DH et al. The Comparative Safety of Opioids for nonmalignant pain in older adults. Arch Intern Med 2010; 170(22): 1979-1986.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	<p>Ischemic events include the following fatal and non-fatal events: MI, unstable angina, and cerebrovascular accident  Other serious CV events include the following fatal and non-fatal events: congestive heart failure and serious arrhythmia.  Note: Alvimopan group includes the following alvimopan dose and regimen: 0.5 mg BID ( N = 538)</p> <p>In the CV safety assessment of Relistor, 2 cases (subjects 053-2484 and 198-083624) serve as examples of the CV safety concern that has not been adequately evaluated in the submitted safety database. The sNDA contains only 4 weeks of controlled data (4 wk PC, DB) in study 3356, and the long term safety trial 3358 with 48 wks of Relistor treatment data was conducted in an OL manner.</p>	
<p><b>Risk Management</b></p>	<p><b>Summary of evidence:</b> There are unanswered questions regarding the CV safety of Relistor when used chronically to treat OIC in patients with chronic non-cancer pain. The CV concern that has been identified in the long term safety trial 3358 cannot be adequately addressed in the product labeling.</p> <p>Currently, based on the available data in studies 3356 and 3358, it is not possible to identify a sub-population that would incur all the benefits without the potential CV AEs. In addition, exhibiting opioid withdrawal symptoms with the first dose (administered at the study site) is not necessarily predictive of a potential future CV event. In reviewing the safety database, there were no patterns identified regarding timing of Relistor dosing or dose duration that would predict the onset of the CV event. However, based on limited PK data, review of the narratives and morphine equivalent doses used, it appears that subjects on higher morphine equivalent doses (MEDs) for treatment of chronic non-cancer pain might be more sensitive to the effects of Relistor (see clinical review of sNDA 21-964 dated 3-26-2012, pages 63 to 67 and 111 to 112). Thus, the potential interaction between Relistor and the most commonly used opiates (with regards to safety and efficacy) and the higher MEDs should be further explored using a formal and prespecified methodology.</p>	<p><b>Conclusions (implications for decision):</b>  The Sponsor should conduct an adequate and well controlled trial to assess the CV safety of Relistor. The design of the CV safety trial should incorporate similar recommendations provided to Adolor, the sponsor of Entereg (IND 56,553 SPA advice letter dated March 23, 2009), when Adolor was interested in pursuing an OIC indication for alvimopan.</p> <p>In addition, the Sponsor should obtain PK/PD data in a subset of subjects who are receiving commonly used opioid medications for chronic non-cancer pain management and are enrolled in the OIC trials to better elucidate the potential interaction between the multiple and various opioids and doses used and Relistor. The Sponsor should stratify OIC subjects based on their MEDs and ensure that any changes in scheduled and as needed opioid doses are adequately documented and tracked</p>

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
		<p>throughout the trial. Based on some of the thoughts of the opioid withdrawal mechanisms as described on page 34 of this amendment, subjects who have been on opioids chronically might be hypersensitive to the effects of <math>\mu</math> receptor antagonists and might need a lower dose of Relistor to antagonize the constipating effects of opioids.</p>
<p style="text-align: center;"><b>Benefit-Risk Summary and Assessment</b></p> <p>Relistor is approved for treatment of OIC in patients with advanced illness receiving palliative care. The Sponsor is seeking to expand the indication to patients with chronic non-cancer pain receiving opioids and OIC. The use of opioids for management of chronic non-cancer pain has increased over the years in the United States (see Figure 1), and with the increase use of opioids for non-cancer pain, more patients are presenting with OIC. In a meta-analysis of 11 placebo-controlled, randomized studies, OIC affected an average of 41% of patients taking opioids for up to 8 weeks.<sup>5</sup> Tolerance does not develop for constipation, and the prevalence of OIC increases with increase duration of opioid use.</p>		

5 Camilleri, M. Opioid-Induced Constipation: Challenges and Therapeutic Opportunities. Am J Gastroenterol 2011; 106: 835-842.



Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
<p><b>Figure 1: The increase in therapeutic opioid use in the United States (g/100,000 population) from 1997 to 2006</b></p>  <p>Figure reproduced from Figure 1 in the published article by Camilleri<sup>6</sup></p> <p>OIC is a persistent side effect that results from chronic opioid therapy but does not cause mortality or significant morbidity. It can be a debilitating condition and can have a negative impact on patient's quality of life (i.e. discontinue opioid treatment or reduce dose of opioid with a compromise in pain relief). Although there are no FDA approved products for OIC in patients with chronic non-cancer pain, there are multiple therapeutic options including non-pharmacologic therapies (increased fluid and fiber intake, manual evacuation, increased activity) that are used in clinical practice (see 5.1 Laxatives used to treat Opioid induced constipation). Relistor at 12 mg SC Q D provides a new therapeutic option that has demonstrated adequate efficacy in the target population.</p> <p>However, the long term OL safety trial 3358 revealed some concerning potential CV signal. Due to the lack of a well-designed safety trial (48 wks of OL Relistor treatment), it is challenging to adequately assess the CV safety of Relistor. In addition, there are plausible mechanisms in humans that have been reported in the literature by which <math>\mu</math> opioid antagonists have been observed to contribute to a CV event (i.e. myocardial infarction), see Division of Cardiovascular and Renal Products consult dated July 2, 2012.</p> <p>An example of the index case is as follows: <b>Subject MOA7283358-198-083624</b>: 59 yo M w/ OIC, complex regional pain syndrome, HTN, hyperlipidemia, tobacco abuse, and GERD who was taking methadone for pain management experienced SAEs of congestive heart failure on 10-29-09 (study day 43), CAD and MI on 9-22-09 (study day 6), and worsening HTN on (b) (6) (study day 57). The subject was started on</p>		

6 Camilleri, M. Opioid-Induced Constipation: Challenges and Therapeutic Opportunities. Am J Gastroenterol 2011; 106: 835-842.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	<p>Relistor on Sept 17, 2009, and he experienced severe abdominal cramping, moderate nausea, diarrhea, sweating, rhinorrhea, muscle twitching, hot and cold flashes, and lacrimation after the first injection and thereafter for the first 2 wks. Despite the aforementioned symptoms, the subject remained on a consistent dose of methadone, 125 mg TID, throughout the 2 week period. On Sept 23, 2009, the subject contacted the study site and reported that he had experienced retrosternal chest pain at 2 am on Sept 22, 2009, which woke him up from sleep. He took ASA and the pain subsided and he went back to sleep. At 11:30 am on Sept 22, 2009, the subject developed retrosternal chest pain (lasted for approximately 10 min.) with nausea and cold sweating while walking slowly. In addition, the subject reported SOB at rest and with exertion for a 2 wk period. However, he did not seek any medical attention. At a study visit on (b) (6) he was found to be hypertensive with a sitting BP of 180/108 mmHg. ECG revealed marked T wave inversion consistent with a recent septal MI and he was admitted to the hospital. CXR performed on (b) (6) revealed CHF and the patient continued to report SOB with exertion. Cardiac catheterization done on (b) (6) revealed total occlusion of the LAD after the first diagonal, with 90% narrowing of first diagonal, and 70-80% narrowing of the RCA.</p> <p>The subject continued to take opioid analgesics for the complex regional pain syndrome but Relistor was discontinued from (b) (6) to (b) (6). Relistor was re-started since the patient experienced OIC. On (b) (6), the subject's BP was 146/73 at 15:35. He received Relistor at 15:40 and experienced "moderate to severe painful abdominal cramps" as he had previously with his other Relistor injections. Between 15:50 and 16:00, he had several large bowel movements. He also reported perspiration and some rhinorrhea. The subject's BP at 16:01 was 165/88 and the abdominal cramping lasted for 90 minutes. The subject did not experience any chest pain and his blood pressure at 17:15 decreased to 133/75 mmHg and by this time, the abdominal cramps were very mild and subsided shortly thereafter. Per the investigator, it was noted that despite antihypertensive medications, there had been significant increases in BP associated with the painful abdominal cramps.</p> <p>A myocardial perfusion scan was done on (b) (6) and it revealed a small to moderate anterior septal infarct, moderate to large apical infarct, and EF of 41%. On (b) (6), a cardiac MRI was done for pre-bypass assessment and revealed a moderate sized transmural antero-septal infarct with adjacent subendocardial anterior infarct, transmural inferoapical infarct with subendothelial adjacent inferior infarct, and global hypokinesis more marked to the inferoapical region. On (b) (6), subject underwent triple coronary bypass surgery.</p> <p><i>The investigator considered MI and worsening HTN related to study medication. Per the investigator, the subject had preexisting untreated "borderline HTN" by history. He was significantly hypertensive when admitted to the hospital and BP normalized when treated with ramipril and bisoprolol. However, with a Relistor challenge, there was a significant increase of his BP during the time he was experiencing painful abdominal cramps ("this SAE is an expected physiological response to pain"). Per the investigator, in the setting of a severe narrowing of the LAD, a significant rise in BP might have contributed to the acute cardiac event (since the subject had taken 5 doses of Relistor and with each dose, the subject experienced severe abdominal cramps). He was taking lidocaine injections, dimenhydrinate, sodium docusate, and acetaminophen.</i></p> <p><u>Relistor dosing:</u> He administered 7 injections per wk from wks 1 to 8 except for wk 7 where he administered 5 injections. He decreased to a</p>	

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	range of 1 to 5 injections per wk from wks 9 to 36 except he administered 7 injections at wk 32 and 6 injections at wk 31.	
	The benefit of treatment of OIC using Relistor is not favorably balanced in light of the lingering unanswered concern of the potential for Relistor to contribute to the worsening of cardiovascular risk and events of an already high CV risk patient population. Targeted therapies (i.e. $\mu$ receptor specific) and more therapeutic options in the existing armamentarium for treatment of OIC are necessary. Nevertheless, Relistor does not offer a unique benefit for OIC treatment (i.e. prevents pseudo-obstruction, relieves impaction, benefit in patients who have failed all laxative therapies).	



### 3 Review of Safety

#### 3.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

##### **Dosing in the long term open label safety trial 3358**

When subjects were provided a choice of as needed use of Relistor, the median use of Relistor was 6 injections per week in study 3358 (see Table 2, below).

**Table 2: Summary of Average Number of weekly injections during open-label: all subjects population**

Characteristic	Treatment MOA-728 12 mg (n = 1034)
<b>Weekly injections, N</b>	
N	1034
Mean	<b>5.18</b>
Standard deviation	1.96
Minimum- Maximum	0.05 -7.14
Median	<b>5.98</b>

Source: Reviewer's table modified from Sponsor's table 10-2, CSR protocol 3200K1-3358-WW, page 65

The distribution of average number of weekly injections in study 3358 is provided in Table 3 below. The majority of subjects (49.2%) administered on average more than 6 and up to and including 7 injections per week and 5% of subjects administered less than 1 injection per week.

**Table 3: Distribution of Average number of weekly injections during open-label: all subjects population**

# Doses Exposed/week, N (%)	Treatment MOA-728 12 mg (n = 1034)
≤ 1	52 (5)
>1-2	42 (4.1)
>2-3	74 (7.2)
>3-4	115 (11.1)
>4-5	108 (10.4)
>5-6	130 (12.6)
<b>&gt;6-7</b>	<b>509 (49.2)</b>
>7	4 (0.4)

Source: Reviewer's table modified from Sponsor's table 10-3 in CSR, Protocol 3200K1-3358-WW page 66

Table 4 provides a tabulation of the number of patients that were administering  $\geq 5$  injections of Relistor per week on average at the 3, 4, 5, and 6 month timepoints in study 3358 for each month separately, as well as cumulatively.

**Table 4: Number and % of subjects administering  $\geq 5$  injections of MNTX per week on average for months 3, 4, 5, and 6 in study 3358 in the safety population**

	Response at the month ( $\geq 5$ injections/wk on average at the specific month)		Cumulative response up to the month ( $\geq 5$ injections/wk on average every month from month 1 up to the specific month)	
	N = 1034		N = 1034	
Month	$\geq 5$ injections/wk n*	%*	$\geq 5$ injections/wk n*	(%)*
Month 3	648	62.7	613	59.3
Month 4	592	57.3	555	53.7
Month 5	543	52.5	505	48.8
Month 6	497	48.1	455	44.0

Note: A subject who was administering  $\geq 5$  injections/week at a specific month separately was defined as a subject who was administering  $\geq 5$  injections/week on average only at the specific month. A subject who was administering  $\geq 5$  injections/week at a specific month cumulatively was defined as a subject who was administering  $\geq 5$  injections/week on average every month from Month 1 up to the specific month, inclusive.

\*number of subjects regardless of whether they were responders or non-responders who administered  $\geq 5$  injections/week on average and the percentages are based on the N of 1034 rather than the number of subjects who remained in the trial

Source: Reviewer's table modified from Sponsor's table 13 in IR response to IR request letter dated May 9, 2012

**Reviewer comments:** *Adequate numbers of subjects (497 subjects) have been exposed to Relistor 12 mg (at least administering 5 injections/week) at the 6 month timepoint meeting the ICH-E1A guidance recommendations (300-600 patients treated for 6 months and 100 patients treated for a minimum of 12 months).*

### 3.2 Submission Specific Primary Safety Concerns

#### **Cardiovascular (CV) Safety Evaluation**

SAS transport datasets (.xpt) of all AEs that were reported for studies 3356 and 3358 were reviewed for verbatim and preferred terms that might signal cardiovascular signs and symptoms. The following terms were identified as a potential signal for cardiovascular AEs in the datasets: syncope, angina pectoris, chest pain, cardiac failure congestive, musculoskeletal chest pain, loss of consciousness, pulmonary congestion, hypertension, hypotension, non-cardiac chest pain, dyspnea, chest discomfort, breast pain, vision blurred, electrocardiogram QT prolonged, stroke, cardiac arrest, thrombosis, vagal shock, myocardial infarction, nuclear magnetic imaging abnormal, pleural effusion, edema peripheral, troponin increased, blood creatinine phosphokinase increased, coronary artery disease, Prinzmetal angina, dysarthria, dyspnea exertional, sudden death, respiratory distress, angina unstable, acute respiratory failure, in-stent coronary artery restenosis, dyspepsia, palpitations, mental

status changes, right leg numbness, pulmonary embolism, electrocardiogram PR prolongation, HR decreased, Atrioventricular block second degree, and hypoaesthesia,

The Sponsor had provided narratives for fatal SAEs, non-fatal SAEs, and AEs that led to discontinuations. However, narratives were requested for all the AEs that had the aforementioned listed terms. In addition, more information was requested for the submitted narratives that were assessed to be inadequate or contained limited information. Additional data and analyses provided by the Sponsor in IR responses dated 4/23/12, 6/11/12, and 6/26/12 were reviewed during this review extension cycle.

In reviewing the narratives, this reviewer evaluated the narratives to make a determination of whether the reported signs and symptoms might be categorized as withdrawal symptoms potentially precipitating a CV event. The tables of narratives in this clinical review amendment do not contain all the subject narratives that were requested by the reviewer and submitted by the Sponsor (see section 5.2 All Subjects (N = 95) with CV AE events of interest in whom narratives were submitted and reviewed. Post assessment of the submitted narratives, the reviewer summarized the narratives and presented them in tables. It should be noted that some summaries of the narratives may not necessarily illustrate CV events of interest (i.e. subject MOA 7283358-084-083439 who had AEs of COPD and dyspnea in Table 13).

#### **CV events of interest in studies 3356 and 3358**

Table 5 provides a tabulation of cardiovascular events of interest obtained from datasets and Sponsor provided narratives, see Table 9, Table 11, and Table 12. Study 3356 had a 4 week double blind period where subjects received either placebo, MNTX 12 mg Q D, or MNTX 12 mg QOD and an 8 wk open label period where all subjects received MNTX 12 mg as a prn dosing (no more than one 12 mg SC injection per day and no less than 12 mg SC once a week).

**Table 5: CV events of interest reported by investigators in study 3356 in the safety population\***

4 wk double blind phase			
Preferred term	MNTX 12 mg Q D N = 150	MNTX 12 mg QOD N = 148	Placebo N = 162
chest pain	0	1	0
musculoskeletal chest pain	0	0	1
angina pectoris	1	0	0
blood pressure increase	0	0	1
congestive heart failure	0	1	0
electrocardiogram QT prolonged	2	0	1
electrocardiogram changes	0	1	0

**Table 5 cont'd: CV events of interest reported by investigators in study 3356 in the safety population\***

8 wk open label phase			
	MNTX 12 mg prn N = 364		
hot flush	1		
hyperhidrosis	1		
hypertension	2		
chest discomfort	1		
dyspnea	1		
chest pain	1		
loss of consciousness	1		
syncope	2		

\*safety population = all subjects who received at least one dose of the study medication but are not mutually exclusive (i.e. if a subject experienced both hot flush and hyperhidrosis that subject would be counted in both preferred terms AE category)

Source: Reviewer's table made using data obtained from review of narratives, see Table 9, Table 11, and Table 12 and JMP datasets provided by Sponsor

Reviewer comments: *It is challenging to make any meaningful conclusions of the CV adverse events reported in study 3356 since the double blind phase was short (4 wks duration) and the 8 wk OL trial did not have a control comparator.*

Table 6 provides a tabulation of the CV events of interest obtained from JMP datasets and Sponsor provided narratives reported in study 3358, the long term open label safety trial, see Table 7, Table 13, Table 15, and Table 16. MNTX 12 mg was dosed on a prn basis with a minimum of one 12 mg SC injection per week to a maximum of one 12 mg SC injection per day.

**Table 6: CV events of interest reported by investigators in study 3358 in all-subjects population\***

Preferred term	MNTX 12 mg prn N = 1034 n (%)
<i>fatal</i> cerebrovascular accident	1 (0.1)
<i>fatal</i> cardiac arrest	1 (0.1)
<i>fatal</i> sudden death	1 (0.1)
<i>fatal</i> myocardial infarction	1 (0.1)

**Table 6 cont'd: CV events of interest reported by investigators in study 3358 in all-subjects population\***

<i>non-fatal</i> myocardial infarction	3 (0.3)
cardiac failure congestive	1 (0.1)
coronary artery disease	2 (0.2)
in-stent coronary artery stenosis	1 (0.1)
angina pectoris	7 (0.7)
angina unstable	1 (0.1)
prinzmetal angina	1 (0.1)
chest pain	4 (0.4)
chest discomfort	4 (0.4)
non-cardiac chest pain	8 (0.8)
musculoskeletal chest pain	2 (0.2)
dyspnea	8 (0.8)
dyspnea exertional	2 (0.2)
hyperhidrosis	2 (0.2)
hypertension	2 (0.2)
blood pressure increased	1 (0.1)
hypotension	3 (0.3)
electrocardiogram QT prolonged	7 (0.7)
palpitations	1 (0.1)
Atrioventricular block second degree	1 (0.1)
electrocardiogram PR prolongation	1 (0.1)
heart rate decreased	2 (0.2)
drug withdrawal syndrome	2 (0.2)
vision blurred	2 (0.2)
musculoskeletal pain	2 (0.2)
blood creatine phosphokinase increased	1 (0.1)
COPD	1 (0.1)
respiratory distress	1 (0.1)
acute respiratory failure	1 (0.1)
dysarthria	1 (0.1)
hypoesthesia	1 (0.1)
pneumonia	1 (0.1)
troponin increased	1 (0.1)
syncope	1 (0.1)
right leg numbness	1 (0.1)
nuclear magnetic resonance imaging abnormal	1 (0.1)
pulmonary embolism	1 (0.1)

\*all subjects population = (1034 subjects) defined as any subject who took at least one dose of study medication in the open-label trial but are not mutually exclusive (i.e. if a subject was reported as having myocardial infarction, cardiac failure congestive and coronary artery disease, that subject would be counted in all 3 AE preferred term categories).

Source: Reviewer's table made using data obtained from review of narratives, see Table 7, Table 13, Table 15, and Table 16 and JMP datasets provided by Sponsor



Reviewer comments: *It is challenging to make any meaningful conclusions regarding the CV events reported in study 3358 since the trial lacks a control arm.*

## Deaths

Below is a narrative of the 4 subjects that died in the open label long term safety trial. The dosing for Relistor in the long term safety trial 3358 was on as needed basis as long as subjects administered the study medication a minimum of once a week and no more often than once a day. Relistor dosing information is provided for each subject that experienced a fatal SAE (see Table 7).

**Table 7: Narratives of Death (fatal SAE) in study 3358 (long term OL safety trial)**

Study 3358	Probable Cause of Death*	Time interval of MNTX dose
<p><b>Subject MOA7283358-008-080235:</b> 45 yo F with HTN, back pain, sinus bradycardia, obesity (wt. 137 Kg and BMI = 46), anxiety disorder was receiving oxycodone hydrochloride for back pain. Patient had OIC and received her last dose of MNTX 12 mg Q D the same day she died suddenly. She was taking Lisinopril for HTN and Xanax for anxiety disorder. Patient administered the last dose of Relistor on (b) (6) (study day 211) and the fatal event occurred on (b) (6). Death certificate listed cause of death as stroke with HTN and an autopsy was not performed. There were no records provided that documented a CT of the brain was performed.</p> <p><u>Relistor dosing:</u> Patient took 7 injections per wk from wk 1 to wk 30 except on wks 8 and 9 where she administered 6 injections each and wk 5 where she administered 8 injections. Patient died at wk 31 after taking one injection. Subject administered 7 injections/wk for each wk of the 4 wks prior to event.</p>	Cerebrovascular Accident (CVA)	0 days after last dose
<p><b>Subject MOA7283358-020-080651:</b> 67 yo F with HTN, obesity (242 lb, BMI = 46.5), abdominal hernia, previous tobacco abuse (quit in 1971), and OIC died suddenly while sleeping in a car. The patient had complained of abdominal pain 24 hrs prior to her death. On (b) (6) (study day 62), her daughter reported that she took her to an urgent care center to be evaluated for abdominal pain. Patient reportedly received a prescription for pain medication (Vicodin) and phenergan, and the daughter did not think she took any of the pain medication during the drive home. On the way home, her daughter reported that patient became somnolent. The daughter could not get her mother out of the car and she left her mother in the car to sleep overnight. The daughter checked on her mother periodically throughout the night and she reported that she was snoring and somewhat arousable. However, in the morning hours (at 6 am), she noticed that her mother was not breathing. She took her to the ER and the patient was found to be in asystole. The patient was intubated and CPR was initiated, but the resuscitation efforts failed (date of death (b) (6), study day 63, 6 days after last Relistor dose). Drug screen identified acetaminophen at 15.3 ug/mL (nl range 10 to 50 ug/mL) with no other drugs identified. Etoh level was negative. No other laboratory evaluations were performed.</p> <p><u>Relistor dosing:</u> She administered 7 injections per wk from wks 1 to 8 except for wk 9 where she administered 1 injection. Subject administered 7 injections/wk for each wk of the 4 wks prior to event except 1 wk prior to the event where she administered 1 injection.</p>	Cardiac Arrest	6 days after last dose

**Table 7 cont'd: Narratives of Death (fatal SAE) in study 3358 (long term OL safety trial)**

Study 3358	Probable Cause of Death*	Time interval of MNTX dose
<p><b>Subject MOA7283358-073-081899:</b> 46 yo M (wt 66 kg, BMI = 24) with ALS, asthma, depression, tobacco abuse, seizure disorder, urinary retention, "low oxygen saturation", and muscle spasms was receiving morphine and oxycodone for pain management. He had OIC and had received his last dose of MNTX 12 mg Q D 7 days prior to his death suddenly. The fatal event occurred on study day 257. The patient was taking soma, lexapro, azmacort, combivent inhaler, singular, baclofen, and flomax for muscle spasms, asthma, and depression.</p> <p>On Oct 7, 2009, the subject underwent "total mouth teeth extraction" and developed oral abscesses that began on the same day. The subject received Augmentin from Oct 7, 2009 to Oct 21, 2009 to treat the oral abscesses. He received his last dose of Relistor on (b) (6) (study day 250). On (b) (6) (study day 257), the subject died. The investigator reported the death as sudden death. The subject's spouse declined to provide death certificate and autopsy report.</p> <p><u>Relistor dosing:</u> He administered 4 injections the first wk, increased to 5 injections on wks 2-5, and then increased to 7 injections per wk from wks 6 to 35. However, he administered 6 injections on wk 8 and 5 injections on wk 36. Subject administered 7 injections/wk for each wk of the 4 wks prior to event except 1 wk prior to the event where he administered no injection.</p>	Sudden death	7 days after last dose
<p><b>Subject MOA7283358-200-083696:</b> 57 yo M (wt 88 kg, BMI = 29) with CAD with prior MI and stent placement X 2, HTN, hyperlipidemia, cervical herniated disks, tobacco abuse and migraine headaches was receiving fentanyl and hydromorphone for chronic neuropathic pain. The patient was withdrawn (on (b) (6)) from the trial 13 days prior to his death due to non-compliance with protocol. He was taking ramipril, valium, prevacid, domperidone, plavix, tamsulosin, metoprolol, lipitor, gabapentin, and diltiazem.</p> <p>On Jan 23, 2010, the subject was diagnosed with angina pectoris by a local physician and was prescribed nitroglycerin 0.4 mg sublingual as needed. On (b) (6), study day 278 and 13 days after his last dose of Relistor (received Relistor through (b) (6), study day 265), the subject was found dead with "cadaveric rigidity" by a friend who had not heard anything from him for one week. No autopsy was performed. The death report and the ER physician documented "patient with past history of cardiovascular disease, presenting with rigidity and no sign of violence; diagnosis: myocardial infarction".</p> <p><u>Relistor dosing:</u> He administered 7 injections per wk from wks 1 to 37 except for 6 injections at wks 4 and 38, 4 injections at wk 25, 3 injections at wks 29 and 31 and 2 injections at wk 30. Subject administered 7 injections/wk for each wk of the 4 wks prior to event except 2 wks prior to the event where he administered 1 injection and 1 wk prior where he administered no injection.</p>	Myocardial infarction	13 days after last dose

\*Verbatim term per investigator

Source: Reviewer's table created from data in final CSR, Protocol 3200K1-3358-WW pages 69-70, subject narrative information pages 554, 573, 677, and 788-789, and IR 12 Listings 7.1b and 7.2b from IR response to IR letter dated April 18, 2012

**Reviewer comments:** *It is challenging to attribute the death of these 3 subjects (008-080235, 020-080651, 200-083696) that experienced CVA, cardiac arrest and myocardial infarction, respectively to the study drug (Relistor) since study 3358 lacks a comparator arm. Although all 3 subjects probably are at high risk for cardiovascular disease, it does not negate a potential contribution from Relistor treatment. Limited data are available in the 3 death cases, which makes adjudication of these deaths rather difficult.*

*Subject 073-081899 might have had respiratory muscle weakness associated with his diagnosis of ALS, which probably contributed to his sudden death from respiratory failure.*

Table 8 provides the dosing of Relistor for each week of the 4 weeks preceding the fatal SAEs. In addition, the last column in the table below provides the overall average weekly injection frequency of MNTX 12 mg in study 3358 for the 4 subjects excluding the 4 weeks prior to the fatal SAEs.

**Table 8: Wkly use of MNTX 12 mg of each wk of the 4 wks preceding the fatal SAE and overall average weekly injection frequency of MNTX 12 mg excluding the 4 wks prior to the non-fatal SAE**

Subject id	Preferred term	Injection 1 wk prior	Injection 2 wks prior	Injection 3 wks prior	Injection 4 wks prior	overall avg* wkly injection
008-080235	CVA	7	7	7	7	7
020-080651	cardiac arrest	1	7	7	7	7
073-081899	sudden death	0	7	7	7	7
200-083696	myocardial infarction	0	1	7	7	7

\*Average weekly injection is not displayed for subjects with  $\leq 28$  days of exposure

Source: Reviewer's table modified from Sponsor's table IR 12 Listing 7.2b from IR response to IR letter dated April 18, 2012

Table 9 below provides brief description of non-fatal SAEs that occurred in the 4 week double blind period of study 3356 and the Relistor doses administered by the subjects.

**Table 9: Non-fatal SAEs in double blind phase of study 3356**

Treatment Subject id	Demographics/Preferred Term/Verbatim term Relistor doses administered	Relationship*	Outcome
MNTX 12 mg Q D			
MOA7283356-004-000136	41 yo F/syncope/syncope <u>Relistor dosing:</u> administered (8 wk OL pd) 1-3 injections from wks 1 to 10 except at wk 1 and 3 where she administered 5 and 6 injections, respectively	unrelated	completed (SAE occurred 11 days post last dose)
MOA7283356-004-0157	41 yo M/road traffic accident/life threatening car accident which led to back surgery <u>Relistor dosing:</u> administered 7 injections each for wks 1 and 2 and 1 injection at wk 3	unrelated	withdrawn from study at wk 3



**Table 9 cont'd: Non-fatal SAEs in double blind phase of study 3356**

Treatment Subject id	Demographics/Preferred Term/Verbatim term Relistor doses administered	Relationship*	Outcome
MNTX 12 mg Q D			
MOA7283356-028-1219	39 yo M/renal cancer/L renal mass 3.1 cm s/p L radical nephrectomy White blood cell count increased/elevated white cell count hypokalemia/low potassium at 2.2 mmol/L abdominal pain/upper abdominal discomfort with pain chills/chills White blood cell count increased/elevated WBC count pyrexia/severe fever with temperature of 101°F  <u>Relistor dosing:</u> administered 3 injections at wk 1	unrelated	withdrawn from study at wk 1
MOA7283356-033-1494	52 yo F/pneumonia/pneumonia that required hospitalization  <u>Relistor dosing:</u> administered 7 injections per wk for wks 1 to 4 and 1 injection at wk 5	unrelated	completed study
MOA7283356-033-1495	43 yo F/pancreatitis/ severe pancreatitis suspected etiology alcohol induced  <u>Relistor dosing:</u> administered 7 injections per wk for wks 1 to 3 and 5 injections at wk 4	unrelated	withdrawn from study at investigator request due to alcohol and drug abuse at wk 4
MOA7283356-063-2926	54 yo F/Thrombosis/right arm blood clot (U/S revealed acute RUE DVT)  <u>Relistor dosing:</u> administered 4 injections at wk 1	unrelated	subject withdrew at wk 1
MOA7283356-223-4708	48 yo M/dehydration/diuretic induced dehydration with acute renal failure, Creat 5 myoclonus/severe myoclonic jerks  <u>Relistor dosing:</u> administered 7 injections per wk for wks 1 to 3 and 3 injections at wk 4	unrelated	subject withdrew at wk 4
		unrelated	

**Table 9 cont'd: Non-fatal SAEs in double blind phase of study 3356**

Treatment Subject id	Demographics/Preferred Term/Verbatim term Relistor doses administered	Relationship*	Outcome
MNTX 12 mg QOD			
MOA7283356-053-2484	<p>50 yo F (wt. 60 kg, BMI = 22)/extrasystoles/chest pain, palpitations and abnl EKG with bigeminy (initially 1 hr post-dose, subject c/o diarrhea, nausea, vomiting and abdominal cramps. She had one episode of emesis, and approximately 5 episodes of diarrhea. Then experienced chest pain and diaphoresis)</p> <p>Screening blood pressure/pulse (study day -14): 126/93 (standing), 152/97 (supine), 76 bpm (supine), 68 bpm (standing).</p> <p>Blood pressure/pulse (study day 1 (10-Jul-2008)-predose): 132/106 (standing), 162/102 (supine), 62 bpm (supine), 66 bpm (standing).</p> <p>Blood pressure/pulse (study day 1-postdose): 178/138 (standing), 209/109 (supine), 60 bpm (supine), 62 bpm (standing).</p> <p>Blood pressure/pulse (early withdrawal (17-Jul-2008): 156/110 (standing), 157/111 (supine), 70 bpm (supine), 66 bpm (standing).</p> <p>The subject was sent to the ED for evaluation. BP (sitting) was 127/71 and pulse was 84 in the ED approximately 3 hrs (at 12:26 pm) post first dose of Relistor (administered at 9:35 am). Troponin was 0.01 ng/mL (nl &lt; 0.04), myoglobin 32 ng/mL (nl &lt; 62), and potassium was 4 mmol/L. ECG revealed cardiac dysrhythmia and ventricular bigeminy. CXR revealed no radiographic evidence of acute cardiopulmonary disease.</p>	related	withdrawn from study at wk 1 post first dose (45 minutes post first dose)
Placebo			
MOA7283356-004-0139	54 yo M/musculoskeletal chest pain/musculoskeletal chest pain with nl adenosine myocardial perfusion imaging	unrelated	completed study
MOA7283356-022-0964	29 yo M/hematemesis/vomiting of blood, refused endoscopy	unrelated	withdrawn from study at wk 2

\*Relationship to study drug as assessed by the investigator

Source: Reviewer's table modified from Sponsor's table 25 in 5.3.5.3, Integrated summary of safety, pages 90-91 and created from data in final CSR, Protocol 3200K1-3356-VW, page 122 and subject narrative information pages 783, 792-797, 828, 808, 758-760, 805-806; IR 12 Listing 7.1a from IR response to IR letter dated April 18, 2012

**Reviewer comments:** Subject 053-2484 experienced diarrhea, nausea, vomiting, abdominal cramps, chest pain, diaphoresis and elevation in blood pressure within close proximity to time of dosing. It appears that the subject experienced not only an exaggerated response of Relistor (diarrhea) but also AEs (abdominal cramps, nausea, vomiting, diaphoresis and elevation in blood pressure). Although the Sponsor asserts that there is evidence to distinguish between central and peripheral withdrawal, based on the available literature and current understanding of opioid withdrawal in the clinical setting, this assertion remains controversial and unsubstantiated.

A table adopted from uptodate and CURRENT Diagnosis & Treatment: Psychiatry (see Table 10) provides the clinical features of opioid withdrawal. A distinction between

*peripheral and central opioid withdrawal is not provided - rather the clinical features are grouped by organ systems that are affected. Hence, it is difficult to ascribe the signs and symptoms exhibited by subject 053-2484 to either central or peripheral opioid withdrawal, rather it appears to be a consequence of treatment with Relistor ( $\mu$  opioid antagonist) and the organ systems that it potentially affects.*

**Table 10: Clinical features of opioid withdrawal**

<b>Vital Signs (autonomic hyperactivity)</b>
blood pressure increased (hypertension) or unchanged; decreased if hypovolemic
heart rate increased (tachycardia) or unchanged
respiratory rate increased (tachypnea) or unchanged
temperature unchanged or hyperthermia
Sweating
Hyperreflexia
<b>Gastrointestinal</b>
nausea, vomiting
Diarrhea
increased bowel sounds
gastrointestinal cramping
<b>Neurological/Psychiatric</b>
mental status usually normal, irritable
depressed mood
Anxiety
Dysphoria
Craving
Restlessness
seizures (neonates only)
Tremor
Yawning
Insomnia
<b>HEENT (head, eyes, nose, throat)</b>
Lacrimation
Mydriasis
Photophobia
Rhinorrhea
<b>Musculoskeletal and Analgesia</b>
Hyperalgesia
joint and muscle aches
<b>Skin</b>
piloerection ("goose flesh")

Source: Reviewer's table adopted from uptodate<sup>7</sup> and Current Diagnosis & Treatment: Psychiatry<sup>8</sup>

7 Stolbach A. and Hoffman, Robert S. Opioid withdrawal in the emergency setting. [www.uptodate.com](http://www.uptodate.com)

Table 11 provides narratives of CV events of interest that led to discontinuations in study 3356 during the double blind or open label phases. In the 8 wk OL phase of study 3356, subjects were allowed to dose MNTX 12 mg on as needed basis as long as they administered MNTX 12 mg a minimum of one injection/wk and no more than one injection/day.

**Table 11: Narratives of CV events of interest that led to discontinuation in study 3356 (DB and OL period)\***

Study 3356	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
<b>Subject MOA7283356-005-000183:</b> 61 yo M w/ DM, back pain, and weakness to right lower extremity who was receiving hydrocodone, oxycodone, methadone for pain management experienced AEs of hot flash sensation, sweating, and high blood pressure. He reported moderately severe AEs of hot flash sensation, sweating, and high blood pressure on 4-19-08 (the first day of OL study drug) and study medication was discontinued on 5-14-08. All AEs resolved on 5-14-08, the day study drug was discontinued. He was taking metformin and benazepril.	hot flush hyperhidrosis hypertension  27 days  discontinued study  <i>related**</i>	0 days after last dose
<b>Subject MOA7283356-012-000498:</b> 43 yo F w/ anemia, panic attacks, asthma, and coccyx fracture who was receiving fentanyl patch and acetaminophen + hydrocodone for pain management experienced AEs of heart burn and muscle spasms at injection site. She began taking MNTX 12 mg Q D (DB pd) on 3-5-08 and experienced the AEs on 3-7-08. The AEs resolved on 3-8-08 after she discontinued the study drug on 3-7-08. She was taking albuterol, tiotropium, temazepam and lorazepam.	dyspepsia injection site reaction  3 days  discontinued study  <i>related**</i>	0 days after last dose
<b>Subject MOA7283356-015-000637:</b> 46 yo M (wt. 121 kg, BMI = 37) w/ anxiety, bipolar disorder, HTN, GERD, Hyperlipidemia, DM, and BPH who was receiving morphine and oxycodone for pain management experienced AEs of abdominal cramping, "fell down and black out". The subject started taking MNTX 12 mg QD (DB pd) on 3-18-08 and OL study drug on 4-15-08. He discontinued the study medication on 4-28-08 after he experienced the AEs on 4-27-08. Abdominal cramping resolved on 4-29-08. He was taking alprazolam, esomeprazole, rosuvastatin, metformin, insulin glargine, and lisinopril.	loss of consciousness  fall  abdominal pain (related)  41 days  discontinued	0 days after last dose (last dose 4-28-08)

2012.  
8 Martin PR. Chapter 15. Substance-Related Disorders. In: Ebert MH, Loosen PT, Nurcombe B, Leckman JF, eds. *CURRENT Diagnosis & Treatment: Psychiatry*. 2nd ed. New York: McGraw-Hill; 2008.  
<http://www.accessmedicine.com/content.aspx?aID=3283393>. Accessed July 6, 2012.



Study 3356	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
<p><b>Subject MOA7283356-049-002300:</b> 53 yo F w/ obesity, tobacco abuse, CAD, pseudotumor cerebri s/p VP shunt placement X 3, depression, s/p hysterectomy, appendectomy, cholecystectomy, blindness s/p bilateral optic nerve decompression, panic attack, headaches, restless leg syndrome, and GERD who was receiving morphine sulfate for pain management experienced AEs of abdominal cramping, chest pressure, diarrhea, dyspnea, and vomiting on 5-30-08. She was started on placebo treatment (DB pd) on 4-15-08, enrolled in OL phase on 5-16-08, and started her first OL study drug on 5-23-08. The subject took OL MNTX 12 mg on 5-27-08 and 5-29-08 and experienced the AEs on 5-30-08, which resolved (chest pressure, dyspnea, and vomiting) on the same day. The AEs of abdominal cramping and diarrhea resolved on 5-31-08. She was taking naproxen, hypromellose ophthalmic lubricant, cyclosporin (for eyes), butalbital + acetaminophen + caffeine, mometasone furoate, fluoxetine, cyclobenzaprine, prolamine iodine, and Zypan.</p>	<p>chest discomfort dyspnea abdominal pain diarrhea vomiting</p> <p>46 days</p> <p>discontinued</p> <p><i>related**</i></p>	<p>1 day after last dose (last dose 5-29-08)</p>
<p><b>Subject MOA7283356-022-000950:</b> 63 yo F (wt. 52 kg, BMI = 22) w/ hyperlipidemia, GERD, s/p hysterectomy and oophorectomy, s/p appendectomy, plantar fasciitis s/p surgery of left foot, and reflex sympathetic dystrophy experienced SAEs of gastroenteritis and HTN on (b) (6). The subject started placebo treatment (DB pd) on (b) (6) and enrolled in the OL phase on 11-12-07 and took her first OL MNTX dose on 11-16-07. The subject reported diarrhea, nausea, and vomiting to her PCP on (b) (6), and she was referred to the ER for further evaluation. In the ER, she was noted to have dehydration and increased BP. On (b) (6) and on admission, her BP was 173/134 mmHg with HR of 133 beats/min. The abdominal exam revealed mild distension with mild diffuse tenderness without bowel sounds. CT of abd performed on (b) (6) (study day 59) revealed colonic distension and questionable thickening to the posterior wall of the distal rectum suspicious for infiltrative process of the bowel wall such as neoplasm. Laboratory evaluations revealed hgb of 16.8 g/L, WBC 10.4 x 10<sup>9</sup>/L, BUN 19 mg/dL, and Hct of 50%. The subject was treated with IVFs and ECG was done on (b) (6). The ECG revealed flat P-wave in leads II, III, and AVF, sinus rhythm at 118 beats per min, borderline T abnormalities inferior leads, PR interval 148, QRS duration 74, QT interval 336 and QTc 471. Vital signs on (b) (6) were BP of 158/91 mmHg and pulse of 95 bpm. She received nitroglycerin (b) (6) to (b) (6) and metoprolol (b) (6), on-going) to treat the HTN and promethazine for vomiting. Colonoscopy was performed and was noted to be unremarkable. The subject's nausea and vomiting were thought to be secondary to colonic obstruction due to her chronic use of high dose morphine and absence of bowel sounds at admission. Gastroenteritis was considered to be the initial etiology of hospitalization as she had diarrhea for 2 days prior to admission but no diarrhea during hospitalization.</p> <p>(b) (6) (study day -14, screening): supine blood pressure 125/87 mmHg, 135/80 mmHg, pulse 93 bpm; standing blood pressure 116/76 mmHg, 111/78 mmHg, pulse 100 bpm.</p> <p>(b) (6) (study day 1): pre-dose supine, blood pressure 115/79 mmHg, 105/(not provided) mmHg, pulse 88 bpm; pre-dose standing, blood pressure 92/68 mmHg, 84/62 mmHg, pulse 109 bpm; post-dose supine,</p>	<p>HTN gastroenteritis</p> <p>59 days</p> <p>discontinued study on 1-1-08 (protocol violation, missed diary calls)</p>	<p>4 days after last dose</p>

Study 3356	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
<p>blood pressure 112/65 mmHg, 111/66 mmHg, pulse 82 bpm; post-dose standing, blood pressure 97/61 mmHg, 64/65 mmHg, pulse 89 bpm.</p> <p>(b) (6) (study day 59): BP 173/134 mmHg, HR 133 bpm.</p> <p>(b) (6) (study day 60): BP 158/91 mmHg, HR 95 bpm.</p> <p>(b) (6) (study day 63): BP 145/80 mmHg, pulse 96 bpm</p> <p>The subject's last dose of Relistor prior to the onset of the SAE was (b) (6) but her last dose of Relistor in the trial was 1-1-2008.</p> <p>Additional AEs reported fever (100.6°F on 12-8-07 to 12-11-07), insomnia ((b) (6) to (b) (6)), body aches (12-8-07 to 12-20-07), cold sore upper lip, nausea, left foot swelling, and running nose. She was taking gabapentin, simvastatin, estradiol and morphine 60 mg TID for pain management.</p>		
<p><b>Subject MOA7283356-082-004523:</b> 51 yo F w/ HTN, depression, back pain, hyperlipidemia, migraine, DM, GERD, s/p hysterectomy experienced SAE of change in mental status. The subject started placebo treatment (DB pd) on (b) (6) and entered OL pd on 7-24-08. Subject was taken to the ER on (u) (o) due to "confused state and not responding properly", preceded by an episode of migraine headache on 7-26-08, which was on-going. Laboratory evaluations revealed potassium of 2.9 mmol/L and increased WBC count. Urine drug screen was negative for drug abuse. LP could not be performed since the subject was combative but patient was empirically treated for meningitis (Ceftriaxone 2 grams). CT of brain revealed that a small hemorrhage could not be ruled out, and MRI of brain was performed. MRI of brain revealed non-specific mild periventricular white matter disease but no evidence of ICH. The subject was initially diagnosed with alcoholism, drug abuse, infection and head trauma and admitted to the ICU. Subject improved with repletion of potassium and treatment of HTN with enalapril. Discharge diagnoses were hypokalemia, HTN, anxiety, depression, migraine, hyperlipidemia, AMS. Additional AEs reported were as follows: migraine ((b) (6)), chest pain ((b) (6)), worsening HTN ((b) (6)) and hypokalemia ((b) (6)).</p> <p>She was taking ibuprofen, famotidine, HCTZ, sumatriptan succinate, glipizide, simvastatin, promethazine, and bupropion. Medications used for pain management were not provided.</p> <p>Testing done during the hospitalization (29 Aug 2009)</p> <p>(b) (6) (study day 35) - CKMB 1.0 NG/ML (1.0 – 8.0), TNI &lt;0.05 NG/ML (0.05-0.40), BNP 49.9 PG/ML (5-170), MYO 85.9 NG/ML (5-170), K = 2.9 MMOL/L (3.5-5.3), TC02 =22 MMOL/L (23-32), glucose 169 MG/DL (65-99), BUN = 29 MG/DL (6-20)</p>	<p>mental status changes</p> <p>35 days</p> <p>discontinued</p>	<p>1 day after last dose (last dose (b) (6))</p>

Study 3356	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
<b>Subject MOA7283356-051-002386:</b> 42 yo M w/ anxiety and spinal cervical pain who was receiving hydrocodone for pain management experienced AEs of metallic taste, headaches, and elevated blood pressure values. The subject started placebo treatment (DB pd) on 3-7-08. He reported a metallic taste on 3-8-08, severe headaches on 3-15-08, and elevated BP values on 3-18-08. BP readings on 3-20-08 were: 128/87 supine as compared to predose values of 138/96 and post dose values of 136/81 on 3-7-08. He discontinued study drug on 3-23-08 and BP elevation and headaches resolved on 4-1-08 but the AE of metallic taste was on-going. He was taking acetaminophen, celecoxib, acetaminophen + butalbital + caffeine, escitalopram oxalate, and alprazolam.	blood pressure increase (12 days) dysgeusia (2 days) headache (9 days)  discontinued  <i>related**</i>	0 days from last dose

\*Subjects who withdrew due to non-fatal SAEs in study 3356 are only included in Table 9 and are not included in this table

\*\* Relationship to study drug as assessed by the investigator

Source: Reviewer's table modified from Sponsor's table 16.133, subject narrative information in final CSR, Protocol 3200K1-3356-WW, pages 753 to 828.

Reviewer comments: *Both subjects (005-000183 and 049-002300) experienced opioid withdrawal symptoms based on evaluations of the narratives submitted.*

*The diagnosis of opioid withdrawal is made by history alone and some or all of the symptoms described in Table 10 may be present. The severity of the opioid withdrawal symptoms depends on the individual's tolerance to opioids, the continued presence of opioid in the serum and end organs, and the duration of time over which the withdrawal has occurred.<sup>9</sup> Findings that characterize opioid withdrawal include mydriasis, yawning, increased bowel sounds, and piloerection. Due to their specificity, the presence of yawning and lacrimation are helpful in distinguishing other withdrawal (i.e. ethanol, sedative-hypnotic) or intoxication syndromes.*

*During opioid withdrawal, it is possible for patients to experience vital sign changes (heart rate, blood pressure, respiratory rate, and temperature increases). Subject 005-000183 exhibited hot flush, hyperhidrosis, and hypertension post first dose of Relistor, which is concerning since vital changes resulting in hypertension are almost always a result of a surge in catecholamines from iatrogenically-induced withdrawal.<sup>10</sup>*

*Most of the literature and clinical data on opioid withdrawal results from observations in the acute opioid withdrawal syndrome setting seen in humans. There remains a scarcity of data on the long term physiological effects of intermittent or recurring opioid withdrawal, especially in humans, possibly due to the impracticality of such studies (i.e. non-compliance). In the clinical setting, opioid receptor antagonists are used in the*

<sup>9</sup> Stolbach, A. and Hoffman, Robert S. Opioid withdrawal in the emergency setting. [www.uptodate.com](http://www.uptodate.com) 2012.

<sup>10</sup> Stolbach, A. and Hoffman, Robert S. Opioid withdrawal in the emergency setting. [www.uptodate.com](http://www.uptodate.com) 2012.



*emergency treatment of opioid overdose, in (ultra) rapid detoxification and in combination with agonists for maintenance therapy (to prevent abuse).<sup>11</sup>*

Table 12 provides brief narratives of AEs of CV interest reported by subjects but *not* classified as SAEs and did *not* lead to discontinuations.

**Table 12: Non-SAEs of CV interest in study 3356 (DB and OL phases)**

Study 3356	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
<p><b>Subject MOA7283356-218-4319:</b> 60 yo M (wt. 86 kg, BMI = 26) w/ hyperlipidemia, HTN, and low back pain who was receiving hydrocodone 10 mg QID, morphine sulfate 30 mg BID, Zanaflex, Cymbalta, Dulcolax, HCTZ, and lisinopril experienced a non-SAE of angina with exertion on Jul 14, 2008. In addition, the subject experienced anxiety, hot and cold flashes, perspiration, piloerection and tremors on June 27, 2008 shortly after administration of the first dose of Relistor. These events resolved within 25 min. of onset. ECG changes were noted post first dose of Relistor: QT interval between the ECG obtained at screening on 12 Jun 2009 and the ECG obtained after the 1st administration of study drug on 27 Jun 2009; QTc Bazett 394 msec and QTc Bazett 486 msec respectively.</p> <p>The subject received first dose of Relistor (DB phase) on June 27, 2008 and received last dose of Relistor on Jul 23, 2008 (DB phase) and entered the OL phase. He took the first dose of OL MNTX 12 mg prn on Jul 25, 2008 and his last dose on Sept 17, 2008. He experienced angina with exertion on Jul 14, 2008, and it resolved on Jul 26, 2008 (lasted approximately 12 days). No other details provided.</p>	<p>angina pectoris</p> <p>18 days</p> <p>completed study</p>	<p>0 days after last dose</p>
<p><b>Subject MOA7283356-060-2799:</b> 48 yo M (113 kg, BMI = 34) w/ GERD who was receiving methadone for pain management experienced AEs of chest pain on Jun 23, 2008 (study day 42). He experienced 2 more episodes of chest pain on Jun 24 and 25, 2008. The chest pain episodes resolved within 24 hrs.</p> <p>He began taking MNTX 12 mg Q D (DB pd) on 5-13-08 and experienced the AEs on 6-23-08. On Jun 11, 2008, the subject received his last dose of Relistor (DB) and entered OL phase. The subject took the first dose of Relistor (OL) on Jun 12, 2008 and his last dose on Aug 3, 2008.</p>	<p>chest pain</p> <p>42 days</p> <p>completed study</p>	<p>0 days after last dose</p>
<p><b>Subject MOA7283356-020-0872:</b> 64 yo F (wt. 94 kg, BMI = 39) w/ hyperlipidemia, DM, HTN, and CAD s/p MI who was receiving fentanyl for pain management experienced non-SAE of congestive heart failure on Aug 15, 2008, which resolved on Sept 10, 2008 (study day 32). The subject complained of SOB and wt gain and was treated with furosemide from Aug 17, 2008 to Sept 15, 2008 (study day 48). On Aug 26, 2008, laboratory results revealed a decreased Hgb value. She was taking acetylsalicylic acid, fenofibrate, levothyroxine, timolol ophthalmic, humalog (insulin lispro</p>	<p>congestive heart failure</p> <p>17 days</p> <p>discontinued study due to AE of anemia</p>	<p>0 days after last dose</p>

<sup>11</sup> LA van Dorp E, et al. Naloxone treatment in opioid addiction: the risks and benefits. Expert Opin. Drug Saf. 2007; 6(2): 125-132



Study 3356	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
injection), hydrochlorothiazide, Lantus, clopidogrel, aliskiren, amlodipine, hydralazine, and lisinopril.  The subject started Relistor treatment (DB pd) on 7-30-08 and enrolled in the OL phase on 8-26-08 and took her first OL MNTX dose on 8-27-08.		
<b>Subject MOA7283356-022-0948:</b> 31 yo F (wt. 79 kg, BMI = 32) w/ OIC who was receiving methadone for pain management experienced non-SAE of chest congestion on Oct 12, 2007, which persisted. Other AEs reported on the same date included laryngitis, diarrhea, and vomiting.  The subject started Relistor treatment (DB pd) on 10-10-07 and was withdrawn from the study due to failure to return. She received one dose of Relistor.	pulmonary congestion  3 days  discontinued study (failed to return)	2 days after last dose
<b>Subject MOA7283356-009-0362:</b> 66 yo F w/ obesity (wt. 102 kg), HTN and hyperlipidemia who was receiving Vicodin for pain management experienced non-SAE of electrocardiogram QT prolonged on May 12, 2008. The subject's QTcB interval was 504 msec, the previous ECG done on study day 1 (April 14, 2008) revealed a QTcB interval of 458 msec and the screening ECG had a QTcB interval of 477 msec. The subject's last dose of Relistor prior to the AE was on May 11, 2008 at 18:00 and the ECG was performed on May 12, 2008 at 10:43. On June 10, 2008 (study day 58), the QTcB interval decreased to 443 msec.  She began taking MNTX 12 mg Q D (DB pd) on 4-14-08 and received last dose of Relistor (DB) on May 11, 2008. She started taking Relistor OL on May 13, 2008 and her last dose of Relistor OL was on July 3, 2008. She was taking hydrochlorothiazide, lisinopril, hydroxychloroquine, prednisone, esomeprazole, fluoxetine, zaleplon and pravastatin.	electrocardiogram QT prolonged  29 days  completed study	0 days after last dose
<b>Subject MOA7283356-029-1273:</b> 64 yo F (wt. 90 kg, BMI = 33) w/ HTN and fibromyalgia who was receiving Lortab for pain management experienced non-SAE of electrocardiogram QT prolonged on June 27, 2008. The subject's QTcF interval was 500 msec and the previous EKG done at screening (Jun 13, 2008) had a QTcF interval of 406 msec; this showed an increase of 94 msec. On Jul 24, 2008, the QTcF interval had decreased to 425 msec. No EKGs were available while subject was receiving Relistor. She was taking Avalide, lorazepam, and lisinopril.  The subject started taking placebo (DB) on 6-27-08 and received last dose of DB placebo on 7-24-08. She received her first dose of OL MNTX on July 26, 2008 and her last dose of Relistor on 9-18-08.	electrocardiogram QT prolonged  1 day (approximately 80 min post first dose)  completed study	0 days after last dose
<b>Subject MOA7283356-206-3231:</b> 43 yo F w/ obesity (wt. 110 kg, BMI = 39) hyperlipidemia who was receiving methadone for pain management experienced non-SAE of electrocardiogram QT prolonged on Nov 14, 2007. The subject's QTcB interval was 500 msec. The previous ECG done at screening (Oct 29, 2007) revealed a QTcB interval of 436 msec; this was an increase of 64 msec. On Dec 13, 2007, the QTcB interval decreased to 447 msec. Other associated AEs included abdominal cramps, flatulence, and nausea.	electrocardiogram QT prolonged  1 day (approximately 1hr post first dose)  discontinued	0 days after last dose

Study 3356	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
She began taking MNTX 12 mg Q D (DB pd) on 11-14-07 and received last dose of Relistor (DB) on Dec 12, 2007. She was taking venlafaxine, furosemide, oxazepam, topiramate, risperidone, and docusate.	study due to protocol violation (subject non-compliant with daily phone calls)	
<p><b>Subject MOA7283356-065-3016:</b> 27 yo M (wt. 63 kg) w/ Wolf-Parkinson-White syndrome who was receiving methadone and oxycodone for pain management experienced non-SAE of electrocardiogram changes on Nov 14, 2007, which resolved on the same day. Other associated AEs included abdominal cramping, nausea, and vomiting.</p> <p>The subject began taking MNTX 12 mg QOD (DB pd) on 11-14-07 and received last dose of Relistor (DB) on Dec 17, 2007. He started taking Relistor OL on Dec 20, 2007 and his last dose of Relistor OL was on Jan 16, 2008 (study day 64). He was taking alprazolam, Nephrocaps vitamin, prednisone, trazodone, methotrexate, and carisoprodol.</p>	<p>electrocardiogram changes</p> <p>1 day (approximately 2 hrs after first dose)</p> <p>discontinued study due to protocol violation</p>	0 days after last dose
<p><b>Subject MOA7283356-219-4344:</b> 49 yo M (wt. 123 kg, BMI = 33) w/ HTN and hyperlipidemia who was receiving morphine ER and morphine IR for pain management experienced non-SAE of syncope on June 9, 2008, which resolved on the same day. Other associated AEs included orthostatic hypotension, which started on May 22, 2008.</p> <p>Vital signs at screening (24 Apr 2008; study day -14): supine - blood pressure 110/78 mmHg, 144/94 mmHg, pulse 114 bpm; standing - blood pressure 108/72 mmHg, 93/65 mmHg, pulse 118 bpm.</p> <p>Vital signs done on study day 29 (05 Jun 2008): supine - blood pressure 127/86 mmHg, 122/92 mmHg, pulse 97 bpm; standing - blood pressure 95/69 mmHg, 94/75 mmHg, pulse 112 bpm.</p> <p>The subject began taking placebo (DB pd) on 5-8-08 and received last dose of placebo (DB) on June 4, 2008. He started taking Relistor OL on June 5, 2008 and his last dose of Relistor OL was on July 31, 2008 (study day 85). He was taking warfarin, multivitamin, glucosamine, bisacodyl, melatonin, Fioricet, Folbic, eszopiclone, quetiapine, ferrous sulfate, loratadine, ibuprofen, pseudoephedrine, metolazone, imipramine, torsemide and zolpidem.</p>	<p>syncope</p> <p>33 days</p> <p>completed study</p>	0 days after last dose

Source: Reviewer's table generated from Sponsor's data submitted in the IR response dated June 26, 2012

**Reviewer comments:** Subject 218-4319 experienced angina pectoris for approximately 12 days; however, there was no information on any other associated symptoms. Since the first dose of Relistor was administered at the study site and data on withdrawal was collected at the time, it was noted that subject 218-4319 experienced anxiety, hot and cold flashes, perspiration, piloerection and tremors. Despite the Sponsor's assertion that Relistor does not cause opioid withdrawal because it does not cross the blood brain barrier, cases such as the one described (subject 218-4319) demonstrate evidence to the contrary.

*Repeated and chronic use of opioids is known to lead to tolerance, which predisposes individuals toward withdrawal. Chronic opioid exposure causes adaptations that increases excitability in the neurons located in the locus ceruleus. The locus ceruleus is the brain's largest concentration of noradrenergic neurons and is responsible for a large proportion of brain cortical activation. When large opiate doses saturate and activate all of its  $\mu$  receptors, its steady rate of action potentials can cease due to the inactivation of potassium channels. When this direct inhibitory effect is sustained over weeks and months of opiate use, a secondary set of regulatory effects take place in the cyclic AMP system that leads to tolerance, dependence, and withdrawal symptoms.<sup>12</sup>*

*“Opiate withdrawal symptoms reflect overactivity of adrenergic neurons that are located in the locus ceruleus. Opiates suppress the activity of these neurons, and when this suppression continues chronically from daily opiate use, a secondary upregulation occurs in adenylyl cyclase enzyme capacity and the production of cyclic AMP from ATP. This upregulation is a homeostatic response to the chronic opiate suppression, but when that suppression is terminated by discontinuing the opiate or administering an opioid antagonist, this enhanced adenylyl cyclase activity leads to a marked increase in cyclic AMP. The now very high levels of cyclic AMP activate the sodium-potassium channels and produce a high level of action potentials in these adrenergic neurons. This adrenergic arousal is one basis for the symptoms of opiate withdrawal and takes about 7 days to readjust to normal levels of adenylyl cyclase activity and the associated resolution of opiate withdrawal symptoms. This molecular model of adrenergic neuronal activation during withdrawal has had important treatment implications, such as the use of clonidine for opioid withdrawal”.<sup>13</sup>*

*Subject 060-2799 experienced chest pain but limited data was provided regarding associated symptoms. Due to the unavailability of a control arm, the short duration of the DB phase in study 3356, and the confounding factors (i.e. GERD, methadone treatment, overweight, age), it is challenging to adequately assess the potential effects of Relistor on the CV system.*

Narratives of non-fatal SAEs of CV events of interest in study 3358 are provided below in Table 13. In addition, Relistor dosing is described for each subject who experienced a non-fatal SAE in study 3358.

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12 Kosten TR. Chapter 393. Opioid Drug Abuse and Dependence. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York: McGraw-Hill; 2012. <http://www.accessmedicine.com/content.aspx?alID=9149707>. Accessed July 4, 2012.

13 Kosten TR. Chapter 393. Opioid Drug Abuse and Dependence. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York: McGraw-Hill; 2012. <http://www.accessmedicine.com/content.aspx?alID=9149707>. Accessed July 4, 2012.

**Table 13: Narratives of non-fatal SAEs of CV events of interest in study 3358**

Study 3358	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
<p><b>Subject MOA7283358-095-082943:</b> 57 yo F (wt 64 Kg, BMI = 23) w/ OIC, rheumatoid arthritis, fibromyalgia, peripheral neuropathy, depression, tobacco abuse, and hyperlipidemia who was taking percocet for pain management experienced a SAE of inferior wall MI requiring stent placement on (b) (6). She was taking Cymbalta, Neurontin, soma, Xanax, and amitriptyline.</p> <p>On (b) (6), the subject was hospitalized with complaints of severe retrosternal chest pain. Troponin level was elevated and ECG revealed an inferior wall ST segment elevation. The same day (b) (6), she underwent a cardiac cath with PTCA and stent placement in the RCA and LAD artery. On (b) (6), she was discharged with the following medications: ASA, clopidogrel, and atorvastatin. Last dose of Relistor prior to the MI was on (b) (6). Relistor was temporarily discontinued, and it was resumed on May 14, 2010 and continued until study completion (last dose received on (b) (6), study day 333).</p> <p><u>Relistor dosing:</u> She administered 7 injections per wk from wks 1 to 40 except at wks 14 and 16 where she administered 6 injections each. She decreased her administration to a range of 2-4 injections per wk from wks 41 to 48</p>	<p>myocardial infarction</p> <p>306 days</p> <p>completed study</p>	<p>2 days after last dose (last dose on (b) (6))</p>
<p><b>Subject MOA7283358-198-083617:</b> 81 yo F w/ OIC, fibromyalgia, back pain, Obesity ( wt. 74 kg, BMI = 32), congenital hiatus hernia, diverticulosis, carotid stenosis s/p right carotid endarterectomy, CVA, hyperlipidemia, hypotension, and depression who was taking Hydromorph Contin and emtec for pain management experienced SAEs of partial small bowel obstruction on (b) (6) and myocardial infarction on (b) (6). She was taking Plavix, Nexium, diltiazem, lipitor, temazepam, citalopram, and depomedrol.</p> <p>On (b) (6) (study day 233), the subject took Relistor in the morning and had a "normal" BM. Several hours later at approximately 12:30pm, she experienced central upper abdominal pain associated with upper abdominal distension, nausea and vomiting. She went to the ER that same evening and an X-ray of the abdomen revealed partial small bowel obstruction (SBO). A nasogastric tube (NGT) was placed and the etiology of the SBO was attributed to adhesions from previous abdominal surgeries (cholecystectomy). Relistor was discontinued during this time, and she did not have any BMs. Patient remained on narcotics analgesics throughout her hospitalization. CT abdomen and pelvis done on (b) (6) confirmed partial small bowel obstruction. On (b) (6), subject began passing flatus, and the NGT was removed. The same day (b) (6) the subject experienced retrosternal chest pain radiating to the right shoulder. ECG revealed T wave inversion in the central pre-cordial leads, and her initial troponin level was elevated at 0.07 mgm/L and further increased to 0.1 mgm/L twelve hours later.</p> <p>On (b) (6), the patient underwent cardiac cath with left ventricular</p>	<p>myocardial infarction</p> <p>243 days</p> <p>completed study</p>	<p>10 days after last dose</p>



Study 3358	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
<p>angiogram, which revealed anteroapical akinesia with EF of 39% consistent with recent anterior myocardial infarction but minimal narrowing of the coronary arteries, etiology of infarct unclear. The patient restarted use of Relistor on (b) (6) (study day 248) and continued to administer it 2-3 times per week until study completion on (b) (6) (study day 341).</p> <p><u>Relistor dosing:</u> She administered 7 injections per wk from wks 1 to 8 except for wks 1 and 4 where she administered 4 and 6 injections, respectively. She decreased to a range of 1 to 6 injections (majority being 2 to 3 injections) from wks 9 to 49.</p>		
<p><b>Subject MOA7283358-198-083624:</b> 59 yo M w/ OIC, complex regional pain syndrome, HTN, hyperlipidemia, tobacco abuse, and GERD who was taking methadone for pain management experienced SAEs of congestive heart failure on (b) (6) (study day 43), CAD and MI on (b) (6) (study day 6), and worsening HTN on (b) (6) (study day 57). The subject was started on Relistor on (b) (6), and he experienced severe abdominal cramping, moderate nausea, diarrhea, sweating, rhinorrhea, muscle twitching, hot and cold flashes, and lacrimation after the first injection and thereafter for the first 2 wks. Despite the aforementioned symptoms, the subject remained on a consistent dose of methadone, 125 mg TID, throughout the 2 week period. On Sept 23, 2009, the subject contacted the study site and reported that he had experienced retrosternal chest pain at 2 am on Sept 22, 2009, which woke him up from sleep. He took ASA and the pain subsided and he went back to sleep. At 11:30 am on Sept 22, 2009, the subject developed retrosternal chest pain (lasted for approximately 10 min.) with nausea and cold sweating while walking slowly. In addition, the subject reported SOB at rest and with exertion for a 2 wk period. However, he did not seek any medical attention. At a study visit on (b) (6), he was found to be hypertensive with a sitting BP of 180/108 mmHg. ECG revealed marked T wave inversion consistent with a recent septal MI and he was admitted to the hospital. CXR performed on (b) (6) revealed CHF and the patient continued to report SOB with exertion. Cardiac catheterization done on (b) (6) revealed total occlusion of the LAD after the first diagonal, with 90% narrowing of first diagonal, and 70-80% narrowing of the RCA.</p> <p>The subject continued to take opioid analgesics for the complex regional pain syndrome but Relistor was discontinued from (b) (6) to (b) (6). Relistor was re-started since the patient experienced OIC. On (b) (6) the subject's BP was 146/73 at 15:35. He received Relistor at 15:40 and experienced "moderate to severe painful abdominal cramps" as he had previously with his other Relistor injections. Between 15:50 and 16:00, he had several large bowel movements. He also reported perspiration and some rhinorrhea. The subject's BP at 16:01 was 165/88 and the abdominal cramping lasted for 90 minutes. The subject did not experience any chest pain and his blood pressure at 17:15 decreased to 133/75 mmHg and by this time, the abdominal cramps were very mild and subsided shortly thereafter. Per the investigator, it was noted that despite antihypertensive medications, there had been significant increases in BP associated with the painful abdominal cramps.</p>	<p>myocardial infarction (6 days, <i>related</i>) HTN (57 days, <i>related</i>)</p> <p>cardiac failure congestive (43 days) coronary artery disease (6 days)</p> <p>discontinued (subject re-located)</p>	<p>0 days after last dose</p>

Study 3358	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
<p>A myocardial perfusion scan was done on (b) (6) and it revealed a small to moderate anterior septal infarct, moderate to large apical infarct, and EF of 41%. On (b) (6), a cardiac MRI was done for pre-bypass assessment and revealed a moderate sized transmural antero-septal infarct with adjacent subendocardial anterior infarct, transmural inferoapical infarct with subendocardial adjacent inferior infarct, and global hypokinesia more marked to the inferoapical region. On (b) (6), subject underwent triple coronary bypass surgery.</p> <p>The investigator considered MI and worsening HTN related to study medication. Per the investigator, the subject had preexisting untreated "borderline HTN" by history. He was significantly hypertensive when admitted to the hospital and BP normalized when treated with ramipril and bisoprolol. However, with a Relistor challenge, there was a significant increase of his BP during the time he was experiencing painful abdominal cramps ("this SAE is an expected physiological response to pain"). Per the investigator, in the setting of a severe narrowing of the LAD, a significant rise in BP might have contributed to the acute cardiac event (since the subject had taken 5 doses of Relistor and with each dose, the subject experienced severe abdominal cramps). He was taking lidocaine injections, dimenhydrinate, sodium docusate, and acetaminophen.</p> <p><u>Relistor dosing:</u> He administered 7 injections per wk from wks 1 to 8 except for wk 7 where he administered 5 injections. He decreased to a range of 1 to 5 injections per wk from wks 9 to 36 except he administered 7 injections at wk 32 and 6 injections at wk 31.</p>		
<p><b>Subject MOA7283358-030-080983:</b> 56 yo M with OIC, cervical/neck pain, HTN, Hyperlipidemia, obesity (115 kg, BMI = 41), CAD s/p MI, stent placement in 2007 and CABG in 1996 experienced "upper chest pain" and saw his PCP who referred him to the ER for a cardiac cath. The patient was hospitalized on (b) (6) (study day 50), and cardiac cath revealed 2 cardiac stents with 70-90% blockage. Patient was treated for "re-stenosis" and it resolved. Patient was discharged on (b) (6) on clopidogrel. The subject did not miss any doses of Relistor, and his last dose was on June 2, 2010.</p> <p>Concomitant medications include atenolol for HTN, isosorbide mononitrate for "cardiac help", lovastatin and trilipix for hyperlipidemia and ASA for "cardiac health". Subject was on Oxycodone and Morphine throughout the study for chronic pain. AE occurred at wk 7 timepoint.</p> <p><u>Relistor dosing:</u> He administered 7 injections per wk of Relistor from wks 1 to 12 and then used 2 to 7 injections from wks 13 to 49.</p>	<p>In-stent coronary artery stenosis</p> <p>50 days</p> <p>completed study</p>	<p>0 days after last dose</p>

Study 3358	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
<p><b>Subject MOA7283358-054-081616:</b> 53 yo F (wt. 104 kg, BMI = 37) with OIC, osteoarthritis, CAD s/p MI, s/p CABG, s/p stent placement, hyperlipidemia, HTN, DM, PVD, hypothyroidism, and previous tobacco abuse (quit in 1997) discontinued Relistor on (b) (6) (study day 126) due to SAE of chest pain considered related to CAD. The subject experienced 3 episodes of chest pain (chest discomfort that had been waxing and waning throughout the day) on (b) (6), which required hospitalization. ECG revealed NSR, non-specific ST-T wave changes, and old inferior and anterior myocardial infarction. Initial cardiac enzymes (CK-MB 2.5 and troponin I &lt; 1, units not provided) and CXR were normal.</p> <p>Cardiac stress testing revealed overall LVSF at the lower limits of normal with EF of 50-55%, mild diastolic dysfunction, RV mildly dilated, mild thickening of mitral valve with mild regurgitation, and no pericardial effusion, intracavitary masses or thrombi. Cardiac catheterization revealed left main 70% stenosis with questionable filling defect; LAD with 95% stenosis, grafted and diagonal 75-90% with graft occluded, left circumflex with 90-95% ostial stenosis proximal to previous stent; RCA with 75-90% stenosis, grafted, left internal mammary artery (LIMA) to LAD patent, saphenous vein graft (SVG) to RCA with three 50-60% ulcerated plaques and SVG to diagonal 100% occluded, previously stented. The recommended treatment was re-do surgical revascularization and patient underwent 3-vessel CABG. She was taking Quinapril, Metformin, Levothyroxine, Lovaza, Metoprolol, Levemir, Furosemide, Humalog, Crestor and Hydrocodone.</p> <p><u>Relistor dosing:</u> She administered 7 injections per wk of Relistor from wks 1 to 18 except on wk 11, she administered 6 injections.</p>	<p>angina pectoris</p> <p>126 days</p> <p>discontinued study</p>	<p>0 days after last dose</p>
<p><b>Subject MOA7283358-078-083349:</b> 51 yo M (wt. 209 lb, BMI = 30) w/ OIC, back pain, HTN, hyperlipidemia, tobacco abuse, and GERD who was taking oxycodone for pain management experienced SAEs of cardiac related chest pain and worsening HTN on (b) (6). The subject presented to the ER with complaint of midsternal chest pain radiating to his left arm for one hour that had gradually worsened in severity. BP in ED 198/117 mmHg and 160/80 mmHg with HR of 93-98 bpm. EKG revealed NSR with nonspecific changes and LVH with strain. CXR showed no acute cardiopulmonary disease. Troponin 0.04 ng/mL (0-0.6), CPK 154 U/L, and CK-MB 1.30 ng/mL (0-3.60). Subject was admitted to the ICU and treated with nitroglycerin drip, enoxaparin, oxygen, morphine, omeprazole, clonidine, metoprolol, valsartan, and ASA. Within 24 hrs, the subject's chest pain had resolved and his morphine dose was decreased and his BP had normalized to 130/80. Cardiac catheterization performed on (b) (6) revealed normal coronary arteries, nl LV function with EF of 60% and nl selective renal angiogram.</p> <p>He was taking Valsartan, Nitrofurantoin, Lovenox, Prilosec, Lisinopril, clonidine, lasix, Avodart, Diovan, methadone 10 mg QID, oxycodone 30 mg three to four times a day, and Simvastatin.</p> <p><b>Vital Signs</b></p>	<p>angina pectoris</p> <p>HTN</p> <p>3 days</p> <p>discontinued study due to protocol violation (it was determined the subject had participated in this trial at another site)</p>	<p>1 day after last dose</p>



Study 3358	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
<p>Screening vital signs (b) (6); study day -14): supine 144/80 mmHg, 142/84 mmHg, pulse 74 bpm; standing 150/84 mmHg, 146/84 mmHg, pulse 72 bpm.</p> <p>Study day 1 pre-dose vital signs (b) (6): supine 144/98 mmHg, 140/92 mmHg, pulse 62 bpm; standing 146/96 mmHg, 138/98 mmHg, pulse 64 bpm.</p> <p>Study day 1 post-dose vital signs (b) (6): supine 142/90 mmHg, 146/90 mmHg, pulse 72; standing 154/92 mmHg, 150/90 mmHg, pulse 86.</p> <p>Study day 3 (hospital, (b) (6)): 198/117 mmHg, 193/117 mmHg and 160/80 mmHg with HR 98 bpm and 93 bpm</p> <p>Study day 4 (hospital, (b) (6)): BP 166/98 mmHg</p> <p>Study day 29, study visit 3 (b) (6): supine 166/108 mmHg, pulse 62 bpm; supine 158/108 mmHg; standing 150/100 mmHg, pulse 60 bpm; standing 146/98 mmHg.</p> <p>Study day 32, (cardiology office, (b) (6)): 140/89 mmHg</p> <p>Study day 39, unscheduled visit (b) (6): 128/88 mmHg, pulse 56bpm</p> <p>Study day 57, study visit 4 (b) (6): supine 140/96 mmHg, pulse 64 and standing 136/98 mmHg, pulse 60.</p> <p><u>Relistor dosing:</u> He administered 7 injections per wk from wks 1 to 33 and 1 injection on wk 34.</p>		
<p><b>Subject MOA7283358-223-082439:</b> 66 yo F (62 Kg, BMI = 23) w/ OIC, back pain, OA, hyperlipidemia, "coronary artery spasms", GERD, hypothyroidism, tobacco abuse, and hysterectomy who was receiving morphine, oxycontin, and hydrocodone experienced SAEs of chest pain radiating to the left arm on (b) (6) (study day 124) and AEs of shortness of breath on exertion on 3-12-09, and palpitations. The first episode of cardiac related chest pain occurred on (b) (6) (study day 66, last dose of study drug 3-4-09) and study medication was discontinued on 3-24-09. The event persisted, and the subject continued administering Relistor on March 06, 08, 10, and 11, 2009. On March 12, 2009, she developed SOB on exertion (dyspnea on exertion) and her symptoms persisted. The subject continued administering Relistor on March 13, 15, 17, 18, 20, 22 and 24, 2009 (when she permanently discontinued Relistor). The chest pain recurred on April 12, 2009, and on (b) (6), the subject experienced chest pain radiating to her left arm. She was hospitalized and treated with ibuprofen, heparin, and nitroglycerin. The patient underwent cardiac stress test, CT scan of the heart, echocardiogram and holter monitoring but results are not available. The patient was taking Vytorin, nitroglycerin, tizanidine, L-thyroxine, verapamil, prevacid, and celebrex.</p> <p><u>Relistor dosing:</u> He administered 7 injections each for wks 1 and 2, 6 injections for wk 3. He decreased his injections to 4 per wk for wks 4 to 12 and administered 1 injection at wk 13.</p>	<p>angina pectoris</p> <p>66 days</p> <p>discontinued study</p>	<p>1 day after last dose</p>



Study 3358	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
<p><b>Subject MOA7283358-129-085920:</b> 45 yo M w/ OIC, OA, DM, HTN, obesity (wt 136 kg, BMI = 41), hyperlipidemia, GERD, "esophagus pain", and "muscle spasms" who was taking Ms Contin, percocet and tramadol for pain management experienced a SAE of single vessel coronary artery disease on (b) (6). On (b) (6), the subject experienced cardiac related chest pain and was hospitalized. He underwent a cardiac catheterization with placement of 2 stents on (b) (6), and he was started on clopidogrel. Relistor was continued uninterrupted. He was taking ranitidine, metformin, gabapentin, nitroglycerin, methocarbamol, piroxicam, insulin, omeprazole, simvastatin.</p> <p><u>Relistor dosing:</u> He administered 7 injections per wk from wks 1 to 47 except for wk 12 and wk 48 where he administered 4 injections and 5 injections, respectively.</p>	<p>coronary artery disease</p> <p>142 days</p> <p>completed</p>	<p>0 days after last dose</p>
<p><b>Subject MOA7283358-199-083669:</b> 50 yo F (wt. 82 kg, BMI 26) w/ OIC, fibromyalgia, tobacco abuse, migraine, anal ulceration, GERD, ovariectomy, and hysterectomy who was taking methadone for pain management experienced a SAE of vasospastic angina on (b) (6) (study day 81). The subject developed chest pain, weakness, and respiratory difficulty at 7:50 am on (b) (6). She was hospitalized and found to have ECG changes that necessitated coronarography evaluation. Cardiac enzymes were not elevated. She underwent a coronarography on (b) (6) and no significant coronary lesion was identified. An ergonovine test was performed and showed significant spasm of the distal anterior interventricular and circumflex arteries, and the patient was treated with 1000 mcg of intra coronary nitroglycerin and the spasm reversed. The exam was confirmed as an ergonovine positive test and the final diagnosis was vasospastic angina. She was prescribed Nitro-Dur patch, 1 mg daily and nitro spray to use if chest pain recurred. The subject was continued on Relistor without interruption during her hospitalization. She was taking Nexium, pregabalin, nasonex, clonazepam, Cymbalta, and novo-topiramate.</p> <p><u>Relistor dosing:</u> She administered alternating 4 to 5 injections per wk from wks 1 to 48 except for wks 38 and 45 where she administered 3 injections each.</p>	<p>prinzmetal angina</p> <p>81 days</p> <p>discontinued due to AE of major depression</p>	<p>1 day after last dose</p>
<p><b>Subject MOA7283358-095-082939:</b> 66 yo F (wt. 57 kg, BMI = 23) w/ OIC, back pain, HTN, hyperlipidemia, depression, tobacco abuse, and GERD who was taking oxycodone for pain management experienced a SAE of non-cardiac chest pain. She was taking celexa, norvasc, prilosec, zanaflex, zantac, and zocor.</p> <p>On (b) (6) (study day 242), the subject experienced precordial chest pain. The next day (b) (6) she presented to the ED with complaints of chest pain of 24 hrs duration, SOB, and "achy stabby pain" that worsened with deep breaths. At the time of admission, her BP was 154/87 mmHg and HR of 73 bpm. Troponin was 0 and her BP decreased with nitroglycerin paste. ECG was nl and troponin remained normal throughout the hospital course. The subject continued to experience chest pain and it was attributed to "bone spurs". Per the investigator when the</p>	<p>non-cardiac chest pain</p> <p>242 days</p> <p>completed</p>	<p>0 days after last dose</p>

Study 3358	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
<p>subject uses a heating pad and pillow on the area, the chest pain subsides, indicating a musculoskeletal problem, "probably bone spurs". The subject continued on Relistor without interruption through study day 333 (b) (6)).</p> <p><u>Relistor dosing:</u> She administered 7 injections per wk from wks 1 to 47 except at wk 17 where she administered 6 injections and wk 48 where she administered 4 injections.</p>		
<p><b>Subject MOA7283358-117-085382:</b> 72 yo F (wt. 62 kg, BMI 27) w/ OIC, back pain, CAD s/p CABG x 4 vessels, PVD, HTN, GERD, chronic cough, hypothyroidism, tobacco abuse, and urinary incontinence who was taking Endocet for pain management experienced a SAE of non-cardiac related chest pain. She was taking Plavix, lisinopril, omeprazole, aspirin, atenolol, oxybutynin, amlodipine, and levothyroxine.</p> <p>On (b) (6), the subject experienced a sudden onset of severe substernal chest discomfort, which she described as a pressure and burning-like sensation with radiation into left shoulder and left arm associated with SOB and nausea without vomiting. The subject was brought to the ED where her initial BP was 131/66 mmHg and pulse was 81 bpm. The initial EKG revealed sinus rhythm with normal intervals and axis, T wave inversions in lead V1 and V2, evidence of a probable old septal myocardial infarction and no acute ST-T segment changes. CXR revealed cardiomegaly but no infiltrates or effusions. CPK 84 U/L (0-211), troponin-T &lt; 0.01 ng/ml but proBNP was elevated at 1809 pg/ml (0-125). She was treated with nitroglycerin, oxygen and aspirin therapy and her chest pain was relieved. Relistor was temporarily discontinued on (b) (6) (study day 135) and restarted on (b) (6) (study day 137).</p> <p>Echo performed on (b) (6) revealed EF of 45%, decreased LVSF with posterior and inferior hypokinesis, mild MR, mild AI, and mild TR. Cardiac enzymes X 3 were negative, and the subject had no recurrence of chest pain while hospitalized. Cardiac stress test (adenosine Myoview study) done on (b) (6) was negative.</p> <p><u>Relistor dosing:</u> She administered 7 injections per wk from wks 1 to 31 except for wk 5 where she administered 6 injections and wk 20 where she administered 5 injections. She administered 3 injections at wk 32, her last week of dosing.</p>	<p>non-cardiac chest pain</p> <p>135 days</p> <p>discontinued at subject request (flying to NC and cannot take too many things with her)</p>	<p>1 day after last dose</p>
<p><b>Subject MOA7283358-123-085599:</b> 58 yo M w/ OIC, back pain, HTN, hyperlipidemia, DM, CAD s/p MI and stent placement, Obesity (wt 118, BMI = 37), diverticulitis, and dyspepsia who was taking oxycontin and oxycodone for pain management experienced a SAE of non-cardiac related chest pain. He was taking plavix, Avapro, lopressor, prilosec, Vytorin, and Byetta.</p> <p>On (b) (6), the subject experienced "non-cardiac" chest pain that required hospitalization. CT and ECG were done but results were not provided. He was treated with lorazepam, and the chest pain resolved. The subject missed his Relistor dose on (b) (6) as a result of the</p>	<p>non-cardiac chest pain</p> <p>240 days</p> <p>completed study</p>	<p>0 days after last dose</p>

Study 3358	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
<p>SAE.</p> <p><u>Relistor dosing:</u> He administered 7 injections per wk from wks 1 to 48 except for where he administered 6 injections at wks 11, 28, and 35. He administered 2 injections at wk 49.</p>		
<p><b>Subject MOA7283358-100-083523:</b> 41 yo F w/ OIC, back pain, Obesity (wt. 82 Kg, BMI = 34), arachnoiditis, failed back surgery syndrome, hypothyroidism, interstitial cystitis depression, anxiety, OA who was taking Avinza, Endocet, and Dilaudid for pain management experienced AEs of burning sensation in feet bilaterally, headache, ataxia, swelling of bilateral ankles, non-cardiac chest pain, tachycardia, T-wave inversion, epigastric pain, and urinary retention. She was taking Elmiron, Pyridium, Synthroid, Aldactone, Wellbutrin, Effexor, Xanax, Klonopin, and ziconotide.</p> <p>On (b) (6), the subject required hospitalization for "non-cardiac" chest pain. The last dose of Relistor was on (b) (6) (study day 164) when Relistor was discontinued at subject's request. ECG (date unknown, (b) (6) 2009) showed marked ST and T wave inversion, HR 96 bpm with no ectopy, normal axis and no atrial or ventricular hypertrophy. CT chest done on (b) (6) revealed no PE. Troponin was nl at &lt; 0.01 and CXR revealed no acute pulmonary disease. On (b) (6), myocardial perfusion scan was normal. Cardiac stress test done on (b) (6) revealed submaximal dipyridamole handgrip stress test electrocardiographically non-diagnostic for ischemia and persistent ribcage pain on deep breathing was non-anginal. Echo performed on (b) (6) showed mild sclerodegenerative mitral valve disease with mild sclerosis, mild holosystolic mitral valve insufficiency and no mitral stenosis, trace pulmonary valve insufficiency on the basis of mild pulmonary annular dilatation, trace tricuspid valve insufficiency on the basis of mild tricuspid annular dilatation, well preserved global and regional left and right ventricular systolic contractile function, and no diagnostic evidence of significant chamber dilatation or thrombus formation.</p> <p><u>Relistor dosing:</u> She administered 7 injections per wk from wks 1 to 23 except at wk 12 where she administered 6 injections and wk 24 where she administered 3 injections.</p>	<p>chest pain-non-cardiac</p> <p>166 days</p> <p>discontinued at subject request (subject unwilling to complete study)</p>	<p>2 days after last dose</p>
<p><b>Subject MOA7283358-084-083439:</b> 43 yo F (wt 60 kg, BMI 26) w/ OIC, back pain, tobacco abuse, fibromyalgia, migraines, GERD, hyperlipidemia, carotid stenosis, seizure disorder who was taking oxycodone for pain management experienced SAEs of COPD and shortness of breath (SOB). The subject was hospitalized for SOB and COPD and was treated with DuoNeb (albuterol/ipratropium) and SoluMedrol. ECG and CXR were done but results were not provided. She was taking Lyrica, Prevacid, tizanidine, Detrol LA, Topamax, and gemfibrozil.</p> <p><u>Relistor dosing:</u> She administered 7 injections per wk from wks 1 to 20 and 2 injections on wk 21.</p>	<p>COPD dyspnea</p> <p>119 days</p> <p>discontinued study drug due to AEs of increased back pain</p>	<p>0 days after last dose</p>



Study 3358	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
<p><b>Subject MOA7283358-093-082848:</b> 50 yo F w/ OIC, back pain, obesity (137 kg, BMI = 50), DM, HTN, hyperlipidemia, tobacco abuse, depression, urinary incontinence, hypothyroidism, and asthma who was taking oxycodone and morphine sulfate for pain management experienced SAEs of acute cholecystitis, cholelithiasis on 7-26-09 (study day 73, 1 day after last dose of Relistor) and respiratory distress on 8-25-09 (study day 103). She was taking enalapril, simvastatin, metformin, Enablex, levothyroxine, Paxil, Ritalin, lasix, Flexeril, Lyrica, bactrim, and Novolin insulin.</p> <p><u>Relistor dosing:</u> She administered 7 injections per wk from wks 1 to 10 except at wks 3 and 4 where she administered 6 injections and wk 11 where she administered 2 injections.</p>	<p>respiratory distress</p> <p>103 days</p> <p>discontinued study</p>	<p>32 days after last dose</p>
<p><b>Subject MOA7283358-053-081571:</b> 27 yo F with OIC, back pain, obesity (157 kg, BMI = 54), schizoaffective disorder, GERD, fibromyalgia, tobacco abuse, and polyneuropathy experienced multiple AEs at different timepoints. On June 4, 2009 (study day 15), she developed cholecystitis and underwent laparoscopic cholecystectomy on (b) (6). The subject experienced chills, fatigue, nausea, and loss of appetite on 6-11-09, vomiting and abdominal pain on 6-12-09, loss of appetite on 6-15-09, abdominal pain, intermittent vomiting, shortness of breath, and nausea on 6-23-09, subsegmental atelectasis right lung, suprahepatic abscess, and bile leak after cholecystectomy on 6-25-09, pancreatitis on 6-26-09, abdominal pain, nausea, diarrhea on 7-5-09, and swelling extremities on 7-6-09. She discontinued Relistor on 6-18-09 (study day 29). The subject developed SAEs of dyspnea, peripheral edema, and pleural effusion s/p laparoscopic cholecystectomy with subsequent post-op complication of bile leak. She was taking Geodon, Topomax, Lexapro, Lyrica, Omeprazole, and Oxycodone for bipolar depression, fibromyalgia, GERD, and pain management.</p> <p><u>Relistor dosing:</u> She administered 7 injections per wk of Relistor from wks 1 to 4 and one injection on wk 5.</p>	<p>dyspnea</p> <p>34 days</p> <p>discontinued study due to missing more than 7 diaries</p>	<p>5 days after last dose</p>
<p><b>Subject MOA7283358-123-085625:</b> 45 yo M w/ OIC, back pain, obesity (122 kg, BMI = 36), fibromyalgia, HTN, hyperlipidemia, arthritis, COPD, asthma, migraine, and neuropathic pain who was taking morphine for pain management experienced multiple SAEs of URI on (b) (6) (study day 186), weakness and renal failure on (b) (6) (study day 213), and septic shock, ARF, acute respiratory failure, hypotension, and decreased response secondary to morphine overdose on (b) (6) (study day 226). He was taking diovan, neurontin, Lyrica, advair, proventil nebulizer, and tricar.</p> <p><u>Relistor dosing:</u> He administered 7 injections per wk from wks 1 to 25 except at wks 5 and 24 where he administered 6 injections each. He administered a range of 2 to 5 injections from wks 26 to 32 except for 7 injections each at wks 29 and 30.</p>	<p>acute respiratory failure</p> <p>226 days</p> <p>discontinued (at investigator's request, considered not an ideal patient)</p>	<p>5 days after last dose</p>
<p><b>Subject MOA7283358-076-081978:</b> 44 yo F (90 kg, BMI = 33) w/ OIC, back pain, HTN, hyperlipidemia, anxiety, and depression who was receiving Norco and duragesic for pain management experienced SAEs of slurred speech, blurred vision, and left arm and leg numbness. She was taking gabapentin, valium, Ambien, Azor, Robaxin, furosemide, and Pravachol.</p>	<p>Dysarthria, hypoaesthesia vision blurred</p> <p>333 days</p>	<p>0 days after last dose</p>

Study 3358	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
<p>On (b) (6), the subject was hospitalized for slurred speech, blurred vision, and left arm and left leg numbness. She became lightheaded and developed horizontal diplopia at approximately 11:30 am on (b) (6). In the ER, her BP was 130/86 mmHg and HR of 62 bpm. In the ER, she was answering questions slowly, speech was slurred at times, and she was noted to have some memory impairment. The subject did not take any Relistor from (b) (6) (study day 333) to (b) (6) (study day 336) because she did not have access to the study drug while she was hospitalized. She restarted Relistor on (b) (6) (study day 337).</p> <p>Head CT done on (b) (6) revealed poor definition of the ventricles and cortical sulci, which raised the question of increased intracranial pressure; however, the gray-white matter differentiation appeared normal. Neuro exam at the time of admission was reported to be "essentially negative". LP was performed on (b) (6), and the findings were wnl. EEG done on (b) (6) was nl in the wake and sleep states. MRA of brain was noted to be unremarkable. MRI of brain revealed no acute findings and areas of paraventricular white matter changes in the left parietal region that were minimal. Transthoracic echo with cardiac doppler bubble study done on (b) (6) revealed nl LVSF with EF of 55-60%, no patent foramen ovale demonstrated, right ventricular chamber size and systolic function wnl, nl RA, no AS or AR, mild MR, nl TV and nl PV. Carotid doppler done on (b) (6) revealed 0-49% stenosis bilaterally. Discharge diagnosis was mental status changes of unclear etiology.</p> <p><u>Relistor dosing:</u> She administered 7 injections per wk from wks 1 to 15. She was taking 5 to 7 injections per wk from wks 16 to 49 except wk 48 she administered 3 injections.</p>	completed study	
<p><b>Subject MOA7283358-115-085291:</b> 58 yo F (wt. 75 kg, BMI = 27) with OIC, fibromyalgia, depression, migraine, HTN, hyperlipidemia, and tobacco abuse who was taking Avinza and morphine sulfate for pain management experienced a SAE of hypotension. The patient was taking propranolol, lisinopril, Flexeril, Ambien, pravastatin, Paxil, Depakote, and Arthrotec. Screening EKG and study day 1 ECG were noted to be normal. Patient received her first dose of Relistor on (b) (6) and was hospitalized for hypotensive shock and acute renal failure on (b) (6). Her last dose of Relistor was administered on (b) (6). On presentation to the ER, the subject's BP was 62/53 mmHg with a HR of 80 bpm, O<sub>2</sub>sat 97% and temp of 97.8 degrees Fahrenheit, and she was noted to be drowsy and obtunded. ER labs revealed CK 289, CK-MB 8, troponin &lt; 0.03, BUN 72, creatinine 6 (units not provided), blood alcohol level &lt; 10, and urine toxicology screen positive for opiates only. CT of the brain revealed no acute intracranial hemorrhage. She was treated in the ICU with inotropic agents, IVFs, and stress doses of hydrocortisone (a random cortisol level done on (b) (6) was 11). She recovered within 24 hrs, her renal function (creatinine 0.5) and BP improved.</p> <p><b>Vital Signs</b> (b) (6) (Study day 1 pre-dose vital signs): BP 167/104 mmHg, 163/105 mmHg, pulse 64 bpm (supine); BP 127/84 mmHg, 141/94 mmHg, pulse 98</p>	<p>hypotension</p> <p>7 days</p> <p>discontinued study</p> <p>related*</p>	2 days after last dose

Study 3358	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
<p>bpm (standing).  (b) (6) (Study day 1 post-dose vital signs): BP 144/94 mmHg, 148/95 mmHg, pulse 66 bpm (supine); BP 129/74 mmHg, 115/91 mmHg, pulse 91 bpm (standing).  (b) (6) (Study day 7, hospital): BP 62/53 mmHg, heart rate 80 bpm.  (b) (6) (Study day 10, hospital): BP 128/86 mmHg, heart rate 85 bpm.</p> <p>The investigator considered the SAE of hypotensive shock as related to study medication. The investigator reported that "2 of 4 randomized subjects' at his site experienced significant cardiovascular events which he did not consider a coincidence and therefore felt this event could potentially be related to the study medication. Other cardiovascular event was a non-serious event of pre-syncope associated with severe bradycardia".</p> <p><u>Relistor dosing:</u> She administered 5 injections at wk 1.</p>		
<p><b>Subject MOA7283358-042-081246:</b> 76 yo M w/ HTN, sick sinus syndrome s/p pacemaker placement, hyperlipidemia, obesity (wt. 110 kg, BMI = 35), OIC and back pain receiving morphine and oxycodone was hospitalized for pneumonia on (b) (6) (study day 255). The subject presented to the hospital with complaints of productive cough with greenish sputum and "acute weakness, right greater than left". CXR done on (b) (6) revealed patchy left basilar infiltrates. He received levofloxacin for the pneumonia and furosemide for "edema secondary to pneumonia". In addition, the subject had an associated non-serious adverse event of elevated troponin (lab values not provided) from (b) (6). The patient was taking metoprolol, sertraline, triamterene, gabapentin, piroxicam, niacin, HCTZ, terazosin, naproxen, and aspirin</p> <p>The subject did not miss any doses of Relistor due to the SAE. His last dose of Relistor was on (b) (6) (study day 338).</p>	<p>pneumonia (SAE)</p> <p>troponin increased (non-serious)</p> <p>255 days</p> <p>completed study</p>	<p>0 days after last dose</p>
<p><b>Subject MOA7283358-004-080049:</b> 32 yo F w/ obesity (wt. 102 kg, BMI = 36) s/p gastric bypass, OIC and back pain who was receiving morphine sulfate for back pain experienced a motor vehicle accident on (b) (6) (study day 295) and was hospitalized. She sustained multiple closed fractures of the upper limbs with rib and sternum involvement and a liver contusion due to trauma. She recovered from the events on (b) (6). The subject had a hospitalization due to a syncopal event on (b) (6) (study day 314) but etiology was unclear (clinical details of hospitalization unavailable). She discontinued Relistor use on Dec 6, 2009.</p> <p><u>Relistor dosing:</u> She administered 7 injections per week from wks 1 to 31 except for wks 26 and 27 where she administered 2 injections and 3 injections, respectively. She decreased her injection usage in the range of 3 to 6 injections per wk from wks 32 to 40.</p>	<p>syncope</p> <p>314 days</p> <p>discontinued (subject unable to return to site)</p>	<p>0 days after last dose (last dose on 12-06-09)</p>



Study 3358	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
<p><b>Subject MOA7283358-198-083618:</b> 59 yo M w/ OIC, neuropathic pain in bilateral feet, polyarteritis nodosa, osteoporosis, migraine, hepatitis C, HTN, and GERD who was receiving hydromorph contin, morphine, and dilaudid for pain management experienced multiple SAEs. He had worsening polyarteritis nodosa on 9-12-09, acute pain right angle, and right leg numbness and weakness on 9-4-09. He was taking felodipine, lorazepam, bisoprolol, septria, fosamax, pantoloc, zomiggraval, and temazepam.</p> <p><u>Relistor dosing:</u> He administered 7 injections per week from wks 1 to 7 except for wks 2 and 3 where he administered 5 injections and 6 injections, respectively. She administered 1 injection at wk 8.</p>	<p>right leg numbness</p> <p>16 days</p> <p>discontinued study</p>	0 days after last dose
<p><b>Subject MOA7283358-111-085104:</b> 56 yo F w/ OIC, RA, OA, neck surgery, HTN, hypothyroidism, and hyperlipidemia who was receiving oxycontin and hydrocodone for pain management experienced SAEs of right shoulder pain and arthroplasty. She was taking Xanax, tofranil, triavil, tiazac, Lyrica, and thyroxine.</p> <p><u>Relistor dosing:</u> She administered 7 injections per week from wks 1 to 21 except for wks 4, 16, 17, and 21 where she administered 6, 5, 5, and 5 injections, respectively.</p>	<p>musculoskeletal pain</p> <p>54 days</p> <p>discontinued (unsatisfactory response, efficacy)</p>	0 days after last dose
<p><b>Subject MOA7283358-217-082301:</b> 58 yo M w/ OIC, OA, degenerative disc disease, and anxiety who was receiving lortab for osteoarthritis experienced a SAE of right shoulder pain. He was taking alprazolam for anxiety.</p> <p><u>Relistor dosing:</u> He administered 7 injections per week from wks 1 to 30 except for wk 31 where he administered 4 injections.</p>	<p>musculoskeletal pain</p> <p>14 days</p> <p>discontinued due to protocol violation (patient was participating in 2 clinical trials simultaneously)</p>	0 days after last dose
<p><b>Subject MOA7283358-071-081841:</b> 81 yo M (wt 80 kg, BMI = 26) w/ OIC, back pain, scoliosis, hyperlipidemia, HTN, DM, Parkinson's disease, and depression who was receiving Roxicodone for pain management experienced SAEs of abnormal MRI of the spine and spinal osteoarthritis on 10-9-09. He was taking Neurontin, norvasc, Ambien, Cymbalta, Diazide, Prevacid, levodopa, Crestor, and Prandin.</p> <p>MRI of lumbar spine with and without contrast done on Oct 8, 2009 (study day 289) revealed T12-L1 disc with mild desiccation and advanced endplate spondylosis but no herniation; L1-L2 with advanced endplate spondylosis, edema and fluid about the L1-L2 disc space with edema involving the adjacent soft tissues anteriorly; L2-L3 with endplate spondylosis; L3-L4 with no herniation; L4-L5 was narrowed but no herniation; L5-S1 were normal; and advanced scoliotic curve convex to the left of L1-L2 with posterior stabilization devices in place. MRI impression noted findings were suspicious for discitis and adjacent osteomyelitis and paraspinal abscess at L1-2, and showed extensive surgery from L2-L5.</p>	<p>nuclear magnetic resonance imaging abnormal</p> <p>291 days</p> <p>completed study</p>	0 days after last dose

Study 3358	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
<u>Relistor dosing:</u> He administered 7 injections per week from wks 1 to 49 except for wks 6, 7 and 49 where he administered 6 injections each and wks 33 and 42 where he administered 4 injections each.		
<p><b>Subject MOA7283358-021-084685:</b> 79 yo M w/ OIC, back pain, and atrial fibrillation s/p pacemaker placement who was receiving hydromorphone for pain management was hospitalized for a SAE of pulmonary embolus. A CT scan revealed an acute pulmonary embolus in the segmental pulmonary branches to the lateral segment of the RLL. On admission his INR was 1.8.</p> <p><u>Relistor dosing:</u> He administered 7 injections per week from wks 1 to 44 except for wks 36 and 44 where he administered 6 and 4 injections, respectively.</p>	<p>pulmonary embolism</p> <p>281 days</p> <p>discontinued due to protocol violation (unable to comply with clinphone calls and administer study medication during hospitalization)</p>	0 days after last dose

\*Relationship to study drug as assessed by the investigator

Source: Reviewer's table modified from Sponsor's table 15.19, subject narrative information in final CSR, Protocol 3200K1-3358-WW, pages 541 to 815 and IR 12 Listing 7.1a from IR response to IR letter dated April 18, 2012

Reviewer comments: Subject 198-083624 could be considered the index case for what might potentially occur if opioid withdrawal is unintentionally induced using a  $\mu$  receptor antagonist such as Relistor to treat OIC. Due to the documentation provided by the investigator in subject 198-083624's AEs reporting, it appears that Relistor administration caused opioid withdrawal symptoms (sweating, rhinorrhea, muscle twitching, hot and cold flashes, lacrimation).

In addition, hyperthermia, tachycardia, and hypertension have been described as signs that can be observed during opioid withdrawal.<sup>14</sup> Subject 198-03624 had documented hypertensive episodes (180/108), which might have contributed to his cardiac symptoms and findings (myocardial infarction). As noted in uptodate and is known in clinical practice, a young patient might tolerate a HR of 120; however, an older patient with unknown or known coronary artery disease should not remain hypertensive and tachycardic for prolonged periods.<sup>15</sup>

<sup>14</sup> Becker, GL et al. Antagonist-precipitated and discontinuation-induced withdrawal in morphine-dependent rhesus monkeys. Psychopharmacology 2008; 201: 373-382.

<sup>15</sup> Stolbach, A. and Hoffman, Robert S. Opioid withdrawal in the emergency setting. www.uptodate.com 2012.



*During episodes of opioid withdrawal where a patient is experiencing vomiting and diarrhea, hypotension might occur in the setting of volume depletion. Subject 115-085291 experienced hypotension; however, there was limited information to accurately assess the cause of the hypotension.*

*There have been 2 cases of stress-induced cardiomyopathy or Tako-Tsubo syndrome ("broken heart syndrome") described in the setting of opioid withdrawal in opioid dependent patients.<sup>16,17</sup> The broken heart syndrome is a transient LV apical ballooning that occurs in patients after emotional or physical stress. It is thought that these patients have supraphysiologic levels of plasma catecholamines and stress-related neuropeptides that cause them to present with symptoms and complications similar to an acute coronary syndrome.<sup>18</sup> Several subjects (095-082943, 030-080983, 054-081616, 223-082439, 129-085920, 199-083669) described above in Table 13 experienced cardiac related non-fatal SAEs, which could be attributed to a stress-induced cardiomyopathy occurring in the setting of treatment with a  $\mu$  receptor antagonist, Relistor.*

*This reviewer agrees with the Sponsor who asserts that the target patient population (chronic non-cancer pain with OIC) is at high risk for cardiovascular disease.<sup>19</sup> In light of an open label trial (study 3358), it is challenging to assess the additional risk of chronic treatment with Relistor ( $\mu$  receptor antagonist) on the baseline high cardiovascular risk of this particular patient population.*

Table 14 provides the dosing of Relistor for each week of the 4 weeks preceding the non-fatal SAE. In addition, the last column in the table below provides the overall average weekly injection frequency of MNTX 12 mg in study 3358 for subjects excluding the 4 weeks prior to the non-fatal SAE.

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16 Rivera, JM et al. "Broken Heart Syndrome" After Separation (From OxyContin). Mayo Clinic Proceedings 2006: 81(6): 825-828.

17 Lemesle, F et al. First case of stress cardiomyopathy as a result of methadone withdrawal secondary to drug-drug interaction. The American Journal of Emergency Medicine 2010: 28: 387e5-387e6.

18 Wittstein, IS et al. Neurohumoral Features of Myocardial Stunning Due to Sudden Emotional Stress. N Engl J Med 352(6): 539-548.

19 Carman, WJ et al. Coronary heart disease outcomes among chronic opioid and cyclooxygenase-2 users compared with a general population cohort. Pharmacoepidemiology and Drug Safety 2011: 20: 754-762

**Table 14: Wkly use of MNTX 12 mg of each wk of the 4 wks preceding the non-fatal SAE and overall average weekly injection frequency of MNTX 12 mg excluding the 4 wks prior to the non-fatal SAE**

Subject id	Preferred term	Injection 1 wk prior	Injection 2 wks prior	Injection 3 wks prior	Injection 4 wks prior	overall avg wkly injection*
004-080049	syncope	0	0	0	0	3.6
030-080983	in stent coronary artery restenosis	7	7	7	7	7
053-081571	dyspnea	2	7	7	7	7
054-081616	angina pectoris	7	7	7	7	7
076-081978	dysarthria hypoesthesia vision blurred	6	7	7	7	7
078-083349	angina pectoris HTN	3	0	0	0	
084-083439	dyspnea	7	7	7	7	7
093-082848	respiratory distress	0	0	0	0	7
095-082939	non-cardiac chest pain	7	7	7	7	7
095-082943	myocardial infarction	3	3	4	5	7
100-083523	non-cardiac chest pain	5	7	7	7	7
115-085291	hypotension	5	0	0	0	
117-085382	non-cardiac chest pain	6	7	7	7	7
123-085599	non-cardiac chest pain	7	7	7	7	6.8
123-085625	acute respiratory failure	2	1	7	7	4.3
129-085920	coronary artery disease	7	7	7	7	7
198-083617	myocardial infarction	1	2	2	2	3.2
198-083624	cardiac failure congestive	7	7	7	7	7
	coronary artery disease	6	0	0	0	
	HTN	6	5	7	7	7
	myocardial infarction	6	0	0	0	
199-083669	prinzmetal angina	4	4	4	5	4.7
223-082439	angina pectoris	0	0	0	0	4.1
021-084685	pulmonary embolism	6	7	7	7	6.8
071-081841	nuclear magnetic resonance imaging abnormal spinal osteoarthritis	7	7	7	7	7
111-085104	musculoskeletal pain	7	7	7	7	6.7
	shoulder arthroplasty	6	7	7	7	7

**Table 14 Cont'd: Wkly use of MNTX 12 mg of each wk of the 4 wks preceding the non-fatal SAE and overall average weekly injection frequency of MNTX 12 mg excluding the 4 wks prior to the non-fatal SAE**

Subject id	Preferred term	Injection 1 wk prior	Injection 2 wks prior	Injection 3 wks prior	Injection 4 wks prior	overall avg wkly injection*
198-083618	muscular weakness	6	6	2	0	
	hypoesthesia	6	6	2	0	
	arthralgia	6	6	2	0	
	polyarteritis nodosa	7	6	5	3	
217-082301	musculoskeletal pain	7	7	0	0	

\*Average weekly injection is not displayed for subjects with  $\leq 28$  days of exposure

Source: Reviewer's table modified from Sponsor's IR 12 listing 7.2b, pages 1 to 17, from IR response to IR letter dated April 18, 2012

**Table 15: Narratives of CV events of interest that led to discontinuations in study 3358\***

Study 3358	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
<p><b>Subject MOA7283358-046-081385:</b> 57 yo F (wt. 78 kg, BMI = 30) w/ OIC, back pain, right bundle branch block, MVP, and hyperlipidemia who was taking Norco and morphine sulfate for back pain experienced AE of unstable angina. Concomitant medications started at onset of AE were as follows nitroglycerin, fenofibrate, and aspirin. She had a thallium stress test done but results were not provided. She was taking estradiol, zolpidem, duloxetine, pregabalin, promethazine, and eszopiclone.</p> <p>On May 12, 2009, the subject was started on Relistor and received her last dose of Relistor on June 8, 2009 (study day 28). Relistor was discontinued and the subject was withdrawn from the study as a result of the AE.</p>	<p>angina unstable</p> <p>15 days</p> <p>discontinued</p>	<p>0 days after last dose</p>
<p><b>Subject MOA7283358-200-083701:</b> 59 yo M (wt. 110 kg, BMI = 39) w/ hyperlipidemia, HTN, and previous tobacco abuse who was taking oxycodone and morphine SR for back pain experienced AE of angina pectoris on Jan 23, 2010. The subject had stopped taking Relistor on Nov 22, 2009 (study day 29) due to an AE of abdominal pain.</p>	<p>angina pectoris</p> <p>131 days</p> <p>discontinued due to AE of abdominal pain</p>	<p>69 days after last dose</p>
<p><b>Subject MOA7283358-020-080657:</b> 51 yo F (wt. 107 kg, BMI = 36) w/ OIC, GERD, s/p gastric bypass and OA of both knees who was taking Darvocet and Vicodin for joint pain experienced AE of chest heaviness on 7-18-09 (study day 40), which resolved on 7-23-09. The investigator considered the AE related to the study medication and thought it was "most likely related to an allergic reaction".</p> <p>She temporarily discontinued Relistor from 7-19-09 to 7-21-09 due to the AE of chest heaviness, and then resumed dosing on 7-22-09 (the event recurred) after which "they discontinued due to the adverse event". No other AEs were reported during the study. The subject was taking gabapentin, lansoprazole, triameterene, escitalopram, and conjugated estrogen.</p>	<p>chest discomfort</p> <p>40 days</p> <p>discontinued</p> <p>related**</p> <p>+re-challenge as assessed by this reviewer</p>	<p>0 days after last dose</p>

Study 3358	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
<b>Subject MOA7283358-079-082035:</b> 63 yo M w/ OIC, back pain, HTN, hyperlipidemia, "heart disease", ED, anxiety, and panic attacks who was receiving oxycodone for pain management experienced AEs of chest heaviness, claustrophobia, dizziness, and sweating. The investigator considered the AEs related to the study medication. The subject had no other AEs during the study. He was taking Plavix, lisinopril, carvedilol, xanax, simvastatin, and norvasc.	chest discomfort  1 day (post first dose)  discontinued  <i>related**</i>	0 days after last dose
<b>Subject MOA7283358-108-085041:</b> 70 yo F (wt. 55 kg, BMI = 21) w/ OIC, back pain, fibromyalgia, migraines, HTN, GERD, hyperlipidemia who was receiving tramadol for pain management experienced a AE of chest tightness and nausea on Aug 18, 2009 and resolved on Aug 19, 2009. The subject received her first dose of Relistor on Aug 18, 2009 and Relistor was discontinued due to the AE. The investigator considered the AEs related to the study medication. The subject had no other AEs during the study. She was taking cyclobenzaprine, simvastatin, Cephadyn, verapamil, enalapril, and benzonatate.	chest discomfort  1 day (post first dose)  discontinued  <i>related**</i>	0 days after last dose
<b>Subject MOA7283358-141-086375:</b> 53 yo M w/ OIC, neuropathic pain, HTN, DM, hyperlipidemia, Obesity (135 kg, BMI = 38), GERD, and anxiety who was receiving oxycodone, Dilaudid and morphine for pain management experienced AE of chest pain on Dec 9, 2009 (developed chest pain after taking Relistor and the CP resolved on Dec 10, 2009). The subject informed the study site that "he wanted to discontinue study participation as he did not like how he felt after taking the study drug".  The investigator considered the AE not related to the study medication. The subject had no other AEs during the study. He was taking atenolol, benazepril, lovastatin, omeprazole, metformin, Humulin 70/30, Humalog, lasix, and clonazepam.  <i>Relistor dosing:</i> The subject started OL Relistor on Aug 18, 2009 and his last dose of Relistor was on Dec 9, 2009 (study day 114).	chest pain  114 days  discontinued	0 days after last dose
<b>Subject MOA7283358-008-080232:</b> 62 yo M (wt. 102 kg, BMI = 44) w/ OIC, back pain, HTN and CAD s/p CABG X 3 vessels who was receiving methadone for back pain experienced AE of "chest pain of non-cardiac origin", which started on 2-23-10 and resolved on 2-24-10. The subject discontinued study medication on 2-26-10. The subject had an AE of bronchitis from 2-5-10 to 2-20-10, and the investigator considered the AE related to the diagnosis of bronchitis. No other AEs were reported during the study. He was taking clarithromycin and methylprednisone from 2-5-10 to 2-11-10.  The subject began taking Relistor on May 18, 2009 and his last dose of Relistor was on 2-26-2010 (study day 285). Relistor was discontinued as a result of the AE.	Non-cardiac chest pain  282 days  discontinued	0 days after last dose



Study 3358	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
<p><b>Subject MOA7283358-005-080102:</b> 58 yo F (wt. 76 kg, BMI = 30) w/ OIC, hyperlipidemia, multiple sclerosis, UC, GERD, COPD, muscle spasm and s/p cholecystectomy who was receiving methadone and morphine for MS experienced AEs of fatigue, shortness of breath, restlessness, anxiety, muscle twitches, abdominal cramps, vomiting, hot and cold flashes, nausea, and perspiration which occurred the same day as the first dose administration (5-20-09). Nausea resolved on 5-25-09, fatigue resolved on 6-1-09. She took phenergan, and decadron on 5-20-09, and phenergan suppositories from 5-20-09 to 5-25-09. The investigator assessed all the AEs as related to Relistor. She was taking Miralax for constipation, sulfasalazine, and ranitidine.</p> <p>The subject received her first dose of Relistor on May 20, 2009 at 13:32 and was discontinued from the study on the same day due to the AEs (timeframe of AEs relative to first dose not specified).</p>	<p>dyspnea  abdominal pain  anxiety  fatigue  feeling of body temperature change  hyperhidrosis  muscle twitching  nausea  restlessness  vomiting</p> <p>1 day (post first dose)  discontinued  related**</p>	<p>0 days after last dose</p>
<p><b>Subject MOA7283358-199-083661:</b> 50 yo M (wt. 74 kg, BMI = 25) w/ OIC, "chronic lumbalgia due to central neuralgia", depression, hyperlipidemia, myofascial pain syndrome, dislocation of vertebra, GERD, HTN, asthma, and pollen allergy who was receiving morphine for pain management experienced AE of dyspnea on June 22, 2009. The subject had no other AEs during the study. He was taking Maalox, effexor, clonazepam, acetaminophen, and cesamet.</p> <p>The subject was started on Relistor on June 9, 2009 and his last dose of Relistor was on June 28, 2010 (study day 20).</p>	<p>dyspnea  14 days  discontinued</p>	<p>0 days after last dose</p>
<p><b>Subject MOA7283358-049-081474:</b> 30 yo M w/ OIC, back pain, heart palpitations, anxiety, and depression who was receiving tramadol and oxycontin for back pain experienced AE of worsening palpitations which started on 3-11-09, the first day of study medication and resolved on 3-17-09. Additional AEs included abdominal cramping (3-11-09 to 3-12-09) and worsening anxiety (3-14-09 to 3-17-09). He was taking ativan (3-14-09 to 3-14-09) and klonopin (3-14-09 to cont'd) for worsening anxiety.</p>	<p>palpitations  1 day (post first dose)  discontinued</p>	<p>0 days after last dose</p>
<p><b>Subject MOA7283358-023-080754:</b> 51 yo M w/ OIC, hyperlipidemia, hyperglycemia, COPD, Obesity (wt. 118 kg), back pain who was receiving methadone and Dilaudid for back pain had lengthening QT which started on 8-12-09, the first day of study medication and continued. A screening ECG revealed a borderline prolonged QTcB 472 msec. On day 1, ECG performed after the first dose of study drug was administered revealed a QTcB interval of 545 msec with a change from baseline of &gt; 60 msec ("technical quality of ECG was poor" and accurate measurement of intervals was difficult).</p> <p>On day 10, ECG was repeated and revealed a QTcB of 547 msec. On day 15, ECG was repeated (post study drug discontinuation visit) and QTcB interval returned to baseline of 472 msec. Additional AEs that began on 8-12-09 included abdominal cramping that resolved on 8-27-09 (study drug</p>	<p>electrocardiogram QT prolonged  1 day (post first dose)  discontinued  related**</p>	<p>0 days after last dose</p>

Study 3358	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
discontinued on 8-25-09). No new concomitant medications were started during the study. The investigator considered the SAE of electrocardiogram QT prolonged as related to Relistor.		
<p><b>Subject MOA7283358-042-081244:</b> 42 yo F (wt. 137 kg, BMI = 43) w/ OIC, eosinophil myalgia syndrome, borderline prolonged QT (since 12-16-08), and obesity who was receiving Ms Contin and morphine for eosinophil myalgia syndrome had worsening prolongation QT, which started on 1-2-09 and continued. No other AEs were reported. Screening ECG revealed borderline increased QTcB interval of 492 msec. She received her first dose of study medication on day 1, and ECG done 1 hr post dose revealed a QTcB of 520 msec. Subject was discontinued from the study and ECG done on day 13 revealed slightly decreased but prolonged QTcB interval at 511 msec. No new concomitant medications were started during the study.</p> <p>The subject started taking Relistor on 1-2-2009, and her last dose of Relistor was on 1-6-2009 (study day 5).</p>	<p>electrocardiogram QT prolonged</p> <p>1 day (post first dose, approximately 1 hr post dose)</p> <p>discontinued</p> <p>related**</p>	<p>0 days after last dose</p>
<p><b>Subject MOA7283358-060-083965:</b> 69 yo M (wt. 79 kg, BMI = 25) w/ OIC, back pain, HTN, and cardiac arrhythmia who was receiving fentanyl for back pain had AEs of prolonged QTcB interval and occasional premature ventricular contractions which started on 6-25-09 and resolved on 7-6-09. The QTcB interval on day 1 (6-25-09) post first dose of study drug was 495 msec, which represented an increase of 88 msec from the baseline value of 407 msec. No additional adverse events were reported.</p> <p>He was taking Miralax, Senokot, Metamucil, Tambocor, and Zestril. At ET visit on 7-6-09 and follow-up visit on 7-16-09, the QTcB interval was 420 msec (study drug discontinued on 7-1-09).</p>	<p>electrocardiogram QT prolonged ventricular extrasystoles</p> <p>1 day (post first dose)</p> <p>discontinued</p>	<p>0 days after last dose</p>
<p><b>Subject MOA7283358-198-083611:</b> 29 yo M (wt. 77 kg, BMI = 27) w/ OIC, neuropathic pain, restless leg syndrome, and depression who was receiving methadone for pain management had AE of abnormal ECG-QTcB prolonged &gt; 500 msec on 6-11-09. The investigator considered the AE related to the study medication and study medication was discontinued on 6-22-09. On follow-up ECG done on 6-25-09, the QTcB was 493 msec.</p> <p>The subject had experienced other AEs of abdominal cramps, chills, anxiety, restlessness, perspiration, and diarrhea during the study. He was taking temazepam, Sinemet, ibuprofen, and triazolam.</p>	<p>electrocardiogram QT prolonged</p> <p>1 day (study drug started on 6-11-09, approximately 1 hr post dose)</p> <p>discontinued</p> <p>related**</p>	<p>0 days after last dose</p>
<p><b>Subject MOA7283358-198-083619:</b> 42 yo F (wt. 55 kg, BMI = 22) w/ OIC, fibromyalgia, migraine, thoracic outlet syndrome, degenerative disc disease, and depression who was receiving methadone for pain management had borderline prolonged QTc interval on 8-28-09, first day of study drug administration. The investigator considered AE related to the study drug and the study drug was discontinued on 9-3-09. On follow-up ECG, QT interval had normalized (QT interval 420 msec, QTcB 405 msec, and QTcF 410 msec).</p> <p>The subject experienced other AEs of abdominal cramps, rhinorrhea, and stinging at injection site during the study. She was taking Avmys, Advair, and imitrex nasal spray.</p>	<p>electrocardiogram QT prolonged</p> <p>1 day (approximately 1 hr post first dose)</p> <p>discontinued</p> <p>related**</p>	<p>0 days after last dose</p>

Study 3358	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
<b>Subject MOA7283358-128-085865:</b> 51 yo M w/ OIC, back pain, abnormal ECG 1st degree AV block and poor pre-cordial R wave progression, hyperlipidemia, bilateral edema of extremities, depression, MS, and anxiety who was receiving morphine and methadone for pain management had AE of Mobitz 1 AV block. The investigator considered the AE related to the study medication. The subject started the study drug on 6-24-09 and discontinued the study drug on 6-26-09. The subject had additional AEs of diarrhea and tingling tongue during the study. He was taking pregabalin, baclofen, clonazepam, diazepam, fluoxetine, copaxone, and promethazine.	Atrioventricular block second degree  1 day  discontinued  <i>related**</i>	0 days after last dose
<b>Subject MOA7283358-125-085686:</b> 74 yo M w/ OIC, back pain, HTN, hyperlipidemia, hypothyroidism, first degree AV block, sinus bradycardia, GERD, and chronic renal failure who was receiving morphine and percocet for pain management had AE of increased PR interval and decreased heart rate on 7-7-09, first day of study drug administration. The study drug was discontinued on 7-9-09. The subject had no other AEs reported during the study. He was taking atenolol, omeprazole, lovastatin, and synthroid.	electrocardiogram PR prolongation HR decreased  1 day  discontinued	0 days after last dose
<b>Subject MOA7283358-115-085285:</b> 45 yo F w/ OIC, migraine, neck pain, fibromyalgia, GERD, hypothyroidism, depression, peptic ulcer, and asthma who was receiving tylenol #3 and morphine sulfate for pain management had AE of low pulse rate, which required a ER visit on (b) (6). She started study drug on (b) (6) and discontinued study medication on (b) (6). The subject had other AEs of worsening GERD and cellulitis during the study. She was taking Neurontin, effexor, trazodone, levoxyl, zanaflex, fiorinal/butanol, and propranolol.	heart rate decreased  52 days  discontinued	
<b>Subject MOA7283358-120-085460:</b> 68 yo F w/ OIC, back pain, HTN, stroke, aneurysm of aortic arch, hyperlipidemia, COPD, and GERD who was receiving oxycodone and morphine for pain management had AEs of low blood pressure and urinary incontinence. The investigator considered those AEs related to the study drug. The subject experienced other AEs of loss of appetite, numbness, and bloating during the study. She was taking HCTZ, benazepril, simvastatin, Zegerid, and Oxybutynin.	hypotension  33 days  discontinued  <i>related**</i>	0 days after last dose
<b>Subject MOA7283358-132-086046:</b> 56 yo F w/ OIC, back pain, hyperlipidemia, GERD, depression, and anxiety who was receiving percocet for pain management had AE of hypotension. The subject started study drug on 7-29-09, hypotension began on 8-25-09 and study drug was discontinued on 8-27-09. The subject had additional AE of sinus cyst during the study. She was taking simvastatin, oxybutynin, omeprazole, and prozac.	hypotension  28 days  discontinued	0 days after last dose
<b>Subject MOA7283358-034-081063:</b> 51 yo M w/ OIC, back pain, HTN, and diverticulitis who was receiving methadone and percocet had AEs of abdominal cramps and elevated blood pressure. The study drug was started on 3-31-09 and discontinued on 4-27-09. Abdominal cramps started on 3-31-09, the first day of study drug and resolved on 4-29-09. Elevated BP started on 4-28-09 and resolved on 6-8-09. Screening BP readings were: 128/86 supine, 127/86 supine, 127/91 standing, and 140/87 standing. At the ET visit on 4-28-09, BP readings were: 173/96 supine, 181/108 supine, 161/100 standing, and 159/96 standing. At f/u visit on 6-8-09, BP readings were: 147/86 supine, 155/87 supine, 155/79 standing, and 147/86 standing.	blood pressure increased (29 days post first dose)  abdominal pain (same day as first dose)  discontinued	1 day after last dose (BP increased)



Study 3358	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose																																							
<p><b>Subject MOA7283358-019-080605:</b> 36 yo M (wt. 91 kg, BMI = 27) with HTN had multiple AEs post first dose of study drug: cramping in abdomen intermittently, diarrhea (3 episodes), feeling faint, rumbling in abdomen, hot flashes intermittently, diaphoretic intermittently, nausea and blurred vision. He was started on study drug on 5-20-09 and discontinued study drug on 5-20-09. He was taking hydromorphone 8 mg BID, methadone 40 mg TID (until 5-23-09), oxycodone 30 mg six times/day, temazepam, amlodipine, and lisinopril.</p> <p>Vital signs at screening (05 May 2009, study day -15): supine - blood pressure 110/80 mmHg, 118/78 mmHg, pulse 56 bpm; standing - blood pressure 118/78 mmHg, 106/76 mmHg, pulse 68 bpm.</p> <p>Vital signs on study day 1 pre-dose (20 May 2009): supine - blood pressure 120/76 mmHg, 118/80 mmHg, pulse 80 bpm; standing - blood pressure 120/86 mmHg, 110/76 mmHg, pulse 88 bpm.</p> <p>Vital signs on study day 1 post-dose (20 May 2009): supine - blood pressure 112/70 mmHg, 114/80 mmHg, pulse 80 bpm; standing - blood pressure 106/76 mmHg, 108/76 mmHg, pulse 88 bpm.</p>	<p>vision blurred nausea hyperhidrosis malaise gastrointestinal sounds abnormal dizziness diarrhea abdominal pain</p> <p>discontinued</p> <p>related**</p>	0 days after last dose																																							
<p><b>Subject MOA7283358-038-081107:</b> 56 yo M w/ OIC and OA who was receiving methadone for OA experienced AE of opioid withdrawal symptoms, which started on 5-24-09 and resolved on 5-28-09. No additional AEs were reported.</p> <p>The objective opioid withdrawal scores (OOWS) and subjective opioid withdrawal scores (SOWS) were administered pre- and post-dosing on the first day of study treatment. These scales were not administered at any other time points in study 3358. The subject received treatment with Relistor 12 mg Q D from May 18, 2009 (study day 1) through May 24, 2009 (study day 7). However, the OOWS and SOWS evaluation was not performed on day 7 when subject experienced the AE.</p> <p>OOWS scores as rated by the study site trained observer (study day 1)</p> <table border="1"> <thead> <tr> <th>OOWS Symptom</th><th>Pre-Dose Score</th><th>Post-Dose Score</th></tr> </thead> <tbody> <tr><td>Yawning</td><td>0</td><td>0</td></tr> <tr><td>Rhinorrhea</td><td>0</td><td>0</td></tr> <tr><td>Piloerection</td><td>0</td><td>0</td></tr> <tr><td>Perspiration</td><td>0</td><td>1</td></tr> <tr><td>Lacrimation</td><td>0</td><td>0</td></tr> <tr><td>Mydriasis</td><td>0</td><td>0</td></tr> <tr><td>Tremors</td><td>0</td><td>0</td></tr> <tr><td>Hot and cold flashes</td><td>0</td><td>0</td></tr> <tr><td>Restlessness</td><td>0</td><td>0</td></tr> <tr><td>Vomiting</td><td>0</td><td>0</td></tr> <tr><td>Muscle twitches</td><td>0</td><td>0</td></tr> <tr><td>Abdominal cramps</td><td>0</td><td>0</td></tr> </tbody> </table>	OOWS Symptom	Pre-Dose Score	Post-Dose Score	Yawning	0	0	Rhinorrhea	0	0	Piloerection	0	0	Perspiration	0	1	Lacrimation	0	0	Mydriasis	0	0	Tremors	0	0	Hot and cold flashes	0	0	Restlessness	0	0	Vomiting	0	0	Muscle twitches	0	0	Abdominal cramps	0	0	<p>drug withdrawal syndrome</p> <p>7 days</p> <p>discontinued</p>	0 days after last dose
OOWS Symptom	Pre-Dose Score	Post-Dose Score																																							
Yawning	0	0																																							
Rhinorrhea	0	0																																							
Piloerection	0	0																																							
Perspiration	0	1																																							
Lacrimation	0	0																																							
Mydriasis	0	0																																							
Tremors	0	0																																							
Hot and cold flashes	0	0																																							
Restlessness	0	0																																							
Vomiting	0	0																																							
Muscle twitches	0	0																																							
Abdominal cramps	0	0																																							

Study 3358			AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
Anxiety	0	0		
Anxiety				
Total Score	0	1		
0 = not present; 1 = present				
SOWS scores as rated by subject (study day 1)				
SOWS Symptom	Pre-Dose Score	Post-Dose Score		
Anxiety	2	1		
Yawning	1	0		
Perspiration	1	2		
Tearing eyes	0	0		
Running nose	0	0		
Gooseflesh	0	0		
Shaking	0	0		
Hot flashes	1	1		
Cold flashes	0	0		
Bones and muscle aching	2	0		
Restlessness	1	1		
Nausea	0	1		
Felt like vomiting	0	0		
Muscle twitches	0	0		
Stomach cramps	0	1		
Opioid craving	1	0		
Trouble sleeping	0	0		
Poor appetite	0	0		
Diarrhea	0	0		
Total Score	9	7		
0 = not at all; 1 = a little; 2 = moderately; 3 = quite a bit; 4 = extremely				
<b>Subject MOA7283358-142-086426:</b> 65 yo F w/ OIC, back pain, asthma, anxiety, and hypoparathyroidism who was receiving actig and duragesic for pain management experienced AE of symptoms consistent with opioid withdrawal. The investigator considered the AE related to the study medication. The subject had other AE of abdominal pain during the study. She was taking rocaltrol, proventil, serevent, and flovent.			drug withdrawal syndrome	0 days after last dose
The objective opioid withdrawal scores (OOWS) and subjective opioid withdrawal scores (SOWS) were administered pre- and post-dosing on the first day of study treatment. These scales were not administered at any other time points in study 3358.			1 day (post first dose)	
OOWS scores rated by the study site trained observer (study day 1)			discontinued	
OOWS Symptom	Pre-Dose Score	Post-Dose Score	related**	
Yawning	0	0		
Rhinorrhea	0	0		
Piloerection	0	1		

Study 3358			AE/Onset of AE from time of <i>first</i> dose/Outcome	Time interval of MNTX dose
Perspiration	0	0		
Lacrimation	0	0		
Mydriasis	0	0		
Tremors	1	1		
Hot and cold flashes	0	1		
Restlessness	0	1		
Vomiting	0	1		
Muscle twitches	0	0		
Abdominal cramps	0	1		
Anxiety	1	1		
Anxiety	"Mild"	"Moderate"		
Total Score	2	7		
0 = not present; 1 = present				
SOWS scores as rated by subject (study day 1)				
SOWS Symptom	Pre-Dose Score	Post-Dose Score		
Anxiety	1	2		
Yawning	2	2		
Perspiration	3	2		
Tearing eyes	0	0		
Running nose	1	1		
Gooseflesh	0	2		
Shaking	3	3		
Hot flashes	0	3		
Cold flashes	2	3		
Bones and muscle	4	3		
Restlessness	1	3		
Nausea	1	4		
Felt like vomiting	1	4		
Muscle twitches	2	4		
Stomach cramps	2	4		
Opioid craving	3	2		
Trouble sleeping	3	0		
Poor appetite	3	2		
Diarrhea	0	0		
Total Score	32	44		
0 = not at all; 1 = a little; 2 = moderately; 3 = quite a bit; 4 = extremely				

\*Subjects who withdrew due to non-fatal SAEs in study 3358 are only included in Table 13 and are not included in this table

\*\*AE considered related by investigator

Source: Reviewer's table modified from Sponsor's table 15.19, subject narrative information in final CSR, Protocol 3200K1-3358-WW, pages 541 to 815.

**Reviewer comments:** Multiple subjects (046-081385, 020-080657, 079-082035, 108-085041, 141-086375) experienced angina unstable, chest discomfort, and chest pain. Each of the investigators considered the chest discomfort experienced by the 3 subjects (020-080657, 079-082035, 108-085041) as related to the study medication and based on their underlying medical history, all 3 subjects are considered at high risk for an acute coronary syndrome. Subject 141-086375 also experienced chest pain and reported that he "did not like how he felt after taking the study drug". In all these instances, data was not provided or not available in terms of a cardiac work-up, and it is difficult to conclude whether the chest discomfort/chest pain might be the presenting symptoms for a CV event (i.e. myocardial infarction). Furthermore, without a control arm, it is challenging to evaluate the added CV risk of treatment with Relistor.

Subjects 005-080102 and 019-080605 both experienced symptoms (anxiety, hyperhidrosis, restlessness, nausea, abdominal pain, diarrhea, muscle twitching, feeling of body temperature change, vomiting) that appear to be consistent with opioid withdrawal. Subject 142-086426 was noted to have a drug withdrawal syndrome with post-dose OOWS and SOWS that increased. Although the Sponsor asserts that Relistor is a "peripherally" acting mu receptor antagonist and does not cross the BBB, it appears based on the 3 described cases that the effect of Relistor treatment does not seem to be limited to the gastrointestinal tract. Thus, treatment with Relistor for OIC has the potential to predispose certain patients to opioid withdrawal that affect other organ systems besides gastrointestinal.

Table 16 provides brief narratives of AEs of CV interest reported by subjects but *not* classified as SAEs and did *not* lead to discontinuations.

**Table 16: Non-SAEs of CV interest in study 3358**

Study 3358	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
<p><b>Subject MOA7283358-027-080874:</b> 49 yo F (wt 114 kg, BMI = 40) w/ CAD s/p MI, DM, hyperlipidemia, back pain s/p back surgery X 2 who was taking Avinza 90 mg Q D and Lortab 10 mg prn for pain management experienced a non-SAE of cardiac related chest pains on (b) (6), which resolved on (b) (6). Cardiac catheterization was done on (b) (6), but results were not available. She was taking amitriptyline, metformin, esomeprazole, lisinopril, insulin 70/30, gabapentin, zolpidem, promethazine, metoclopramide, senna, and simvastatin.</p> <p>On Feb 12, 2009, the subject started taking Relistor 12 mg prn (OL) and her last dose of Relistor was Jan 15, 2010 (study day 338).</p>	<p>angina pectoris</p> <p>200 days</p> <p>completed study</p>	<p>0 days after last dose</p>
<p><b>Subject MOA7283358-027-080884:</b> 49 yo F (wt 100 kg, BMI = 35) w/ hyperlipidemia and HTN who was taking oxycodone 10 mg BID and Oxycontin 30 mg BID for pain management experienced non-SAE of cardiac related chest pains on Feb 1, 2010, which persisted until the end of the study. She was taking zolpidem, lactulose, estradiol, atenolol, omeprazole, simvastatin, carisoprodol, phentermine, and bisacodyl</p>	<p>angina pectoris</p> <p>299 days</p> <p>completed study</p>	<p>0 days after last dose</p>



Study 3358	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
On April 9, 2009, the subject started taking Relistor 12 mg prn (OL) and her last dose of Relistor was March 7, 2010 (study day 333).		
<p><b>Subject MOA7283358-030-080990:</b> 64 yo M (83 kg, BMI = 29) w/ CAD s/p MI and CABG who was taking hydrocodone for pain management experienced non-SAE of cardiac chest pain on March 26 and 28 2010. He was treated with ASA on both occasions and the chest pain resolved on the same day as onset.</p> <p>On Aug 12, 2009, the subject started taking Relistor 12 mg prn (OL) and his last dose of Relistor was July 14, 2010 (study day 337).</p>	<p>angina pectoris</p> <p>227 days 229 days</p> <p>completed study</p>	0 days after last dose
<p><b>Subject MOA7283358-036-084539:</b> 49 yo M (105 kg, BMI = 33) with HTN who was taking oxycodone for pain management experienced non-SAE of chest pain on March 22, 2010, which resolved on the same day without any treatment. No cardiac testing was performed. He was taking amlodipine, venlafaxine, valacyclovir and Micardis.</p> <p>The subject was started on Relistor on Sept 14, 2009 and his last dose of Relistor was on Aug 7, 2010 (study day 328).</p>	<p>chest pain</p> <p>190 days</p> <p>completed study</p>	5 days after last dose (last dose prior to AE was on March 17, 2010, study day 185)
<p><b>Subject MOA7283358-049-081485:</b> 23 yo F (wt. 73 kg, BMI = 24) with OIC and back pain s/p spinal fusion who was receiving oxycodone for pain management experienced a non-SAE of intermittent chest pain on June 24, 2010 (study day 346). In addition, the subject reported that she experienced "extreme cramping with hot flashes" when she had bowel movements and "she almost went into the hospital". She was taking levothyroxine, cyclobenzaprine, ibuprofen, ranitidine, quetiapine, and gabapentin.</p> <p>The subject started OL Relistor on July 14, 2009 and her last dose of Relistor was on June 21, 2010 (study day 343).</p>	<p>chest pain</p> <p>346 days</p> <p>completed study</p>	3 days after last dose
<p><b>Subject MOA7283358-134-086135:</b> 33 yo M (wt. 69 kg, BMI = 22) w/ OIC, and neuropathic pain who was taking Actiq, Duragesic patch, Myprodol, S-morphine, Ultracet, and oxycodone for pain management experienced non-SAE of chest pain unknown on Mar 14, 2010, which resolved on the same day.</p> <p>The subject was started on Relistor on Sept 21, 2009 and his last dose of Relistor was on Aug 20, 2010 (study day 334).</p>	<p>chest pain</p> <p>175 days</p> <p>completed study</p>	0 day after last dose
<p><b>Subject MOA7283358-023-080740:</b> 62 yo M (wt. 105 kg, BMI = 30) with DM, CAD s/p MI and CABG, hyperlipidemia, HTN, PVD, previous tobacco abuse, OIC and back pain s/p spinal fusion who was receiving morphine ER for pain management experienced a non-SAE of chest tightness on April 3, 2010 (study day 334) and resolved on April 6, 2010. He was taking metformin, aspirin, quinapril, simvastatin, amlodipine, clonidine, nitroglycerin, clopidogrel, pioglitazone, pregabalin, and isosorbide.</p>	<p>chest discomfort</p> <p>334 days</p> <p>completed study</p>	0 day after last dose

Study 3358	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
The subject was started on Relistor on May 5, 2009 and his last dose of Relistor was on April 5, 2010 (study day 336).		
<p><b>Subject MOA7283358-011-080322:</b> 42 yo F (wt. 90 kg, BMI = 32) with DM, OIC and back pain s/p L5-S1 fusion who was receiving methadone and Percocet for pain management experienced a non-SAE of non-cardiac chest pain and pulmonary congestion on Dec 26, 2009. She was treated with diphenhydramine, pseudoephedrine, and acetaminophen. The pulmonary congestion resolved on Jan 5, 2010 and the non-cardiac chest pain resolved on Feb 3, 2010. She was taking metformin, insulin, pantoprazole, Humalog insulin, sertraline, lamotrigine, trazodone and gabapentin.</p> <p>The subject was started on Relistor on Sept 14, 2009 and her last dose of Relistor was on Aug 18, 2010 (study day 339).</p>	<p>non-cardiac chest pain</p> <p>pulmonary congestion</p> <p>104 days</p> <p>completed study</p>	0 day after last dose
<p><b>Subject MOA7283358-021-084704:</b> 47 yo F (wt. 63 kg, BMI = 21) with HTN, hyperlipidemia, OIC and low back pain s/p lumbar discectomy who was receiving morphine for pain management experienced a non-SAE of non-cardiac chest pain on Mar 31, 2010 (study day 205). The non-cardiac chest pain resolved on April 22, 2010 (study day 227). She was taking cyclobenzaprine hydrochloride, meloxicam, methylprednisolone, ramipril, senna, and atorvastatin.</p> <p>The subject was started on Relistor on Sept 8, 2009 and her last dose of Relistor was on Aug 11, 2010 (study day 338).</p>	<p>non-cardiac chest pain</p> <p>205 days</p> <p>completed study</p>	0 day after last dose
<p><b>Subject MOA7283358-223-082446:</b> 50 yo M (wt. 75 kg, BMI = 26) with OIC and low back pain s/p L4-5 laminectomy who was receiving hydromorphone and morphine IR for pain management experienced a non-SAE of non-cardiac related midsternal chest pain on Nov 28, 2009. The non-cardiac chest pain resolved on Nov 30, 2009. He was taking cyclobenzaprine, carisoprodol, baclofen, and venlafaxine.</p> <p>The subject was started on Relistor on May 27, 2009 and his last dose of Relistor was on April 27, 2010 (study day 336).</p>	<p>non-cardiac chest pain</p> <p>186 days</p> <p>completed study</p>	0 day after last dose
<p><b>Subject MOA7283358-223-082456:</b> 52 yo M (wt. 102 kg, BMI = 32) with OIC and low back pain s/p lumbar fusion L4-5 who was receiving hydrocodone for pain management experienced a non-SAE of musculoskeletal right upper chest pain on Nov 27, 2009. The musculoskeletal chest pain resolved on Dec 4, 2009. He was taking fluticasone, montelukast, salbutamol, prednisone, bupropion, and albuterol/ipratropium.</p> <p>Of note: The AE occurred around the timeframe of a bike accident and fall on Nov 25, 2009, and the subject experienced right shoulder pain on Nov 27, 2009, which resolved on Dec 4, 2009.</p>	<p>musculoskeletal chest pain</p> <p>110 days</p> <p>completed study</p>	0 day after last dose

Study 3358	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
The subject was started on Relistor on Aug 10, 2009 and his last dose of Relistor was on July 14, 2010 (study day 339).		
<p><b>Subject MOA7283358-073-081910:</b> 59 yo M (wt. 104 kg, BMI = 30) with OIC and muscle spasms who was receiving morphine for pain management experienced a non-SAE of musculoskeletal chest pain on Aug 26, 2009. The musculoskeletal chest pain was treated with aspirin from Aug 26 to 30, 2009, and it resolved on Aug 30, 2009. EKG done on Aug 26, 2009 was reported as normal. He was taking carisoprodol and mometasone furoate.</p> <p>The subject was started on Relistor on June 2, 2009, and his last dose of Relistor was on May 9, 2010 (study day 342).</p>	<p>musculoskeletal chest pain</p> <p>86 days</p> <p>completed study</p>	<p>0 day after last dose</p>
<p><b>Subject MOA7283358-034-081068:</b> 57 yo F (wt. 125 kg, BMI = 49) with OIC, HTN, and hyperlipidemia who was receiving oxycodone, Vicodin, and tramadol for pain management experienced a non-SAE of increased shortness of breath on May 15, 2010, which persisted until end of the study. Other AEs that occurred around the same timeframe were bilateral extremity edema, weight gain, and increased tiredness. She was taking lisinopril, levothyroxine, fluticasone, albuterol, docusate and methotrexate.</p> <p>The subject was started on Relistor on June 9, 2009, and her last dose of Relistor was on May 10, 2010 (study day 336).</p>	<p>dyspnea</p> <p>341 days</p> <p>completed study</p>	<p>5 days after last dose</p>
<p><b>Subject MOA7283358-073-081896:</b> 54 yo F (wt. 101 kg, BMI = 37) with OIC, HTN, DM, and hyperlipidemia who was receiving Vicodin for pain management experienced a non-SAE of shortness of breath on July 23, 2009, which resolved on the same day. Other AEs that occurred around the same timeframe were bilateral arm pain, dehydration, and left foot infection post surgery. She was taking levothyroxine, furosemide, topiramate, duloxetine, hydroxychloroquine, pregabalin, metformin, carisoprodol, temazepam, lisinopril, and amlodipine.</p> <p>The subject was started on Relistor on Mar 18, 2009, and her last dose of Relistor was on Feb 15, 2010 (study day 335).</p>	<p>dyspnea</p> <p>128 days</p> <p>completed study</p>	<p>0 day after last dose</p>
<p><b>Subject MOA7283358-208-086781:</b> 52 yo F (wt. 57 kg, BMI = 22) with OIC and COPD who was receiving oxycontin and morphine for pain management experienced a non-SAE of intermittent shortness of breath on July 12, 2010. The investigator reported that the subject had a cough and wheezing (per auscultation) at the same time. She was treated with Ventolin. She was taking clonidine, estrogen, sumatriptan, dimenhydrinate, diclofenac ointment, zopiclone, valproate, docusate, and clonazepam.</p> <p>The subject was started on Relistor on Sept 21, 2009, and her last dose of Relistor was on Aug 22, 2010 (study day 336).</p>	<p>dyspnea</p> <p>295 days</p> <p>completed study</p>	<p>0 day after last dose</p>



Study 3358	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
<p><b>Subject MOA7283358-094-082899:</b> 56 yo F (wt. 63 kg, BMI = 24) with OIC, HTN, and hyperlipidemia who was receiving Vicodin for pain management experienced a non-SAE of shortness of breath on Aug 5, 2009, which resolved on Aug 24, 2009 (study day 20). She was taking lisinopril, estradiol, hydrochlorothiazide, omeprazole, levothyroxine, simvastatin, vitamin D, calcium magnesium complex, fexofenadine, escitalopram, docusate, Adderall XR, and Miralax.</p> <p>The subject was started on Relistor on Aug 5, 2009, and her last dose of Relistor was on Oct 28, 2009 (study day 85).</p>	<p>dyspnea</p> <p>1 day (post first dose but timing in relation to first dose unknown)</p> <p>discontinued study due to unsatisfactory (efficacy) response</p>	<p>0 day after last dose</p>
<p><b>Subject MOA7283358-021-084690:</b> 76 yo M (wt. 103 kg, BMI = 31) with OIC, HTN, and GERD who was receiving Endocet and morphine for pain management experienced a non-SAE of exertional dyspnea on Jan 6, 2010, which persisted until the study ended. Other AEs that occurred were dizziness from Feb 2, 2010 to April 9, 2010, atrial fibrillation on Feb 10, 2010 and persisted until end of study, and pedal edema on March 11, 2010 and persisted until end of study. He was taking oxazepam, bupropion, temazepam, testosterone undecanoate, baclofen, naproxen, mineral oil, docusate, Miralax 17 gm, senna, clonazepam, fosinopril, and hydrochlorothiazide.</p> <p>The subject was started on Relistor on Aug 18, 2009, and his last dose of Relistor was on July 18, 2010 (study day 335).</p>	<p>dyspnea exertional</p> <p>142 days</p> <p>completed study</p>	<p>2 days after last dose</p>
<p><b>Subject MOA7283358-073-081914:</b> 69 yo F (wt. 111 kg, BMI = 40) with OIC, HTN, and Atrial fibrillation who was receiving Lortab and oxymorphone for pain management experienced a non-SAE of exertional dyspnea on Jan 30, 2010, which resolved on March 2, 2010 (study day 225). She was taking warfarin, digoxin, furosemide, lisinopril, phenytoin, propafenone, fenofibrate, sertraline, flecainide, diltiazem, calcium, vitamin D and docusate.</p> <p>The subject was started on Relistor on Jan 21, 2009, and his last dose of Relistor was on June 19, 2010 (study day 334).</p>	<p>dyspnea exertional</p> <p>194 days</p> <p>completed study</p>	<p>0 days after last dose</p>
<p><b>Subject MOA7283358-206-083803:</b> 44 yo F (wt. 121 kg, BMI = 43) with OIC, HTN, and DM who was receiving methadone for pain management experienced a non-SAE of electrocardiogram QT prolonged on July 2, 2009. The subject's QTcB interval was 508 msec and the previous EKGs done at screening (Jun 18, 2009) noted a QTcB interval of 493 msec; this showed an increase of 15 msec. On follow-up, the ECG revealed the QTcB interval had decreased to 447/459 msec.</p> <p>She was taking fluticasone, salbutamol, topiramate, furosemide, risperidone, rabeprazole, rosuvastatin, cyclobenzaprine, tolterodine, venlafaxine, spironolactone, glibenclamide, metformin, flurazepam, docusate and sennosides. The subject was started on Relistor on July 2, 2009, and her last dose of Relistor was on June 3, 2010 (study day 337).</p>	<p>electrocardiogram QT prolonged</p> <p>1 day (approximately 1 hr post first dose)</p> <p>completed study</p>	<p>0 days after last dose</p>

Study 3358	AE/Onset of AE from time of first dose/Outcome	Time interval of MNTX dose
<p><b>Subject MOA7283358-019-080598:</b> 52 yo F (wt. 64 kg) with OIC and hyperlipidemia who was receiving methadone for pain management experienced a non-SAE of electrocardiogram QT prolonged on Feb 13, 2009. The subject's QTcB interval was in the range of 490-513 msec, which was an increase of 31-38 msec from screening ECG. The previous EKGs done at screening (Jan 28, 2009) noted a QTcB interval range of 459-475 msec. Repeat ECG done on Feb 25, 2009 revealed a QTcB interval in the range of 449-482 msec.</p> <p>She was taking glycerol suppository, amitriptyline, famotidine, calcium/magnesium/zinc, methylsulfonylmethane, celecoxib, tizanidine, and fluoxetine. The subject was started on Relistor on Feb 13, 2009.</p>	<p>electrocardiogram QT prolonged</p> <p>1 day (approximately 1 hr post first dose)</p> <p>completed study</p>	<p>0 days after last dose</p>
<p><b>Subject MOA7283358-112-085148:</b> 50 yo F (wt. 65 kg, BMI = 26) with OIC and HTN who was receiving Kadian and Lortab for pain management experienced a non-SAE of elevated CPK on (b) (6), which occurred during a hospitalization from (b) (6). The subject was admitted for nausea, vomiting and diarrhea that began after she underwent a nerve block the week prior.</p> <p>Lab results (b) (6) at 5:44, CPK 289 U/L (30-195), CK-MB quant 6.3 ng/mL (0-10.4), (b) (6) 11:24, CPK 762 U/L, CKMB quant 8.3 ng/mL, Troponin I &lt; 0.04; (b) (6) at 23:49, CPK 97 U/L, Troponin I &lt; 0.04 ng/mL (0.0-0.03).</p> <p>The subject was started on Relistor on (b) (6), and her last dose of Relistor was on May 27, 2010 (study day 337). Relistor was discontinued on (b) (6) and resumed on May 23, 2010 (study day 334).</p>	<p>blood creatine phosphokinase increased</p> <p>332 days</p> <p>completed study</p>	<p>2 days after last dose</p>

Source: Reviewer's table generated from Sponsor's data submitted in the IR response dated June 26, 2012

Reviewer comments: Multiple subjects shown in blue in Table 16 experienced angina pectoris, chest pain, chest discomfort, dyspnea, and dyspnea exertional. Although the listed AEs were used to assess the safety database for a cardiovascular signal, due to the limited available information in the narratives, it was difficult to make any meaningful conclusions.

## 4 Postmarket Experience

An updated review dated June 11, 2012 was completed by the Division of Pharmacovigilance 1 (DPV 1), Office of Surveillance and Epidemiology (OSE) to evaluate cases of GI perforation, opioid withdrawal syndrome and myocardial infarction.

Two cases of myocardial infarction (MI) were identified in the review, and one of the cases was in the setting of a clinical trial (subject MOA7283358-198-083624, see narrative in this clinical review). The other case of MI occurred in an 85 yo female with

multiple risk factors, but the documentation was limited. However, the patient experienced "very high blood pressure, rapid pulse rate (170 beats per minute) and an acute MI on EKG". For details, please see page 4 of DPV 1 review.

In addition, 3 cases of opioid withdrawal were reported in the DPV 1 review page 5. Please see page 5 of the DPV 1 review for details of the 3 cases.

Reviewer comments: *I agree with the assessment and comments provided in the DPV 1 review dated June 11, 2012.*

## 5 Appendices

### 5.1 Laxatives used to treat Opioid induced constipation

Laxative	Usual adult dose*	Onset of action	Side effects
Bulk-forming laxatives**			
Psyllium	Up to 1 tablespoon (3.5 grams fiber) TID	12 to 72 hrs	impaction above strictures, fluid overload, gas, and bloating
Methylcellulose	Up to 1 tablespoon (2 grams fiber) or 4 caplets (500 mg fiber per caplet) TID	12 to 72 hrs	
Polycarbophil	2 to 4 tabs (500 mg fiber per tab) Q D	24 to 48 hrs	
Wheat dextrin*	1 to 3 caplets (1 gram fiber per caplet) or 2 teaspoonful (1.5 gram fiber per teaspoon) up to 3 times per day	24 to 48 hrs	
Surfactants (softeners)			
Docusate sodium	100 mg BID	24 to 72 hrs	Well tolerated. Use lower dose if administered with another laxative. Contact dermatitis reported.
Docusate calcium	240 mg Q D	24 to 72 hrs	
Osmotic agents			
Polyethylene glycol (macrogol)	8.5 to 34 grams in 240 mL (8 ounces) liquids	1 to 4 days	nausea, bloating cramping
Lactulose	10 to 20 grams (15 to 30 mL) every other day. May increase up to 2 times/day	24 to 48 hrs	abdominal bloating, flatulence
Sorbitol	30 grams (120 mL of 25 percent solution) 1 time/day	24 to 48 hrs	abdominal bloating, flatulence
Glycerin (glycerol)	one suppository (2 or 3 grams) per rectum for 15 minutes 1 time/day	15 to 60 min	rectal irritation
Magnesium sulfate	one to 2 teaspoonful (5-10 grams) dissolved in 240 mL (8 ounces) water 1 time/day	0.5 to 3 hrs	Watery stools and urgency. Caution in renal insufficiency (magnesium toxicity)
Magnesium citrate	200 mL (11.6 grams) 1 time/day	0.5 to 3 hrs	
Stimulant laxatives			

Bisacodyl	10 to 30 mg as enteric coated tabs 1 time/day	6 to 10 hrs	gastric irritation
	10 mg suppository per rectum 1 time/day	15 to 20 minutes	rectal irritation
Senna	2 to 4 tabs (8.6 mg sennosides per tab) or 1 to 2 tabs (15 mg sennosides per tab) as a single daily dose or divided twice daily	6 to 12 hrs	melanosis coli
<b>Other</b>			
Lubiprostone	24 mcg BID	24 to 48 hrs	nausea, diarrhea

\*All doses shown are for oral administration unless otherwise noted. Phosphate containing laxatives are not recommended. Mineral oil (enema and oral liquid) laxatives are not generally recommended except as enema following disimpaction.

\*\*Initiate at one half or less shown and gradually increase as needed to minimize gas and bloating. Administer with 180-360 mL (6 to 12 ounces) of water or fruit juice. Do not administer one hour of other medications. Fiber content per dose may vary.

Source: Reviewer's table adopted from table in uptodate<sup>20</sup>

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20 Stolbach, A. and Hoffman, Robert S. Opioid withdrawal in the emergency setting. [www.uptodate.com](http://www.uptodate.com) 2012.



## 5.2 All Subjects (N = 95) with CV AE events of interest in whom narratives were submitted and reviewed

According to the Sponsor, the total number of subjects was updated due to review and validation of search criteria and applicable MedDRA preferred terms and to be conservative in terms of ensuring full capture of relevant subjects for review and evaluation of adverse events (AEs) of special interest. Of the 95 subjects, 33 met the criteria for serious adverse event (SAE) and 62 were categorized as AEs. The Sponsor confirmed that the IR responses submitted to the Agency on June 11 and June 26, 2012 included all 95 narratives collectively. These were the narratives reviewed by the reviewer and some of these narratives were summarized and tabulated in this amendment review.

Study Identifier	Subject ID from 3358	Subject ID from 3356	Description of Planned Arm	PHASE	Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8	Q 9	Q 10	Event & Date(s)
MOA7283356		MOA7283356-004-0136	MOA-728 12MG QD	OL		X	X							X	Syncope 2008-02-19
MOA7283356		MOA7283356-004-0139	Placebo	OL			X							X	Musculoskeletal chest pain 2008-04-23
MOA7283356		MOA7283356-009-0362	MOA-728 12MG QD	DB							X				Electrocardiogram QT prolonged 2008-05-12
MOA7283356		MOA7283356-015-0637	MOA-728 12MG QD	OL		X									Loss of consciousness 2008-04-27
MOA7283356		MOA7283356-020-0872	MOA-728 12MG QOD	DB			X		X						Cardiac failure congestive 2008-08-15
MOA7283356		MOA7283356-022-0948	MOA-728 12MG QOD	DB			X								Pulmonary congestion 2007-10-12
MOA7283356		MOA7283356-022-0950	Placebo	OL						X	X				Hypertension 2007-12-13 (had non-SAE hypertension on 2007-12-19); Electrocardiogram QT prolonged 2007-12-13
MOA7283356		MOA7283356-029-1273	Placebo	DB							X				Electrocardiogram QT prolonged 2008-06-27
MOA7283356		MOA7283356-030-1312	Placebo	OL			X								Rales 2008-09-29
MOA7283356		MOA7283356-049-2300	Placebo	OL			X							X	Dyspnoea & Chest discomfort 2008-05-30
MOA7283356		MOA7283356-053-2484	MOA-728 12MG QOD	DB			X							X	Chest pain 2008-07-10
MOA7283356		MOA7283356-060-2799	MOA-728 12MGQOD	OL			X							X	Chest pain 2008-06-23 & 2008-06-24 & 2008-06-25

Clinical Review Amendment  
Helen Sile, MD  
sNDA 21-964  
Relistor (methylnaltrexone bromide)

MOA7283356		MOA7283356-063-2926	MOA-728 12MGQD	OL						X				Thrombosis (Right arm) 2008-01-16
MOA7283356		MOA7283356-065-3016	MOA-728 12MG QD	DB							X			Electrocardiogram change 2007-11-14
MOA7283356		MOA7283356-071-3592	MOA-728 12MG QD	OL		X							X	Vision blurred 2008-01-07 & 2008-02-15
MOA7283356		MOA7283356-082-4523	Placebo	OL			X						X	Chest pain 2008-07-29
MOA7283356		MOA7283356-206-3231	MOA-728 12MG QD	DB							X			Electrocardiogram QT prolonged 2007-11-14
MOA7283356		MOA7283356-210-3332	MOA-728 12MG QOD	OL		X								Vagal Shock (Neurogenic shock) 2008-04-01
MOA7283356		MOA7283356-218-4319	MOA-728 12MG QOD	DB			X						X	Angina pectoris 2008-07- 14
MOA7283356		MOA7283356-219-4344	Placebo	OL		X	X						X	Syncope 2008-06-09
MOA7283358	MOA7283358-004-080049	MOA7283356-004-0143	MOA-728 12MG QD			X	X						X	Syncope 2009-12-01
MOA7283358	MOA7283358-005-080102		MOA-728 12MG QD				X						X	Dyspnoea 2009-05-20
MOA7283358	MOA7283358-008-080232		MOA-728 12MG QD				X						X	Non-cardiac chest pain 2010-02-23
MOA7283358	MOA7283358-008-080235		MOA-728 12MG QD			X							X	Stroke (CVA)/Death (b) (6)
MOA7283358	MOA7283358-011-080322		MOA-728 12MG QD				X						X	Pulmonary congestion and Non-cardiac chest pain 2009-12-26
MOA7283358	MOA7283358-019-080598		MOA-728 12MG QD								X			Electrocardiogram QT prolonged 2009-02-13
MOA7283358	MOA7283358-019-080605		MOA-728 12MG QD			X							X	Vision blurred 2009-05-20
MOA7283358	MOA7283358-020-080651		MOA-728 12MG QD		X								X	Cardiac arrest (Death) (b) (6)
MOA7283358	MOA7283358-020-080657		MOA-728 12MG QD				X							Chest discomfort 2009-07- 18 & 2009-07-22
MOA7283358	MOA7283358-021-084690		MOA-728 12MG QD				X						X	Dyspnoea exertional 2010-01-06
MOA7283358	MOA7283358-021-084704		MOA-728 12MG QD				X						X	Non-cardiac chest pain 2010-03-31
MOA7283358	MOA7283358-022-080714		MOA-728 12MG QD			X							X	Vision blurred 2009-06-13
MOA7283358	MOA7283358-023-080740		MOA-728 12MG QD				X							Chest discomfort 2010-04- 03
MOA7283358	MOA7283358-023-080754		MOA-728 12MG QD								X			Electrocardiogram QT prolonged 2009-08-12
MOA7283358	MOA7283358-027-080874		MOA-728 12MG QD				X						X	Angina pectoris 2009-08- 30



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MOA7283358	MOA7283358-027-080884		MOA-728 12MG QD				X							X	Angina pectoris 2010-02-01
MOA7283358	MOA7283358-027-080894		MOA-728 12MG QD				X							X	Dyspnoea 2009-08-09
MOA7283358	MOA7283358-030-080983		MOA-728 12MG QD				X						X		In-stent coronary artery restenosis 2009-08-18
MOA7283358	MOA7283358-030-080990		MOA-728 12MG QD				X							X	Angina pectoris 2010-03-26 & 2010-03-28
MOA7283358	MOA7283358-033-084589		MOA-728 12MG QD			X								X	Vision blurred 2010-04-02
MOA7283358	MOA7283358-034-081060		MOA-728 12MG QD				X							X	Dyspnoea 2009-07-17
MOA7283358	MOA7283358-034-081068		MOA-728 12MG QD				X							X	Dyspnoea 2010-05-15
MOA7283358	MOA7283358-036-084533		MOA-728 12MG QD				X								Breast pain 2009-09-01
MOA7283358	MOA7283358-036-084539		MOA-728 12MG QD				X							X	Chest pain 2010-03-22
MOA7283358	MOA7283358-042-081244		MOA-728 12MG QD								X				Electrocardiogram QT prolonged 2009-01-02
MOA7283358	MOA7283358-042-081246	MOA7283356-042-1990	MOA-728 12MG QD									X			Troponin increased 2009-09-10
MOA7283358	MOA7283358-046-081385		MOA-728 12MG QD				X								Angina unstable 2009-05-26
MOA7283358	MOA7283358-049-081485		MOA-728 12MG QD				X							X	Chest pain 2010-06-24
MOA7283358	MOA7283358-049-081492		MOA-728 12MG QD			X	X							X	Syncope 2009-11-18
MOA7283358	MOA7283358-053-081571		MOA-728 12MG QD				X			X				X	Dyspnoea 2009-06-23 & 2009-08-10; Oedema peripheral 2009-07-06; Pleural effusion 2009-07-28 & 2009-08-10 (Non-serious pleural effusion 2009-08-01); Oedema peripheral 2009-08-10
MOA7283358	MOA7283358-054-081616		MOA-728 12MG QD				X							X	Angina pectoris 2009-07-19
MOA7283358	MOA7283358-060-083965		MOA-728 12MG QD								X				Electrocardiogram QT prolonged 2009-06-25
MOA7283358	MOA7283358-071-081841		MOA-728 12MG QD							X					Nuclear magnetic imaging abnormal (spine) 2009-10-09
MOA7283358	MOA7283358-073-081896	MOA7283356-073-3717	MOA-728 12MG QD				X							X	Dyspnoea 2009-07-23
MOA7283358	MOA7283358-073-081899		MOA-728 12MG QD		X								X		Sudden Death (b) (6)

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MOA7283358	MOA7283358-073-081910	MOA7283356-073-3690	MOA-728 12MG QD				X							X	Musculoskeletal chest pain 2009-08-26
MOA7283358	MOA7283358-073-081914		MOA-728 12MG QD				X							X	Dyspnoea exertional 2010-01-30
MOA7283358	MOA7283358-076-081978	MOA7283356-076-3853	MOA-728 12MG QD			X								X	Vision blurred & Dysarthria 2009-12-27
MOA7283358	MOA7283358-078-083349		MOA-728 12MG QD				X			X				X	Angina pectoris & Hypertension 2009-06-12
MOA7283358	MOA7283358-079-082035		MOA-728 12MG QD				X								Chest discomfort 2009-07-29
MOA7283358	MOA7283358-084-083439		MOA-728 12MG QD				X							X	Dyspnoea 2009-09-29 & 2009-10-14
MOA7283358	MOA7283358-091-082778		MOA-728 12MG QD			X								X	Vision blurred 2009-07-07
MOA7283358	MOA7283358-093-082848		MOA-728 12MG QD				X								Respiratory distress 2009-08-25
MOA7283358	MOA7283358-094-082899		MOA-728 12MG QD				X							X	Dyspnoea 2009-08-05
MOA7283358	MOA7283358-095-082939		MOA-728 12MG QD				X							X	Non-cardiac chest pain 2010-02-25
MOA7283358	MOA7283358-095-082943		MOA-728 12MG QD		X								X		Myocardial infarction requiring stent placement 2010-05-07
MOA7283358	MOA7283358-100-083523		MOA-728 12MG QD				X							X	Non-cardiac chest pain 2009-11-23
MOA7283358	MOA7283358-108-085041		MOA-728 12MG QD				X								Chest discomfort 2009-08-18
MOA7283358	MOA7283358-112-085148		MOA-728 12MG QD										X		Blood creatine phosphokinase increased 2010-05-21
MOA7283358	MOA7283358-115-085291		MOA-728 12MG QD							X					Hypotension 2009-07-21
MOA7283358	MOA7283358-117-085382		MOA-728 12MG QD				X							X	Non-cardiac chest pain 2009-12-15
MOA7283358	MOA7283358-118-085820		MOA-728 12MG QD				X							X	Dyspnoea 2009-11-15
MOA7283358	MOA7283358-123-085599		MOA-728 12MG QD				X							X	Non-cardiac chest pain 2010-02-12
MOA7283358	MOA7283358-123-085604		MOA-728 12MG QD			X								X	Vision blurred 2009-07-13
MOA7283358	MOA7283358-123-085625		MOA-728 12MG QD				X			X					Acute respiratory failure & Hypotension 2010-05-01
MOA7283358	MOA7283358-129-085920		MOA-728 12MG QD				X	X						X	Angina pectoris 2010-01-05 & Coronary artery disease 2010-01-15

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MOA7283358	MOA7283358-134-086135		MOA-728 12MG QD				X							X	Chest pain 2010-03-14
MOA7283358	MOA7283358-141-086375		MOA-728 12MG QD				X							X	Chest pain 2009-12-09
MOA7283358	MOA7283358-198-083611		MOA-728 12MG QD								X				Electrocardiogram QT prolonged 2009-06-11
MOA7283358	MOA7283358-198-083617		MOA-728 12MG QD		X								X		Myocardial Infarction 2010-03-31 & 2010-04-05
MOA7283358	MOA7283358-198-083618		MOA-728 12MG QD			X								X	Vision blurred (Left eye) 2009-08-26
MOA7283358	MOA7283358-198-083619		MOA-728 12MG QD								X				Electrocardiogram QT prolonged 2009-08-28
MOA7283358	MOA7283358-198-083624		MOA-728 12MG QD		X		X	X	X	X			X	X	Myocardial Infarction & Coronary artery disease 2009-09-22; Cardiac failure congestive 2009-10-29 and Dyspnoea 2010-05-25; Hypertension 2009-11-12
MOA7283358	MOA7283358-198-083625		MOA-728 12MG QD								X				Electrocardiogram QT prolonged (prolonged at baseline as well) 2009-09-04
MOA7283358	MOA7283358-199-083661		MOA-728 12MG QD				X							X	Dyspnoea 2009-06-22
MOA7283358	MOA7283358-199-083669		MOA-728 12MG QD				X							X	Prinzmetal angina 2009-10-01 & Dyspnoea 2009-12-26
MOA7283358	MOA7283358-200-083696		MOA-728 12MG QD		X								X		Myocardial infarction (Death) (b) (6)
MOA7283358	MOA7283358-200-083701		MOA-728 12MG QD				X							X	Angina pectoris 2010-01-23
MOA7283358	MOA7283358-206-083803		MOA-728 12MG QD								X				Electrocardiogram QT prolonged 2009-07-02
MOA7283358	MOA7283358-208-086781		MOA-728 12MG QD				X							X	Dyspnoea 2010-07-12
MOA7283358	MOA7283358-223-082439	MOA7283356-223-4709	MOA-728 12MG QD				X							X	Angina pectoris 2009-03-05 & 2009-04-12 & 2009-05-02 & 2009-05-18; Dyspnoea 2009-05-07
MOA7283358	MOA7283358-223-082442		MOA-728 12MG QD			X								X	Vision blurred & Dysarthria 2009-05-08 & 2009-05-13
MOA7283358	MOA7283358-223-082446		MOA-728 12MG QD				X							X	Non-cardiac chest pain

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															2009-11-28
MOA7283358	MOA7283358-223-082451		MOA-728 12MG QD			X	X							X	Syncope 2009-08-26, 2009-09-28 & 2009-12-31
MOA7283358	MOA7283358-223-082456		MOA-728 12MG QD				X							X	Musculoskeletal chest pain 2009-11-27

Source: Reviewer's table modified from Sponsor's table submitted via e-mail dated June 26, 2012

### 5.3 Literature Review/References

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SPA Review for IND 56553 (Alvimopan) by Helen Sile, MD dated December 29, 2008

IND 56,553 SPA Advice letter dated March 23, 2009

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Guideline for Industry: The extent of Population Exposure to Assess Clinical Safety:  
For Drugs Intended for Long-term treatment of Non-Life threatening Conditions (ICH-  
E1A), March 1995



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/s/  
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HELEN SILE  
07/27/2012

ROBERT FIORENTINO  
07/27/2012

**4.3 Relistor sNDA: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)  
Consult Review**



**Food and Drug Administration**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**  
**Division of Anesthesia, Analgesia, and Addiction Products**  
10903 New Hampshire Ave.  
Silver Spring, MD 20993-0002

**Response to Consultation Request**

**TO:** Helen Sile, M.D., Medical Officer  
Division of Gastroenterology and Inborn Errors Products (DGIEP)

**FROM:** Elizabeth Kilgore, M.D., Medical Officer  
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

**THROUGH:** Ellen Fields, M.D., MPH, Team Leader, DAAAP

**THROUGH:** Sharon Hertz, MD., Deputy Director, DAAAP

**THROUGH:** Bob Rappaport, M.D., Director, DAAAP

**SUBJECT:** NDA 21-964/S010 (Efficacy Supplement)

**DATE:** 2/24/2012

**Executive Summary-Conclusions:**

- Studies 3356 and 3358 were not adequately designed to fully evaluate study subjects for the presence of opioid withdrawal symptoms.
- There was evidence of opioid withdrawal in some patients taking study drug methylnaltrexone (MNTX) based upon the adverse events profile of double-blind Study 3356 and supportive findings from OL Study 3358.
- There did not appear to be evidence of clinically important change in pain scores or increased daily opioid analgesic use in MNTX -treated patients in Studies 3356 or 3358.
- As a result of our review, we do not concur with the labeling proposed by the Sponsor regarding the absence of withdrawal symptoms in study subjects treated with MNTX, and the absence of changes in pain scores and increases in opioid requirements.

**Background:**

Methylnaltrexone bromide, Tradename Relistor, subcutaneous (SC) injection was approved in 2008 under NDA 21-964 for the treatment of opioid induced constipation (OIC) in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient.

There is currently no approved drug specifically for the indication of treatment of OIC in the population of patients receiving opioid therapy for chronic, nonmalignant pain.

On 6/27/11, the Sponsor submitted Efficacy Supplement 010 to NDA 21-964 for the indication, “Opioid-Induced Constipation in Patients with Non-Cancer Pain.”

As taken verbatim from the Sponsor’s submission, the proposed mechanism of action for methylnaltrexone bromide is as follows: “N-methylnaltrexone bromide (MOA-728, MNTX) is a quaternary derivative of the  $\mu$ -opioid antagonist naltrexone. The addition of the methyl group at the amine in its ring forms a compound with greater polarity and lower lipid solubility. These physical/chemical properties restrict the ability of MOA-728 to cross the blood-brain barrier and gain access to the central nervous system, and therefore provide MOA-728 with the potential to block the undesired peripheral (noncentral nervous system) side effects of opioid agonist medications, while not interfering with the centrally mediated analgesic effect.”

**Consultation Request:** On 8/17/11, DGIEP submitted a Request for Consultation to DAAAP with the following specific consult requests:

Please review the completed study report for studies 3356 and 3358 as it pertains to the questions below:

1. Did the Sponsor use the appropriate instruments to assess withdrawal in studies 3356 and 3358?
2. Based on your assessment of the data in studies 3356 and 3358, is there evidence of opioid withdrawal in the patients that were treated with Relistor (methylnaltrexone) for opioid induced constipation?
3. Based on your evaluation of the data in studies 3356 and 3358, is there evidence of increased analgesic requirements in patients treated with Relistor (methylnaltrexone) for opioid induced constipation?
4. Do you have any other comments regarding the evaluation of pain and/or opioid withdrawal in studies 3356 and 3358?

**Materials Reviewed:**

- NDA 21-964 Efficacy Supplement 010 (relevant sections of the submission including Clinical Study Reports for Studies 3356 and 3358, ISS, Clinical Summary of Safety)
- Applicant’s proposed Annotated Label, Section 1.14 electronic submission
- Sponsor’s response to DAAAP Clinical Information Request (IR) submitted as Efficacy Information Amendment submitted electronically 1/10/2012
- Meetings and discussions with Study Endpoint and Labeling Development (SEALD) and DGIEP
- Approved Relistor label
- NDA 21-964 MO Review, Dr. Ronald Orleans, dated 3/28/08
- Literature<sup>1, 2, 3</sup>

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<sup>1</sup> Handelsman L., Cochrane K. J., Aronson M. J. et al. Two new rating scales for opiate withdrawal. *American Journal of Alcohol Abuse*. 1987;13:293-308.

**Review Organization:** Throughout this review, methylnaltrexone may be referred to as methylnaltrexone bromide, MTNX, Relistor or MOA-728. Two protocols were reviewed, 3356 and 3358, and the information is presented in the following order:

- Criteria Used for Determining Opioid Withdrawal
- Review of Study 3356 protocol, followed by the Sponsor's results of the study, then reviewer comments/conclusions
- Review of Study 3358 protocol, followed by the Sponsor's results of the study, then reviewer comments/conclusions
- Other information relevant to both studies is discussed
- DAAAP responses to DGIEP questions
- Appendix

**Criteria Used by Reviewer for Determining Opioid Withdrawal**

- Objective Opioid Withdrawal Scale (OOWS) and Subjective Opioid Withdrawal Scale (SOWS) Total Scores and Individual Items in studies 3356 and 3358
- Adverse Events consistent with opioid withdrawal based on DSM-IV Opioid Withdrawal Diagnostic Criteria which include the presence of three or more of the following: dysphoric mood; nausea or vomiting; muscle aches; lacrimation or rhinorrhea; pupillary dilation, piloerection, or sweating; diarrhea; yawning; fever; insomnia.

**Protocol 3200K1-3356-WW (subsequently referred to as Protocol 3356)**

**Title:** A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Subcutaneous MOA-728 for the Treatment of Opioid-Induced Constipation in Subjects with Chronic Non-Malignant Pain

**Design:** Efficacy, safety and tolerability Phase 3, randomized, double-blind, parallel-group, placebo-controlled multicenter study of MNTX for the treatment of OIC in patients with non-cancer pain.

**Study Overview:** The duration of the treatment period was 12 weeks and consisted of 3 periods: Screening, Treatment (DB and OL) and Follow up. Eligible patients were randomized to one of three treatment groups with fixed dose subcutaneous injection of MNTX 12mg once daily, MNTX 12mg once every other day (starting on Day 1), or placebo (beginning on Day 2) in a 1:1:1 ratio during the DB period. DB treatment was then followed by 8 weeks of open-label as needed (prn) dosing at a fixed dose of 12mg up to a maximum of one injection per day. A follow-up period occurred 14-days after the end of the OL period. The total duration of the study was 98 days.

**Number Treated:** (DB) N=298 MNTX; 162 Placebo (OL) N=364 MNTX

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<sup>2</sup> Wesson, DR., et. al, The clinical opiate withdrawal scale (COWS); Journal of Psychoactive Drugs, Vol. 35 (2), April-June 2003, p. 253-259.

<sup>3</sup> Diagnostic and Statistical Manual of Mental Disorders. 4<sup>th</sup> ed, Opioid Withdrawal Diagnostic Criteria.

#### Key Inclusion Criteria:

1. Males and females at least 18 years of age
2. History of chronic pain with documentation of a nonmalignant condition underlying the chronic pain of at least 2 months duration before the screening visit
3. Taking oral, transdermal, IV or subcutaneous (SC) opioids for at least 1 month and receiving a daily dose  $\geq 50$  mg of oral morphine equivalents per day for at least 2 weeks before screening with no anticipated changes during the study. (The Sponsor noted that there is no definitive standard for interconversion of opioid doses. Therefore, doses of opioid medication were converted to oral morphine equivalents using information from approved product labels or literature referenced in approved product labels).
4. History of constipation due to opioid use for at least 1 month before screening

#### Key Exclusion Criteria:

1. A history of chronic constipation before the initiation of opioid therapy
2. Urine drug screen negative for the presence of opioids

Analgesic Rescue: Patients were allowed to increase pain medication if needed during the study

#### Co-Primary Efficacy Endpoints

1. The proportion of subjects having a rescue-free bowel movement (RFBM) within 4 hours of the first dose
2. The percentage of active injections resulting in any RFBM within 4 hours during the DB phase

#### Secondary Efficacy Endpoints

1. Time to first RFBM after the first injection, censored at 24 hours or time of the second injection, whichever occurred first
2. Change in weekly number of RFBMs from baseline to the DB phase.
3. Multiple other secondary endpoints

#### Exploratory endpoint

- Pain Intensity

#### **Study Assessments Related to Opioid Withdrawal**

##### ***Total OOWS and SOWS scores***

The Objective Opioid Withdrawal Scale (OOWS) and the Subjective Opioid Withdrawal Scale (SOWS) are questionnaires that primarily assess opioid withdrawal that results from opioid abstinence in patients who are physically dependent on opioids. In this study the OOWS was to be completed by a trained clinician, while the SOWS was to be completed by the patient. The Sponsor referenced Handelsman<sup>1</sup> versions of OOWS and SOWS that were used in the study. The Sponsor modified the SOWS from the original Handelsman version for this study (see Appendix B).

These scales include terms that assess abdominal cramping. However, the Sponsor maintains that abdominal cramping has also been identified as an adverse event in patients with opioid induced



constipation who have been treated with MOA-728. Therefore, all of the Sponsor's analyses of these scales were performed with and without the items relating to cramping.

A description of the key features of the OOWS and SOWS tools is provided below and copies are found in Appendix B of this review:

1. OOWS: Consists of 13 items, each of which is scored 0 (not present) or 1 (present), resulting in a maximum score of 13 (12 if the abdominal cramping item is excluded).
  - Total OOWS score: defined as (sum of non-missing scores on items 1-13/number of items with a score)  $\times$  13. If more than 6 of 13 items had missing scores, the total score was defined as missing.
  - Total OOWS score without the item relating cramping: defined as (sum of non-missing scores on items 1-11 and 13/number of items with a score among items 1-11 and 13)  $\times$  12. If more than 6 of 12 items had missing scores, the total score was defined as missing.
2. SOWS: Consists of 19 items which are statements about how the patient has been feeling the past 24 hours. Each item is scored by the patient according to the following scale: 0 (not at all), 1 (a little), 2 (moderately), 3 (quite a bit), and 4 (extremely). The maximum SOWS score is 76 (72 if the abdominal cramping item is excluded).
  - Total SOWS score defined as (sum of non-missing scores on items 1-19/number of items with a score)  $\times$  19. If more than 9 of 19 items had missing scores, the total score was defined as missing.
  - Total SOWS score without the item relating cramping: defined as (sum of non-missing scores on items 1-14, 16-19/number of items with a score among items 1-14, 16-19)  $\times$  18. If more than 9 of 18 items had missing scores, the total score was defined as missing.

The OOWS and SOWS were performed as safety assessments. The OOWS was administered at baseline (predose) and one hour after dosing on Day 1 and on study days 14 and 28 during the DB period of treatment. The SOWS was administered at baseline (predose) and one hour after dosing on Day 1 and on study days 14 and 28. During the OL period, only the SOWS was administered on study days 42, 56, and 84 or early withdrawal for subjects who used MOA-728 within the previous 24 hours.

The schedule of OOWS and SOWS assessments is shown below.

**Table 1. OOWS and SOWS Assessments Schedule, DB and OL Periods, Study 3356**

Assessment	Double-Blind Period			Open-Label Period		
	Baseline	Day 14	Day 28	Day 42	Day 56	Day 84
OOWS	X	X	X	Not Assessed	Not Assessed	Not Assessed
SOWS	X	X	X	X	X	X

(Table, reviewer)

### ***Pain Intensity Scores***

Pain assessments were completed at baseline Day 1 (after randomization but before test article); and on Days 14, 28, 42, 56, and 84 as shown in Table 2. Patients were asked to describe their

average pain during the past 24 hours on an 11 point NRS, ranging from 0 (no pain) to 10 (worst pain possible).

**Table 2. Pain Assessments Schedule, DB and OL Periods, Study 3356**

Assessment	Double-Blind Period			Open-Label Period		
	Baseline	Day 14	Day 28	Day 42	Day 56	Day 84
Pain Scale	X	X	X	X	X	X

(Table, reviewer)

#### ***Average Daily Morphine Equivalent Dose (MED) Use***

Each dose was to be reported by the subject on a daily paper diary card which included name, dosage, unit, date, time, and route (for stable and breakthrough pain) of medication. Information was recorded on the CRF at each visit.

#### **Study Results Related to Opioid Withdrawal**

##### **A) OOWS Scores**

**Total OOWS Scores (without cramping) DB period:** The raw mean change from baseline in total OOWS score (without cramping) was similar for MOA 12mg QD (0.1) and Placebo (0.0). However, there was a statistically significant difference between MOA QOD (0.3) compared to placebo with  $p < 0.001$  on Day 1 (which measured the change in predose compared to 1 hour postdose). There did not appear to be notable changes on Days 14 and 28 and by Day 28, all treatment groups had a mean change of 0. The Sponsor notes the statistically significant difference in total OOWS scores on Day 1 for MOA QOD but determined that it is “not clinically meaningful”. The Sponsor’s Total OOWS scores without and with cramping during the DB phase are shown in Tables 3 and 4.

Of note, the statistical analyses did not include any correction for the evaluation of multiple endpoints, therefore the analyses are merely descriptive and the p-values are not meaningful in this situation. This holds true for all of the Sponsor’s statistical comparisons that follow in this review.

**Table 3. ANCOVA Results of Total OOWS Scores-Without Cramping by Treatment Group during DB Phase: mITT Population**

DAI	Treatment	N	Raw	Raw Change	Adjusted Change	Difference in adjusted change vs Placebo	p-Value <sup>a</sup>
			Mean(SD)	Mean(SD)	Mean(SE)	Mean (95% CI)	
Day 1	MOA-728 12 mg QD	148	0.4(1.1)	0.1(0.6)	0.1(0.1)	0.1(-0.1,0.3)	0.345
	MOA-728 12 mg QOD	145	0.6(1.6)	0.3(1.3)	0.3(0.1)	0.3(0.1,0.5)	<.001
	Placebo	161	0.2(0.8)	0.0(0.4)	0.0(0.1)		
Day 14	MOA-728 12 mg QD	135	0.4(1.1)	0.1(0.4)	0.1(0.0)	0.1(-0.1,0.2)	0.265
	MOA-728 12 mg QOD	132	0.3(1.0)	-0.0(0.6)	-0.0(0.0)	-0.0(-0.1,0.1)	0.845
	Placebo	152	0.2(0.7)	0.0(0.6)	-0.0(0.0)		
Day 28	MOA-728 12 mg QD	124	0.3(1.1)	0.0(0.7)	0.0(0.1)	0.0(-0.1,0.2)	0.519
	MOA-728 12 mg QOD	120	0.3(1.1)	0.0(0.6)	0.1(0.1)	0.1(-0.1,0.2)	0.474
	Placebo	143	0.2(0.6)	0.0(0.6)	-0.0(0.1)		

(Source: Sponsor's table, Study 3356 Report, p. 137)

**Total OOWS Scores (with cramping) DB period:** In the OOWS scores with cramping, there was a significant difference for the adjusted mean change for MOA-728 QOD vs placebo on Day 1 ( $p < 0.001$ ) as seen in Table 4.

**Table 4. ANCOVA Results of Total OOWS Scores With Abdominal Cramping by Treatment Group During the Double-blind Period: mITT Population Study 3356**

DAI	Treatment	N	Raw	Raw Change	Adjusted Change	Difference in Adjusted Change vs Placebo	P-value <sup>a</sup>
			Mean(Sd)	Mean(Sd)	Mean(SE)	Mean (95% CI)	
Day 1	MOA-728 12 mg QD	148	0.5(1.2)	0.2(0.7)	0.2(0.1)	0.1(-0.1,0.4)	0.195
	MOA-728 12 mg QOD	145	0.7(1.8)	0.4(1.5)	0.4(0.1)	0.4(0.2,0.6)	<.001
	Placebo	161	0.2(0.9)	0.0(0.5)	0.0(0.1)		
Day 14	MOA-728 12 mg QD	135	0.4(1.2)	0.1(0.5)	0.1(0.0)	0.1(-0.1,0.2)	0.294
	MOA-728 12 mg QOD	132	0.3(1.0)	0.0(0.7)	0.0(0.0)	0.0(-0.1,0.1)	0.933
	Placebo	152	0.2(0.7)	0.0(0.6)	-0.0(0.0)		
Day 28	MOA-728 12 mg QD	124	0.3(1.1)	0.0(0.7)	0.1(0.1)	0.1(-0.1,0.2)	0.408
	MOA-728 12 mg QOD	120	0.3(1.1)	0.0(0.6)	0.1(0.1)	0.1(-0.1,0.2)	0.415
	Placebo	143	0.2(0.6)	0.0(0.6)	-0.0(0.1)		

(Source: Sponsor's table, CSR 3356, p. 987)

**Individual items OOWS scores (DB period):** The Sponsor analyzed and presented summary statistics for total OOWS by individual item. According to the Sponsor's analysis, the only individual item which showed a statistically significant trend was perspiration, with a  $p < 0.001$  for MOA-728 QOD on Day 1 compared to placebo with ~12% of patients experiencing perspiration in the QOD group postdose compared to 8% MOA-728 QD and 2% Placebo. Although the statistical analyses are not meaningful due to lack of correction for multiple endpoints, at all assessment points, the percentage of patients who experienced perspiration was higher in the

drug-treated group compared to placebo-treated patients. The summary of the perspiration item is shown in Table 5.

**Table 5. Summary of Perspiration (OOWS Item) by Treatment Group during DB Phase, Study 3356 mITT Population**

Endpoint	DAI	Treatment	N	n(%)	p-Value <sup>a</sup>
Perspiration	Baseline	MOA-728 12 mg QD	149	5 (3.4%)	0.266
		MOA-728 12 mg QOD	148	4 (2.7%)	0.430
		Placebo	162	2 (1.2%)	
	Day 1	MOA-728 12 mg QD	148	12 (8.1%)	0.015
		MOA-728 12 mg QOD	145	17 (11.7%)	<.001
		Placebo	161	3 (1.9%)	
	Day 14	MOA-728 12 mg QD	136	9 (6.6%)	0.074
		MOA-728 12 mg QOD	132	4 (3.0%)	0.708
		Placebo	152	3 (2.0%)	
	Day 28	MOA-728 12 mg QD	124	8 (6.5%)	0.013
		MOA-728 12 mg QOD	120	5 (4.2%)	0.094
		Placebo	146	1 (0.7%)	

(Source: Sponsor's table, CSR 3356; p. 138)

**Individual OOWS item scores (OL period):** OOWS was not assessed during the OL period of study 3356.

#### **B) SOWS Scores**

**Total SOWS Score (DB period):** Total SOWS scores without and with abdominal cramping were analyzed. There was considerable variability and inconsistency for the total SOWS scores, making meaningful interpretation difficult. It is also noted that there was no correlation between the total OOWS scores for an individual patient compared to the SOWS scores assessed at the same visit. Specifically, many patients had relatively high SOWS scores and very low corresponding OOWS scores at the same visit. Additionally, the variability of SOWS and lack of correlation with OOWS occurred in the placebo arm as well and was not restricted to the drug-treated group.

The total SOWS scores without and with cramping during the DB period are noted in Tables 6 and 7 below. Similar findings were seen in the OL period.

**Table 6. ANCOVA Results of Total SOWS Score without Cramping by Treatment Group during the DB Phase: mITT Population Study 3356**

DAI	Treatment	N	Raw	Raw Change	Adjusted Change	Difference in Adjusted Change vs Placebo	
			Mean(SD)	Mean(SD)	Mean(SE)	Mean (95% CI)	p-Value <sup>a</sup>
Day 1	MOA-728 12 mg QD	143	11.5(10.7)	-2.2(7.1)	-2.1(0.5)	1.2(-0.2,2.7)	0.093
	MOA-728 12 mg QOD	137	11.8(11.9)	-1.7(7.4)	-1.7(0.5)	1.7(0.2,3.1)	0.027
	Placebo	154	9.9(9.5)	-3.3(5.9)	-3.4(0.5)		
Day 14	MOA-728 12 mg QD	130	12.7(9.6)	-0.7(8.5)	-0.6(0.6)	-0.6(-2.3,1.1)	0.521
	MOA-728 12 mg QOD	130	12.5(9.8)	-0.6(8.7)	-0.7(0.6)	-0.6(-2.3,1.1)	0.494
	Placebo	151	13.2(10.9)	-0.1(7.2)	-0.1(0.6)		
Day 28	MOA-728 12 mg QD	121	11.4(9.9)	-2.0(8.4)	-2.0(0.7)	-1.9(-3.8,-0.0)	0.046
	MOA-728 12 mg QOD	117	12.2(10.2)	-0.5(9.8)	-0.7(0.7)	-0.6(-2.5,1.3)	0.525
	Placebo	142	13.4(10.7)	-0.2(7.4)	-0.1(0.6)		

Abbreviations: CI = confidence interval; DAI = data analysis interval; mITT = modified intent-to-treat; QD = once daily; QOD = once every other day; SD = standard deviation; SE = standard error.

(Source: Sponsor's table, CSR 3356, p. 139)

**Table 7. ANCOVA Results of Total SOWS Score With Cramping by Treatment Group During the DB Phase: mITT Population Study 3356**

DAI	Treatment	N	Raw	Raw Change	Adjusted Change	Difference in Adjusted Change vs Placebo	
			Mean(Sd)	Mean(Sd)	Mean(SE)	Mean (95% CI)	P-value <sup>a</sup>
Day 1	MOA-728 12 mg QD	143	12.7(11.4)	-2.1(7.6)	-2.0(0.6)	1.7(0.1,3.2)	0.035
	MOA-728 12 mg QOD	137	12.9(12.7)	-1.5(8.0)	-1.5(0.6)	2.1(0.6,3.7)	0.008
	Placebo	154	10.5(10.1)	-3.6(6.2)	-3.7(0.5)		
Day 14	MOA-728 12 mg QD	130	13.8(10.2)	-0.7(9.0)	-0.6(0.7)	-0.5(-2.3,1.3)	0.612
	MOA-728 12 mg QOD	130	13.6(10.3)	-0.4(9.2)	-0.5(0.7)	-0.3(-2.1,1.5)	0.712
	Placebo	151	14.0(11.6)	-0.1(7.8)	-0.1(0.6)		
Day 28	MOA-728 12 mg QD	121	12.2(10.5)	-2.1(9.0)	-2.1(0.7)	-2.0(-3.9,0.0)	0.055
	MOA-728 12 mg QOD	117	13.3(10.8)	-0.3(10.5)	-0.5(0.8)	-0.4(-2.4,1.7)	0.723
	Placebo	142	14.2(11.2)	-0.2(7.9)	-0.1(0.7)		

(Source: Sponsor's table, CSR 3356, p.996)

### C) Pain Intensity Scores

**Pain Intensity Scores (DB period):** The mean pain scores at each evaluation were similar in the three treatment groups, with very little variability over time. The Sponsor reported that the median pain score remained the same throughout the DB phase when the data was analyzed by treatment week. The summary statistics for the worst pain levels at Days 14 and 28 are shown in the table below.

**Table 8. Pain Intensity Score by Treatment during the DB Phase: mITT Population**

DAI	Treatment	N	Raw Mean(SD)	Raw Change Mean(SD)	Adjusted Change Mean(SE)	Difference in Adjusted Change vs Placebo	
						Mean (95% CI)	p-Value <sup>a</sup>
Day 14	MOA-728 12 mg QD	132	6.2(1.9)	-0.0(1.7)	-0.0(0.1)	0.1(-0.3,0.4)	0.686
	MOA-728 12 mg QOD	132	6.1(1.9)	-0.1(1.5)	-0.1(0.1)	-0.0(-0.3,0.3)	0.970
	Placebo	153	6.2(2.0)	-0.1(1.4)	-0.1(0.1)		
Day 28	MOA-728 12 mg QD	122	6.1(1.9)	-0.2(1.6)	-0.2(0.1)	-0.1(-0.5,0.3)	0.645
	MOA-728 12 mg QOD	120	5.9(1.7)	-0.3(1.5)	-0.3(0.1)	-0.3(-0.7,0.1)	0.147
	Placebo	143	6.3(2.0)	-0.1(1.8)	-0.1(0.1)		

Abbreviations: CI = confidence interval; DAI = data analysis interval; mITT = modified intent-to-treat; QD = once daily; QOD = once every other day; SD = standard deviation; SE = standard error.

Note: A scale of 0 (no pain) to 10 (worst possible pain) was used for average pain during the past 24 hours.

a. p-Value vs placebo group was based on ANCOVA Model change = baseline + treatment.

(Source: Sponsor's table, CSR, p. 140)

**Pain Intensity Scores (OL period):** The findings in the OL period were similar to the DB with no significant changes in the median pain intensity score.

#### **D) Average Daily Opioid Morphine Equivalent Dose (MED)**

**Average Daily Opioid Morphine Equivalents:** As per inclusion criteria, patients must have been taking opioids for at least one month and using opioids at an oral daily Morphine Equivalent Dose (MED)  $\geq 50$ mg for at least 2 weeks before the screening visit with no anticipated changes during the study.

**Average Daily Opioid Morphine Equivalents (Baseline):** Table 9 below displays the Baseline Morphine Equivalent Dose (MED) categories. The treatment arms appear to be generally equally distributed for baseline MED, with the greatest percentage of patients taking a baseline MED between 100mg and 400mg MED.

**Table 9. Baseline Morphine Equivalents Study 3356**

Characteristic	Treatment			Total (n = 460)
	MOA-728 12mg QD (n = 150)	MOA-728 12mg QOD (n = 148)	Placebo (n = 162)	
Baseline Morphine Equivalent Dose Category (mg), N				
< 30 mg		2 (1.4)	1 (0.6)	3 (0.7)
30 mg - < 50 mg	1 (0.7)	1 (0.7)	4 (2.5)	6 (1.3)
50 mg - < 60 mg	9 (6.0)	13 (8.8)	14 (8.6)	36 (7.8)
60 mg - < 100 mg	31 (20.7)	30 (20.3)	32 (19.8)	93 (20.2)
100 mg - < 400 mg	91 (60.7)	80 (54.1)	90 (55.6)	261 (56.7)
$\geq 400$ mg	18 (12.0)	22 (14.9)	21 (13.0)	61 (13.3)

Abbreviations: QD = once daily; QOD = once every other day.

(Source: Sponsor's table, CSR 3356, p. 67)

**Average Daily Opioid Morphine Equivalents (DB period):** According to the Sponsor, the average daily use of morphine equivalents appeared to decrease in the MOA-728 QD and QOD



groups compared to placebo, seen in Table 10. More importantly, there did not appear to be an increase in average daily opioid morphine equivalents throughout the DB portion of the study.

**Table 10. Average Daily Opioid Morphine Equivalents by Treatment Group (DB Phase mITT Population)**

DAI	Treatment	N	Raw		Adjusted Change Mean(SE)	Difference in Adjusted Change vs Placebo	
			Mean(SD)	Change Mean (SD)		Mean (95% CI)	p-Value <sup>a</sup>
DB Treatment	MOA-728 12 mg QD	146	208.9(154.3)	-3.1(34.5)	-3.0(2.6)	-4.3(-11.3,2.7)	0.226
	MOA-728 12 mg QOD	139	215.4(205.6)	-5.2(36.8)	-5.2(2.6)	-6.5(-13.6,0.6)	0.072
	Placebo	159	226.9(226.3)	1.3(20.2)	1.3(2.5)		
Week 1	MOA-728 12 mg QD	146	207.2(154.9)	-4.8(31.3)	-4.8(2.5)	-6.7(-13.5,0.1)	0.054
	MOA-728 12 mg QOD	139	212.6(199.2)	-8.0(39.1)	-8.0(2.6)	-9.8(-16.7,-2.9)	0.005
	Placebo	159	227.4(225.4)	1.8(17.6)	1.9(2.4)		
Week 2	MOA-728 12 mg QD	138	206.5(149.7)	-1.8(35.9)	-1.8(2.7)	-2.1(-9.5,5.2)	0.569
	MOA-728 12 mg QOD	135	216.8(207.2)	-3.5(41.3)	-3.5(2.8)	-3.8(-11.2,3.6)	0.315
	Placebo	158	226.7(223.6)	0.3(15.1)	0.3(2.6)		
Week 3	MOA-728 12 mg QD	134	207.3(150.3)	0.2(34.3)	0.4(2.9)	-1.3(-9.0,6.5)	0.750
	MOA-728 12 mg QOD	129	217.1(215.7)	-1.2(38.0)	-1.2(2.9)	-2.9(-10.7,4.9)	0.469
	Placebo	153	230.5(229.8)	1.9(28.3)	1.7(2.7)		
Week 4	MOA-728 12 mg QD	127	210.7(152.1)	2.6(36.4)	2.9(3.2)	0.6(-8.0,9.1)	0.896
	MOA-728 12 mg QOD	124	220.8(215.4)	-1.5(40.1)	-1.6(3.2)	-3.9(-12.5,4.7)	0.372
	Placebo	148	233.8(237.0)	2.6(31.9)	2.3(2.9)		

Abbreviations: CI = confidence interval; DAI = data analysis interval; mITT = modified intent-to-treat; QD = once daily; QOD = once every other day; SD = standard deviation; SE = standard error.

a. p-Value vs placebo group was based on ANCOVA Model change = baseline + treatment.

(Source: Sponsor's table, CSR, p. 143)

**Average Daily Opioid Morphine Equivalents (OL period):** Findings were similar in the OL as the DB with no statistically significant increase in average daily opioid morphine equivalent use over time, based upon the Sponsor's analysis.

#### **IV) Safety Findings Related to Opioid Withdrawal**

***Deaths/SAEs:*** There were no deaths in the study. There were 8/460 (1.7%) patients in the DB period who reported at least one SAE. No SAEs appeared definitely or probably related to opioid withdrawal in this reviewer's opinion based on the types of SAEs. There was one patient who experienced myoclonus in the MOA 12mgQOD arm, but the narrative of this patient did not suggest opioid withdrawal. In addition, one patient experienced an SAE of convulsion. The narrative of that patient documented a preexisting seizure disorder. In the OL phase, 4/364 (1.1%) experienced at least one SAE. The SAEs did not appear to be opioid withdrawal related.

***Discontinuations due to AEs:*** A total of 27 (5.9%) subjects withdrew from the DB period of the study due to AEs. The Sponsor did not specifically analyze AEs as to probability of being related to opioid withdrawal, but did present a table of number (%) of subjects reporting Adverse Events Resulting in Discontinuation during the DB period. This reviewer assessed whether the AE could potentially be related to opioid withdrawal for any AE occurring in  $\geq 1$  patient in study drug treatment group compared to placebo. The AEs selected either met the DSM-IV diagnostic criteria of Opioid Withdrawal and/or were listed as opioid withdrawal signs or symptoms in OOWS/SOWS, respectively. Although abdominal pain, diarrhea and hyperhidrosis are listed in the currently approved Relistor label as common AEs ( $>5\%$ ), these are also potential opioid-withdrawal AEs.

All of the AEs possibly related to opioid withdrawal (except for diarrhea) occurred more frequently in the study-drug treatment arm than placebo, and the incidence of possible opioid withdrawal-related AEs occurred more frequently in the QOD treatment arm.

AEs leading to discontinuation possibly related to opioid withdrawal are shown below in Table 11.

**Table 11. Discontinuations due to AEs Possibly Related to Opioid Withdrawal During DB Period, Study 3356**

Preferred Term	MOA-728 QD N=150	MAO-728 QOD N=148	Placebo N=162
Number experiencing AEs (~%)			
Abdominal pain*	3 (2.0)	5 (3.4)	0
Nausea	2 (1.3)	4 (2.7)	0
Vomiting	0	4 (2.7)	0
Hyperhidrosis*	0	4 (2.7)	0
Abdominal distension	1 (0.7)	2 (1.4)	0
Diarrhea*	1 (0.7)	2 (1.4)	2 (1.2)
Abdominal pain upper	0	2 (1.4)	0
Tremor	0	2 (1.4)	0
Piloerection	0	2 (1.4)	0
Feeling cold	0	2 (1.4)	0
Feeling of body temp change	0	1 (0.7)	0
Anxiety	0	1 (0.7)	0
Restlessness	0	1 (0.7)	0
Chills	0	1 (0.7)	0

\*Currently approved Relistor label >5% Incidence; (Table, reviewer, adapted from Sponsor's Table 10-11, CSR, p. 119-120)

The Sponsor submitted narratives for 53 patients with SAEs, discontinuations due to AEs or other safety-related reasons during the DB, OL, Follow up and Post-study period. Ten of the narratives were in patients in the placebo arm. Of the patients with narratives in the drug-treated group, 13 had abdominal pain, cramping, distention or bloating listed as a preferred term. Narratives for patients who discontinued due to AEs possibly related to opioid withdrawal were reviewed. Selected narratives summarized in Table 12 represent patients who experienced a constellation of symptoms (excluding isolated abdominal pain or abdominal distention with or without associated nausea or diarrhea) possibly associated with opioid withdrawal and includes 5 patients who received MOA-728 QOD and 2 patients who received MOA-728 QD.

**Table 12. Narratives of Patients Discontinued due to AE Possibly Related to Opioid Withdrawal and Associated OOWS/SOWS Total Scores Per Assessment Visit**

<b>Patient ID</b>	<b>Narrative Summary AE Preferred Terms</b>
<b>MOA-728 12 mg QOD</b>	
MOA728 3356-015- 000640	<p><b>Abdominal pain, Anxiety, Chills, Hyperhidrosis, Piloerection, Restlessness, Tremor, and Vomiting</b></p> <p>33-year-old woman, with medical history of neck pain discontinued the study medication on 3/28/08 due to adverse events (AEs) on 3/28/08, the first day of DB study medication. She was taking 146 mg of methadone daily throughout the study. The AEs of abdominal cramps and vomiting were severe, and anxiety, chills, sweating, goosebumps, restlessness, and tremors were moderate in severity. All the AEs resolved on the same day.</p> <p>Total OOWS scores 0, 12 Total SOWS Score 10</p>
MOA728 3356-027- 001175	<p><b>Abdominal pain, Nausea, Vomiting, Feeling cold, Hot flush, and Hyperhidrosis</b></p> <p>34-year-old woman, with multiple chronic medical conditions discontinued the study medication on 11/14/07 (same day she started DB period) because of the onset of the adverse events (AEs) noted on 11/14/07. She was taking 100 mcg/hr of fentanyl patch and 20 mg of oxycodone + acetaminophen daily throughout the study. AEs of abdominal cramps and nausea were severe; cold flashes, hot flashes, and sweating of moderate severity; and vomiting of mild severity. The AEs of cold flashes, hot flashes, and sweating resolved on the same day; nausea and vomiting resolved on 11/15/07; and abdominal cramps resolved on 11/18/07.</p> <p>Total OOWS Scores 0, 6 Total SOWS Scores 52, 54</p>
MOA728 3356-015- 000639	<p><b>Feeling cold, Hot flush, Hyperhidrosis, Nausea; Piloerection; Tremor</b></p> <p>43-year-old man, with medical history of right arm nerve damage and car accident, discontinued the study medication on 4/22/08 (26 days after starting DB period) because of AEs as noted. The subject started double-blind study medication on 3/27/08 and was taking 180 mg of oxycodone hydrochloride daily throughout the study. Reported AEs of cold flashes, hot flashes, sweating, nausea, goosebumps, and tremors on 4/19/08, which were moderate in severity. The last dose of study medication administration prior to the onset of AEs was on 4/18/08. All AEs resolved on 4/23/08.</p> <p>Total OOWS scores 0, 1, 0, 2 Total SOWS scores 13, 20, 13, 56</p>
MOA-728 3356-205- 003224	<p><b>Abdominal pain; Diarrhea; Feeling of body temperature change; Hyperhidrosis; Nausea; Vomiting</b></p> <p>28-year-old woman, with a medical history of lumbar vertebral pain, cervical pain, insomnia, weakness of the left arm and anxiety, discontinued study medication on 3/12/08 (same day she started DB period) because of the AEs noted. She was on 50 mg methadone medication daily since 2003 and throughout the screening period supplemented with 25 to 75 mg of additional methadone daily. The subject started the double-blind study medication on 3/12/08 and reported the AEs on the same day, severe rating. All AEs resolved on 3/12/08. No additional AEs were reported. The subject returned for her termination visit on 3/12/08 and did not return for follow-up visits.</p> <p>OOWS scores: 3, 2 SOWS Scores: 49, 68</p>
MOA-728 3356-073 003702	<p><b>Nausea; Vomiting</b></p> <p>The subject, a 44-year-old woman with a medical history of hysterectomy, muscle spasms, insomnia and osteoporosis, discontinued the study medication on (b) (6) because of adverse events (AEs) of nausea and vomiting. She was taking 2.4 mg of fentanyl patch and 120 mg of oxycodone hydrochloride daily throughout the study. The subject started the double-blind study medication on (b) (6) and on the same day she experienced severe nausea and vomiting. Both the AEs resolved on the same day. The subject was withdrawn from the study and was sent to the emergency room (ER).</p>

	OOWS Scores: 0 SOWS scores 13
<b>MOA-728 12 mg QD</b>	
MOA728 3356-025- 001085	<b>Nausea, Dizziness and Hot sweats</b> 47-year-old woman, with a complex medical history discontinued the study medication on 7/5/08 because of the adverse event (AE) of nausea. The subject was taking 60 mg of methadone and 12 mg of hydromorphone during the study. The subject started the double-blind study medication on 7/3/08 and reported an AE of nausea on 7/6/08 of moderate severity, which resolved on the same day. Additional AEs included <b>dizziness and hot sweats</b> which started and resolved on 7/6/08; neck tightness 7/3/08); and another episode of dizziness, nausea, and hot sweats on 7/3/08, the first day of study medication administration. OOWS Scores: 0, 2, 0 SOWS Scores: 16, 8, 22
MOA728 3356-005- 000183	<b>Hot flush; Hyperhidrosis, Hypertension</b> 61-year-old man, with a medical history of type 2 diabetes mellitus, herniated disc (back pain), and weakness to right lower extremity discontinued study medication on 5/14/08 (approximately one month after start) because of the adverse events (AEs) of hot flash sensation, sweating, and high blood pressure. He was taking 22.5 mg of hydrocodone, 120 mg of oxycodone, and 40 mg of methadone daily throughout the study. The subject started the double-blind study medication on 3/24/08, and entered the open-label study medication on 4/19/08. The subject reported moderately severe AEs of hot flash sensation, sweating, and high blood pressure on 4/19/08, the first day of open-label study medication. OOWS; 0, 0, 0, 0. SOWS: 25, 17, 25, 22

(Source: Table, reviewer)

**Common AEs (DB period):** Overall, TEAEs were reported in 203 (44%) of 460 subjects in the DB period (49.3%, 45.3% and 38.3% in MOA-728QD, MOA-718QOD and placebo, respectively). TEAEs potentially related to opioid withdrawal occurred with greater incidence in the drug treatment group than placebo group except anxiety, rhinorrhea, and feeling cold. Vomiting occurred more frequently in the QOD treatment arm than QD or placebo. These findings are summarized in Table 13 below, modified from the Sponsor's table of TEAEs occurring in  $\geq 2\%$  of patients.

**Table 13. Number (%) Subjects Reporting Percentages  $\geq 2\%$  TEAEs Possibly Causally Related to Drug Withdrawal Symptoms DB Phase Study 3356**

Preferred Term	MOA-728 QD N=150	MAO-728 QOD N=148	Placebo N=162
<b>Number experiencing AEs (~%)</b>			
Abdominal pain*	29 (19)	23 (15)	6 (4)
Nausea	13 (9)	17 (11)	10 (6)
Diarrhea*	9 (6)	17 (11)	6 (4)
Vomiting	1 (<1)	11 (7)	8 (5)
Hyperhidrosis*	9 (6)	9 (6)	2 (1)
Tremor	2 (1)	5 (3)	1 (<1)
Piloerection	1 (<1)	4 (3)	0
Hot flush	4 (3)	5 (3)	3 (2)
Chills	2 (1)	3 (2)	0
Feeling of body temp change	0	4 (3)	1 (<1)
Anxiety	3 (2)	3 (2)	3 (2)
Rhinorrhea	2 (1)	3 (2)	2 (1)
Feeling cold	0	3 (2)	0

\*Currently approved Relistor label  $>5\%$  Incidence (Table, reviewer, modified from Sponsor's Table 10-6, CSR, p. 110-11); percentages rounded

**Common AEs (OL Period):** TEAEs were reported in 155 (43%) of 364 patients in the OL phase who received study drug 12mg prn. The most frequently reported TEAE occurring in  $\geq 2\%$  of patients in the safety population during the OL phase possibly related to opioid withdrawal included abdominal pain (7%). Other potentially related withdrawal AEs included nausea (4.1%), diarrhea (2.7%), headache (2.5%), and hyperhidrosis (2.2%).

#### **V) Reviewer Comments/ Conclusions Study 3356:**

- Seven subjects treated with MNTX discontinued treatment due to AEs possibly related to opioid withdrawal in the double-blind study period .
- Additional subjects experienced AEs possibly related to opioid withdrawal as shown in table 13.
- Evidence of opioid withdrawal occurring during this study is based upon the specific AEs of hyperhidrosis and piloerection which occurred more frequently in drug-treated subjects than placebo-treated subjects.
- The most frequently occurring AE probably related to opioid withdrawal was hyperhidrosis.
- Opioid withdrawal symptoms occurred with increased incidence in the QOD treatment group compared to QD or placebo. The significance of this is unclear.
- Individual item OOWS scores showed that perspiration occurred more frequently than other individual items on the OOWS in subjects treated with MNTX. This most likely correlates with the reported AEs of hyperhidrosis.
- Limitations of the study include the following:



- Infrequent assessments of withdrawal may not have captured symptoms during clinically relevant times. Specifically, OOWS/SOWS were obtained at predose, one hour postdose, and not again until days 14 and 28 during the DB period. Although opioid withdrawal may have occurred at any time during treatment, the clinical expectation is that withdrawal would occur early in treatment, likely within the first 7 to 14 days.
- Patients were allowed to increase pain medication throughout study. This may have masked potential changes in pain intensity (PI) scores if the scores were not collected prior to changes in opioid dose.
- The Sponsor provided no defined criteria for mild, moderate or severe rating for OOWS scores.
- Many of the patients with missing OOWS/SOWS data were those who withdrew due to possible opioid withdrawal AEs. The resulting OOWS/SOWS scores may have been skewed to be lower since those with potentially higher scores withdrew.

**Study 2: Study3200K1-3358-WW (subsequently referred to as Study 3358)**

Title: An Open-Label Study to Evaluate the Long-term Safety of Subcutaneous MOA-728 for Treatment of Opioid-Induced Constipation in Subjects with Nonmalignant Pain

Design: Phase 3, multicenter, open-label study to evaluate long-term safety and tolerability study.

Study Overview: Long-term safety and tolerability study which consisted of three periods: Two-week screening period, a 48-week open-label treatment period, and a two-week post-treatment follow up period. During the OL period, patients were instructed to use MNTX 12mg SC once daily but were permitted to remain in the study if a reduction in dose frequency occurred. Dosing was required to be at least once per week, but not more frequently than one dose per day.

Population: Non-cancer patients with a history of OIC, confirmed during the two-week screening period. Total N=1034

Key Inclusion Criteria:

1. Male or female aged 18 years or older
2. History of pain of at least 2 months' duration before screening due to a documented underlying nonmalignant condition
3. Taking oral, transdermal, IV or subcutaneous (SC) opioids for at least 1 month with anticipated continuing daily opioid therapy for the duration of the study
4. History of constipation due to opioid use during the 1 month before screening. Constipation criteria were defined.

Key Exclusion Criteria:

1. Medical instability
2. A history of chronic constipation before the initiation of opioid therapy
3. A history of alcohol or drug abuse within 1 year before the screening visit

## Study Assessments

### *Total OOWS and SOWS Scores*

The OOWS and SOWS were administered at baseline before administration and approximately one hour after administration on Day 1 of the first dose of study drug. The pre-dose assessment served as the baseline for the patients. These were the only assessment time points for the OOWS and SOWS as shown in Table 14.

**Table 14. OOWS and SOWS Assessments Schedule, DB and OL Periods, Study 3358**

Assessment	BL	Day 1	Week 4	Week 8	Week 12	Week 16	Week 24	Week 32	Week 48	Follow up
OOWS	X	X	Not assessed							
SOWS	X	X								

(Source: reviewer); BL=Baseline

### *Pain Intensity Scores*

Pain assessments were completed as shown in Table 15. Patients were asked to describe their average pain during the past 24 hours on an 11 point NRS, ranging from 0 (no pain) to 10 (worst pain possible).

**Table 15. Pain Intensity Assessments Schedule, Study 3358**

Assessment	Baseline Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 24	Wk 32	Wk 40	Wk 48	Follow Up
Pain Scale	X	X	X	X	X	X	X	X	X	X

(Source: reviewer); Wk=Week

### *Average Daily Morphine Equivalent Dose*

Prior/concomitant medications were recorded at screening, baseline, each study visit and follow up.

## Results

Due to the design of the study, only descriptive summary statistics (n and percentage for categorical variables, and n, mean, standard deviation, median, minimum and maximum for continuous variables and their change from baseline) were reported for the safety and efficacy parameters.

Patients were instructed to use the injections prn, but at least once daily. As can be seen in Table 16, there was a wide variation of use, although approximately 50% used the medication >6-7 doses per week. This variability, as well as the OL design, limits the interpretation of the results.

**Table 16. Distribution of Average Number of Weekly Injections During OL Study 3358 – All Subjects Population**

# Doses Exposed/Week, N (%)	Treatment
	MOA-728 12mg QD (N=1034)
<=1	52 (5.0)
>1-2	42 (4.1)
>2-3	74 (7.2)
>3-4	115 (11.1)
>4-5	108 (10.4)
>5-6	130 (12.6)
>6-7	509 (49.2)
>7	4 (0.4)

Abbreviations: QD = once daily.

Note: The number of doses/week based on the average within each subject.

(Source: Sponsor's table, CSR 3358, p. 66)

### A) Total OOWS and SOWS Scores

There was no appreciable change in the mean scores from baseline to post baseline in both OOWS and SOWS scores. Raw means and mean change from baseline are shown for the total scores OOWS and SOWS with and without the items relating to cramping as shown in Tables 17 and 18 below.

**Table 17. Summary of OOWS: All-subjects Populations (With and Without Cramping)**

Endpoint	DAI	Treatment	N	Mean	Raw Value			N	Change from baseline			
					SD	Median	Min-Max		Mean	SD	Median	Min-Max
OOWS	Baseline	MOA-728 12 mg	1028	0.4	1.0	0.0	0.0-7.0					
	Day 1	MOA-728 12 mg	1021	0.6	1.3	0.0	0.0-12.0	1020	0.2	1.1	0.0	-4.0-10.0
OOWS Score - Without Cramping Item	Baseline	MOA-728 12 mg	1028	0.4	0.9	0.0	0.0-6.0					
	Day 1	MOA-728 12 mg	1021	0.5	1.2	0.0	0.0-11.0	1020	0.1	0.9	0.0	-4.0-9.0

Abbreviations: DAI= data analysis interval; OOWS= Objective Opioid Withdrawal Scale; SD= standard deviation.

Source:/CLINICAL R&D/CLINICAL BIostatISTICS SAS REPORTS/3200K1 MOA-728/3358/ Final Report

(Source: Sponsor's table, CSR, Study 3358 p. 80)

**Table 18. Summary of SOWS: All-subjects Populations (With and Without Cramping)**

Endpoint	DAI	Treatment	N	Mean	Raw Value			N	Change from baseline			
					SD	Median	Min-Max		Mean	SD	Median	Min-Max
Total SOWS Score	Baseline	MOA-728 12 mg	1033	12.3	9.9	10.0	0.0-58.0					
	Day 1	MOA-728 12 mg	1008	9.7	9.3	7.0	0.0-56.0	1007	-2.5	7.1	-1.0	-33.0-44.0
Total SOWS Score - Without Cramping Item	Baseline	MOA-728 12 mg	1033	11.7	9.4	10.0	0.0-54.0					
	Day 1	MOA-728 12 mg	1008	8.8	8.7	6.0	0.0-53.0	1007	-2.8	6.6	-1.0	-33.0-40.0

Abbreviations: DAI = data analysis interval; SOWS = Subjective Opioid Withdrawal Scale; SD = standard deviation.

(Source: Sponsor's table, CSR, Study 3358 p. 82)

**B) Pain Intensity Scores:** As seen in Table 19, there was not a clinically important change in mean scores for PI from baseline to follow-up for the duration of the study.

**Table 19. Summary of Pain Intensity Scale All-Subjects Population**

DAI	Treatment	N	Mean	Raw Value			N	Change from baseline			
				SD	Median	Min-Max		Mean	SD	Median	Min-Max
Baseline	MOA-728 12 mg	1029	6.1	1.9	6.0	0.0-10.0					
Week 4	MOA-728 12 mg	898	6.0	2.0	6.0	0.0-10.0	894	-0.1	1.8	0.0	-8.0-10.0
Week 8	MOA-728 12 mg	789	6.0	2.1	6.0	0.0-10.0	785	-0.0	2.0	0.0	-9.0-8.0
Week 12	MOA-728 12 mg	733	6.1	2.1	6.0	0.0-10.0	729	0.1	1.9	0.0	-7.0-9.0
Week 16	MOA-728 12 mg	689	6.1	2.2	6.0	0.0-10.0	685	0.0	2.0	0.0	-8.0-9.0
Week 24	MOA-728 12 mg	626	6.1	2.2	6.0	0.0-10.0	623	0.0	2.0	0.0	-7.0-9.0
Week 32	MOA-728 12 mg	582	6.1	2.1	6.0	0.0-10.0	579	0.0	2.0	0.0	-9.0-9.0
Week 40	MOA-728 12 mg	521	6.1	2.1	6.0	0.0-10.0	518	0.0	2.0	0.0	-7.0-9.0
Week 48	MOA-728 12 mg	435	6.1	2.1	6.0	0.0-10.0	432	0.0	2.1	0.0	-7.0-10.0
Follow-Up	MOA-728 12 mg	286	6.2	2.2	7.0	0.0-10.0	285	0.1	2.0	0.0	-6.0-7.0

Abbreviations: DAI = data analysis interval; SD = standard deviation.

(Source: CSR, Study 3358, p. 84)

**C) Average Daily Opioid Morphine Equivalents:** Although there was an increase in daily opioid morphine equivalents in some weeks, the Sponsor found no clinically meaningful change in the mean daily opioid morphine equivalent use. The average change from baseline in morphine equivalent use throughout the OL study was 3.0. Without a control group, meaningful interpretation of the data cannot be made. In addition, the inherent variability of prn use of study drug may have affected daily opioid use.

**Table 20. Summary of Average of Daily Opioid Morphine Equivalent, All-Subjects Population**

DAI	Treatment	N	Mean	Raw Value			N	Change from baseline			
				SD	Median	Min-Max		Mean	SD	Median	Min-Max
Baseline	MOA-728 12 mg	1034	199.7	232.2	120.0	1.2-2196.0					
OL Period	MOA-728 12 mg	985	200.9	241.6	118.7	0.0-2203.3	985	3.0	102.1	0.0	-1070-1331.1
Weeks 1-4	MOA-728 12 mg	985	202.8	313.0	117.9	0.0-6740.4	985	4.9	217.5	0.0	-742.9-6412.5
Weeks 5-8	MOA-728 12 mg	866	197.1	242.6	117.3	0.0-2325.7	866	0.8	88.1	0.0	-1130-1331.0
Weeks 9-12	MOA-728 12 mg	777	201.2	241.6	119.0	0.0-2201.8	777	1.3	87.0	0.0	-1173-1331.0
Weeks 13-16	MOA-728 12 mg	736	203.0	245.4	120.0	0.0-2211.4	736	0.6	97.2	0.0	-1173-1331.0
Weeks 17-20	MOA-728 12 mg	694	207.2	249.3	120.0	0.0-2206.1	694	1.9	105.3	0.0	-1173-1331.0
Weeks 21-24	MOA-728 12 mg	653	212.8	267.8	120.0	0.0-2236.6	653	5.5	135.7	0.0	-1173-2140.2
Weeks 25-28	MOA-728 12 mg	624	218.2	310.7	120.0	0.0-4427.5	624	11.5	201.7	0.0	-1173-4331.1
Weeks 29-32	MOA-728 12 mg	600	215.3	267.7	120.0	0.0-2210.4	600	7.7	108.3	0.0	-1173-1331.0
Weeks 33-36	MOA-728 12 mg	575	223.2	278.3	121.1	0.0-2210.4	575	13.6	121.8	0.0	-1173-1331.0
Weeks 37-40	MOA-728 12 mg	538	231.0	405.6	120.4	0.0-7462.3	538	25.4	333.6	0.0	-1173-7235.3
Weeks 41-44	MOA-728 12 mg	512	223.0	269.0	120.0	0.0-2045.7	512	16.8	139.7	0.0	-1173-1331.0
Weeks 45-48	MOA-728 12 mg	496	216.1	262.0	120.0	0.0-2055.7	496	11.7	139.5	0.0	-1295-1312.8
>Week 48	MOA-728 12 mg	248	218.9	285.8	120.0	0.0-1929.6	248	8.2	126.1	0.0	-1173-659.3
Follow-Up	MOA-728 12 mg	873	202.9	253.2	116.5	0.0-2160.0	873	3.9	117.8	0.0	-962.4-1564.5

Abbreviations: DAI = data analysis interval SD = standard deviation.

### **III) Safety Findings Related to Opioid Withdrawal**

Since this was an OL study, safety findings need to be interpreted recognizing that there is no placebo for comparison. For purposes of this review, AEs are discussed primarily from the perspective of opioid withdrawal.

**Deaths/SAEs:** In this reviewer's opinion, there were no deaths or SAEs related to opioid withdrawal symptoms. There were 4 patients who died in Study 3358 (1 during the study and 3 following the study). The narratives of these patients (3358-008-080235, 3358-020-080651, 3358-073-081899 and 3358-200-083696) did not suggest opioid withdrawal related causality.

**Discontinuations due to AEs:** One hundred fifty seven (15%) patients withdrew from the study because of AEs. The most common AEs resulting in withdrawal were abdominal pain (5%), nausea (2%) and diarrhea (2%). All of these AEs may be associated with opioid withdrawal but are also known AEs of the study drug.

Discontinuations due to possible opioid withdrawal included the following preferred terms with number of patients experiencing the AE in parenthesis: Withdrawal Syndrome (2); Abdominal Pain (49); nausea (26), diarrhea (24), hyperhidrosis (16), vomiting (16); hot flush (6); chills (4); feeling of body temperature change (2), cold sweat (2); muscle twitching (2); rhinorrhea (2); piloerection (1); yawning (1); insomnia (1). More than one preferred term may have occurred in the same patient.

Any of the patients who had AEs suggestive of opioid withdrawal could have potentially experienced opioid withdrawal. The review of the OL study does not summarize the narrative of every patient in Study 3358 who had preferred terms which may be associated with opioid withdrawal but focused on those narratives which had a constellation of terms suggestive of opioid withdrawal.

Table 21 summarizes the narratives for 8 patients identified who discontinued due to AEs with possible opioid withdrawal symptoms. Patient 3358-012-080374 had a preferred term of Excessive Thirst as the primary AE, but the narrative suggested other AEs associated with opioid withdrawal.

**Table 21. Narratives of Discontinuations due to AEs – Possibly Opioid Withdrawal Related, Study 3358**

Patient ID	Narrative Summary AE Preferred Terms
<b>MOA-728 12mg QD</b>	
MOA728 3358-019- 080605	<b>Abdominal pain, Diarrhea, Dizziness, Abnormal GI sounds, Hot flush, Hyperhidrosis, Malaise, Nausea, Blurred vision.</b> 36 year old male with AE terms as noted. Start date 5/20/09; stop date 5/20/09. Incomplete information provided.
MOA728 3358-084- 083437	<b>Abdominal pain; Feeling of body temperature change; Hyperhidrosis; Lacrimation increased; Muscle twitching; Piloerection; Rhinorrhea, Tremor; Yawning</b> 42-year-old woman with a history of opioid induced constipation, back pain, depression, anxiety, bipolar disorder, and seasonal allergies, discontinued the study medication on 5/28/09 after onset of symptoms after the first dose of the study medication. The investigator considered the AEs related to the study medication. The subject had no other AEs during the study. Relevant concomitant medications included Xanax, Meloxicam, Neurontin, Tizanidine, and Cymbalta. The subject was taking Oxycodone and Kadian during the study for pain management. The subject had the early termination visit on 7/15/09 and the follow up visit on 7/16/09.
MOA728 3358-012 080373	<b>Hyperhidrosis; Nausea</b> 55 year old man with a medical history of opioid induced constipation, back pain, GERD, and occasional light headedness discontinued study medication on 3/16/09 due to perspiring (3/5/09)

	to 3/21/09) and nausea (3/9/09 to 3/21/09). The subject experienced <b>perspiring, abdominal cramping, nausea, anxiousness, rhinorrhea, and restlessness</b> on 2/17/09, the first day of test article, which all resolved the same day. Additional AEs included heartburn, hot flashes, loss of appetite and proteinuria. The subject was taking OxyIR and OxyContin throughout the study for back pain. Early termination visit on 3/17/09 and the follow up visit on 3/31/09.
MOA728 3358-005- 080102	<b>Restlessness, Anxiety, Muscle twitches, Abdominal cramps, Vomiting, Hot and cold flashes, Nausea, and Perspiration</b> 58 year old woman, with multiple medical conditions discontinued the study medication after the first dose of test article on 5/20/09 due to the adverse events fatigue, shortness of breath, restlessness, anxiety, muscle twitches, abdominal cramps, vomiting, hot and cold flashes, nausea, and perspiration, which occurred on the same day. Shortness of breath, restlessness, anxiety, muscle twitches, abdominal cramps, vomiting, and hot and cold flashes resolved the same day. Was taking methadone and morphine during the study for multiple sclerosis. The subject returned for the early termination visit on 6/2/09 and the follow up visit on 6/17/09.
MOA728 3358-207- 086741	<b>Anxiety, Chills, Sweats, and Insomnia</b> 44-year-old woman with a history of opioid induced constipation, back pain, fibromyalgia, migraine headaches, and insomnia, discontinued study medication on 1/11/09 due to AEs of abdominal cramping, anxiety, chills, sweats, and insomnia. The subject had no other AEs during the study. Concomitant medications included amitriptyline for pain. The subject was taking OxyContin and oxycodone during the study for pain management. The subject had the early termination visit on 1/20/10 and the follow up visit on 1/25/10.
MOA728 3358-012- 080374	<b>Thirst (excessive thirst)</b> 60 year old woman with a medical history of opioid induced constipation and back pain, discontinued study medication on 3/20/09 due to the adverse event excessive thirst, which started on 3/5/09 and resolved on 3/21/09, the day after study medication was discontinued. No other relevant medical history was noted. The subject experienced abdominal cramping, <b>anxiousness, perspiration, rhinorrhea, shaking, cold flashes, muscle aches, restlessness, muscle twitching, and craving to take more opioids</b> , all which started and resolved on 2/19/09, the first day of study medication. The subject was taking Lortab and MS Contin throughout the study for back pain. Early termination visit on 3/24/09, and failed to return for a follow up visit.
Patient MOA728 3358-142- 086426	<b>Drug Withdrawal Syndrome</b> 65-year-old woman with a history of opioid induced constipation, back pain, asthma, anxiety, and hypoparathyroidism, discontinued the study medication on 9/17/09 due to AE of symptoms consistent with opioid withdrawal of moderate severity. The investigator considered the AE related to the study medication. The subject had other AE of abdominal pain during the study. The subject was taking Actiq and Duragesic during the study for pain management. Early termination visit on 9/24/09 and the follow up visit on 10/8/09.
MOA728 3358-038- 081107	<b>Drug Withdrawal Syndrome</b> 56 year old man, with a medical history of opioid induced constipation and osteoarthritis, discontinued the study medication on 5/24/09 due to the adverse event of opioid withdrawal symptoms, which started on 5/24/09, the last day of study medication, and resolved on 5/28/09. No additional adverse events were reported. The subject was taking methadone throughout the study for osteoarthritis. No relevant concomitant medications were reported. The subject had the early termination visit on 5/28/09 and failed to return for the follow up visit

(Source: Table, reviewer)



**Common AEs:** TEAEs were reported in 817 (79.0%) subjects. The most frequently reported system organ class of TEAEs was gastrointestinal disorders (498 subjects, 48.2%). The most frequently reported TEAEs in the gastrointestinal disorders system organ class were abdominal pain (248 subjects, 24.0%), diarrhea (170 subjects, 16.4%), and nausea (156 subjects, 15.1%). Hyperhidrosis was reported in 92 (8.9%) subjects.

#### **IV) Reviewer Comments/Conclusions Study 3358**

- There was evidence of opioid withdrawal symptoms in at least eight patients who received study drug on a prn (12mg daily minimum) basis and discontinued treatment due to these events.
- Hyperhidrosis was reported as the most frequent AE in the cases of those patients who discontinued due to possible opioid withdrawal symptoms.
- There was no definite evidence of increased use of opioids (MED) or consistent pattern to suggest a change in pain intensity scores related to use of study drug.
- The primary study limitation is that it is OL, in addition to the limitations noted for study 3356.

#### **Additional Data Reviewed (Information Request) Studies 3356 and 3358**

In addition to the Sponsor's submission of studies 3356 and 3358, an Information Request was sent to the Sponsor via email on 1/4/2012 for the following clarifications and additional information:

- Provide figures (graphs), one for each treatment group, that contain individual patient data, with the Median Daily Opioid Dose (mg) on the Y-axis and Treatment Days on X-axis.
- Create three figures (graphs), one for each treatment group, that contain individual patient data, with Objective Opioid Withdrawal Scale (OOWS) total scores on the Y-axis and Treatment Days on the X-axis.
- Create three similar figures as described in bullet 2 above, containing individual patient data for the Subjective Opioid Withdrawal Scale (SOWS) total scores.
- Create a table that contains the individual patient data for morphine equivalent doses, OOWS total score and SOWS total score for the 4-week DB period of Study 3356
- Provide the total number of patients completing the OOWS/SOWS and Pain Scores by Assessment Days with detailed explanations to account for the variability in patient number throughout in Studies 3356 and 3358.

The Sponsor provided the requested information on 1/10/12 as an Efficacy Information Amendment, submitted electronically to the NDA.

The review of that data did not result in a change in the findings previously reported in this review.

### **Sponsor's Proposed Label**

The Sponsor proposes the following claims regarding Opioid Use and Pain Scores: *Daily opioid use did not change meaningfully from baseline for either RELISTOR-treated patients or placebo-treated patients. There was no evidence for the occurrence of opioid withdrawal symptoms. There were no clinically relevant changes from baseline in pain scores in either the RELISTOR- or placebo-treated patients.*

Based upon the findings of opioid withdrawal symptoms in DB Study 3356, with support from findings in Study 3358, the Sponsor's proposed labeling claims for opioid withdrawal symptoms would not be acceptable.

From DAAAP's perspective, the wording, “: *Daily opioid use did not change meaningfully from baseline for either RELISTOR-treated patients or placebo-treated patients. ....There were no clinically relevant changes from baseline in pain scores in either the RELISTOR- or placebo-treated patients*, should not be included in the label, since these claims were not based on a statistically appropriate analysis, nor were they replicated.

In addition, since there was evidence of opioid withdrawal in some patients, and the full extent of the risk cannot be determined from the studies submitted, the use of RELISTOR should be limited to patients for whom the need to reduce opioid-associated constipation outweighs the risk for opioid withdrawal. Patients started on RELISTOR should be instructed how to detect symptoms of withdrawal and should be closely monitored for symptoms of opioid withdrawal when therapy with RELISTOR is initiated.

**DAAAP Responses to DGIEP Questions** (the DGIEP question is in regular font and DAAAP response is bolded font)

1. Did the Sponsor use the appropriate instruments to assess withdrawal in studies 3356 and 3358?

**After discussion with, and recommendation by DAAAP, DGIEP obtained a consultation with the Study Endpoints and Labeling Development (SEALD) team to address this question.**

**SEALD declined the consult request with the explanation that these instruments were used as safety assessments and not as primary or secondary study endpoints to support claims. Additionally, SEALD noted that an evidence dossier was not included in the submission that would allow detailed review of the instruments. A meeting was held on 1/12/12 among DGIEP, SEALD and DAAAP representatives to clarify DGIEP's and DAAAP's goals with respect to use of opioid withdrawal scales for use in future studies. The minutes of that meeting are appended in this review.**

**From DAAAP's perspective, historically the most commonly used instruments to assess withdrawal in clinical trials have been the Clinical Opioid Withdrawal Scale (COWS) and the Subjective Opioid Withdrawal Scale (SOWS). Although the OOWS may be acceptable, the granularity of the OOWS is less than the COWS. We**

**do not currently have enough information to determine whether the decreased granularity of the OOWS would affect the assessment of opioid withdrawal in study subjects.**

2. Based on your assessment of the data in studies 3356 and 3358, is there evidence of opioid withdrawal in the patients that were treated with Relistor (methylnaltrexone) for opioid induced constipation?

**Studies 3356 and 3358 were not adequately designed to fully evaluate study subjects for the presence of opioid withdrawal symptoms. The frequency of the opioid withdrawal assessments was not adequate to capture evidence of opioid withdrawal appropriately.**

**Although the use of OOWS and SOWS to assess opioid withdrawal has been determined to be inadequate in terms of frequency of assessments and appropriateness of the instruments, DAAAP analyzed the Sponsor's submitted safety data of adverse events potentially associated with opioid withdrawal to determine if there was evidence of opioid withdrawal in patients treated with methylnaltrexone in Studies 3356 and 3358.**

**In double-blind Study 3356, there was evidence that some patients experienced opioid withdrawal during the double-blind and OL periods of the study based on a review of adverse events, with symptoms severe enough that discontinuation from the study resulted. Further, it is noted that more patients in the QOD dosing arm experienced opioid withdrawal AEs than those in the QD or placebo. The clinical significance of this observation is unclear.**

**In OL Study 3358, although there was no control group, there was evidence of opioid withdrawal-related AEs in some patients severe enough to result in discontinuation from the study.**

3. Based on your evaluation of the data in studies 3356 and 3358, is there evidence of increased analgesic requirements in patients treated with Relistor (methylnaltrexone) for opioid induced constipation?

**There was no definite evidence of increased analgesic requirements in patients treated with methylnaltrexone for opioid induced constipation in Study 3356 or 3358. However, the interpretation of this information is limited by the frequency of assessments of opioid dosage, and the use of concomitant medications that could affect the study subject's pain and need for a change in opioid dosing.**

4. Do you have any other comments regarding the evaluation of pain and/or opioid withdrawal in studies 3356 or 3358?

**Use of an objective opioid withdrawal scale such as the Clinical Opiate Withdrawal Scale (COWS) has been a preferred assessment tool in DAAAP for study designs, in part, because it assigns degree of opioid withdrawal (mild, moderate, severe) which provides more clinically meaningful interpretation of findings, while for the OOWS, the symptom is either present or absent, without assigning a degree of severity.**

**The frequency of the opioid withdrawal assessments must be often enough that if there were to be signs and symptoms of opioid withdrawal, they would be captured by the assessment tools. Specifically, daily assessments should be conducted for the first seven days to two weeks.**

## **Appendix A: SEALD/DGIEP/DAAAP Meeting Minutes**

On 1/12/12, members from the SEALD team, DGIEP and DAAAP met to discuss the implications of the use of OOWS and SOWS in this specific submission as well as future implications of use of these tools in other studies. The summary of the discussion is included below, taken from the meeting minutes summarized by Dr. Elektra Papadopoulos (DARRTS entered 1/13/12)

- DAAAP clarified that a different set of instruments, the COWS and SOWS-H, are widely and routinely used as safety assessments in studies for evaluating risk-to-benefit ratio of the products that they evaluate. Studies are generally not powered on the basis of determining differences in withdrawal symptoms and the data are not described in clinical studies section of labeling.
- DAAAP is providing consultation to DGIEP regarding the Relistor studies and the results of DAAAP's preliminary review is not in agreement with the sponsor's proposed labeling because the study was inadequately designed to support labeling claims of "lack of opioid withdrawal symptoms" and the OOWS may not offer sufficient ability to detect (and discriminate among) patients experiencing varying degrees of opioid withdrawal symptoms. DAAAP has more experience with COWS and SOWS-H, which they consider to be the current standard for opioid withdrawal symptom assessment.
- SEALD stated and it was generally agreed that the sponsor's proposed labeling claim of opioid withdrawal symptoms should be removed from the clinical studies section in Relistor labeling, as it was not supported by substantial evidence. Further, opioid withdrawal symptoms were, in fact, observed in these studies (e.g., hyperhidrosis). Thus, it was determined that a description of these findings may be suitable for the adverse events section of product labeling.
- The meeting also concluded that SEALD study endpoint review was not warranted for the SOWS and OOWS as they are not used as primary or key secondary study endpoints to support claims. Additionally, the review of opioid withdrawal scales would not be an appropriate undertaking under the DDT qualification pathway, because SEALD restricts qualification review to instruments intended for use as either a primary or key secondary endpoint in clinical trials to support labeling claims.
- SEALD advised that when evaluating a safety assessment that is not intended to support claims it is necessary to cast a wide net to evaluate multiple possible adverse events and safety outcomes. In contrast, for the evaluation of efficacy, it is necessary to use well-defined and reliable endpoints assessing a limited set of core concerns in the disease under study.
- The standard of evidence for comparative safety claims is the same as for other types of efficacy claims and both require substantial evidence. If a comparative safety claim is sought in future studies, FDA should review the study endpoint to ascertain whether it meets criteria for a "well-defined and reliable" assessment.

## Appendix B Assessment Tools

**Table 1. Objective Opioid Withdrawal Scale (OOWS)**

Instructions: Read each item below carefully and place an "X" in either the PRESENT or the NOT PRESENT column. Please answer each item.

OBSERVATIONS:	NOT PRESENT (0)	PRESENT (1)	
1. Yawning (One or more = present)	<input type="checkbox"/>	<input type="checkbox"/>	
2. Rhinorrhea (Three or more = present)	<input type="checkbox"/>	<input type="checkbox"/>	
3. Piloerection (Gooseflesh – observe patient's arm)	<input type="checkbox"/>	<input type="checkbox"/>	
4. Perspiration	<input type="checkbox"/>	<input type="checkbox"/>	
5. Lacrimation	<input type="checkbox"/>	<input type="checkbox"/>	
6. Mydriasis (Pupil Dilation)	<input type="checkbox"/>	<input type="checkbox"/>	
7. Tremors (Hands)	<input type="checkbox"/>	<input type="checkbox"/>	
8. Hot & cold flashes (Shivering or huddling for warmth)	<input type="checkbox"/>	<input type="checkbox"/>	
9. Restlessness (Frequent shifts of position)	<input type="checkbox"/>	<input type="checkbox"/>	
10. Vomiting	<input type="checkbox"/>	<input type="checkbox"/>	
11. Muscle twitches	<input type="checkbox"/>	<input type="checkbox"/>	
12. Abdominal cramps (Holding stomach)	<input type="checkbox"/>	<input type="checkbox"/>	
13. Anxiety* (M=mild; MD=moderate; S=severe)	<input type="checkbox"/>	<input type="checkbox"/>	Circle One if present <input type="checkbox"/> M - MD - S
<b>TOTAL</b>	<input type="checkbox"/>		

\*Mild: observable manifestations – foot shaking, fidgeting, finger-tapping

Moderate to severe: agitations, unable to sit, trembling, panicky; complains of difficulty in breathing, choking sensations, palpitation.

(Source: Sponsor's Protocol 3356, Attachment 6, p. 79)

**Table 2. Subjective Opioid Withdrawal Scale (SOWS)**

Instructions: Answer the following statements as accurately as you can. Rate the way you have been feeling the PAST 24 HOURS according to the scale below by placing an "X" in the appropriate box.

<i>Please check the box, which is the most appropriate for how you have been feeling.</i>	Not At All (0)	A Little (1)	Moderately (2)	Quite A Bit (3)	Extremely (4)	
1. I have felt anxious.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2. I have been yawning.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
3. I have been perspiring.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
4. My eyes have been tearing.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
5. My nose has been running.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
6. I have had gooseflesh.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
7. I have been shaking.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
8. I have had hot flashes.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
9. I have had cold flashes.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
10. My bones and muscles have been aching.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
11. I have been feeling restless.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
12. I have been feeling nauseous.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
13. I have felt like vomiting.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
14. My muscles have been twitching.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
15. I have had cramps in my stomach.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
16. I have felt like taking more pain medication.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
17. I have had trouble sleeping.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
18. My appetite has been poor.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
19. I have had diarrhea.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>TOTAL SCORES</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

(Source: Sponsor's Protocol 3356, Attachment 7, p. 80-81)



**Table 3. SOWS (Original Handelsman)**

- 
1. I feel anxious
  2. I feel like yawning
  3. I'm perspiring
  4. My eyes are tearing
  5. My nose is running
  6. I have goose flesh
  7. I am shaking
  8. I have hot flashes
  9. I have cold flashes
  10. My bones and muscles ache
  11. I feel restless
  12. I feel nauseous
  13. I feel like vomiting
  14. My muscles twitch
  15. I have cramps in my stomach
  16. I feel like shooting up now
- 

(Source: Handelsman<sup>1</sup>, L.,1987, p. 296)

**Table 4. Pain Intensity Scale**

Average Pain over 24 Hours

Select the number that best describes your average pain during the past 24 hours.

*(circle one number only)*

0	1	2	3	4	5	6	7	8	9	10
No										Worst
Pain										possible pain

(Source: Applicant's Protocol 3356, Attachment 5)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ELIZABETH M KILGORE  
02/24/2012

ELLEN W FIELDS  
02/25/2012

SHARON H HERTZ  
02/27/2012  
Signing for Bob Rappaport, M.D.

**4.4    *Movantik NDA: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)  
Consult Review***



**Food and Drug Administration**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**  
**Division of Anesthesia, Analgesia, and Addiction Products**  
10903 New Hampshire Ave.  
Silver Spring, MD 20993-0002

### **Response to Consultation Request**

**To:** Anil Rajpal, MD, Medical Team Leader  
Aisha Peterson, MD, Medical Officer  
Division of Gastroenterology and Inborn Errors Products (DGIEP)

**From:** Elizabeth Kilgore, MD, Medical Officer  
Division of Anesthesia, Analgesia and Addiction Products  
(DAAAP)

**Through:** Ellen Fields, MD, MPH, Medical Team Leader, DAAAP  
**Through:** Sharon Hertz, MD, Deputy Director, DAAAP  
**Through:** Bob Rappaport, MD, Director, DAAAP

**Subject:** NDA 204-760 (Naloxegol)

**Consultation Date:** November 26, 2013

**Review Date:** January 29, 2014

### **Executive Summary**

The Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that DAAAP review the key Phase 3 studies in NDA 204-760 to determine whether there is evidence of opioid withdrawal in study subjects receiving naloxegol compared to placebo, and whether naloxegol appears to have an effect on analgesia. The proposed indication for naloxegol is the treatment of opioid induced constipation in adult patients with chronic non-cancer pain.

This review discusses the Applicant's analyses of opioid withdrawal risk conducted prior to receiving Agency advice and post-hoc analyses based upon Agency advice.

In all analyses, there is an imbalance between study drug and placebo in the 12-week placebo controlled studies with more patients in the naloxegol-treated arm identified as

having possible drug withdrawal syndrome (DWS) or at least three preferred terms (PTs) potentially related to DWS compared to placebo.

1. In the clinical trials, there is evidence that symptoms of possible opioid withdrawal may be associated with the use of naloxegol in a small number of patients receiving chronic opioid treatment, with an incidence in study drug greater than that in placebo using the following criteria and analyses:
  - a. Using the Applicant's analysis of patients identified with the Standardized MedDRA Query (SMQ) term of possible DWS, in the 12-week, placebo-controlled studies (04 and 05) there was one patient in the placebo group (0.2%) compared to 2 (0.5%) in the NG 12.5mg group and 5 (1.1%) in the NG 25mg group identified by the investigator as experiencing possible DWS.
  - b. Using broader criteria (based upon Agency advice) for determining potential opioid withdrawal syndrome, defined by the presence of  $\geq 3$  preferred terms (PTs) potentially related to opioid withdrawal, the following incidence of potential opioid withdrawal was reported:
    - i. In Study 04 the occurrence of  $\geq 3$  PTs potentially related to DWS in placebo, NG12.5 mg, and NG 25 mg groups was 5 (2%), 4 (2%), and 10 (5%), respectively.
    - ii. In Study 05 the occurrence of  $\geq 3$  PTs potentially related to DWS in placebo, NG 12.5 mg and NG 25mg was 3 (1%), 7 (3%) and 20(9%).The above criterion is sensitive but not specific for identifying possible clinical DWS in that many patients experienced  $\geq 3$  PTs potentially related to DWS but all of the terms did not occur on the same day or they were GI terms only.
  - c. Using more narrow criteria that may be more clinically relevant (as determined by this reviewer) of patients who experienced  $\geq 3$  PTs potentially related to opioid withdrawal which occurred on the same day and were not all GI PTs (i.e., GI+ non-GI or all non-GI terms), the total cases identified in the pooled 12-week, controlled studies were 1 (<1%), 5 (1%) and 14 (3%) for the placebo, NG 12.5mg, and NG 25mg groups, respectively.
2. In Study 07, the incidence of  $\geq 3$  PTs potentially related to opioid withdrawal using this clinically relevant criteria was 0, 1 (1%), and 1 (1%) in placebo, NG 12.5mg, and NG 25mg groups, respectively.
3. In the open label study (08) the incidence of possible opioid withdrawal syndrome was also higher in naloxegol-treated patients compared to Usual Care.
4. Naloxegol does not appear to have an effect on analgesia, based on analyses of opioid dose and pain scores during the trials. However, these analyses were descriptive in nature as the studies were not designed to assess these endpoints in a statistical manner.
5. The Applicant's proposed labeling claims related to Section 5.3 (Concurrent Methadone Use), Section 10 (Overdosage) and Section 14 (Clinical Studies) are

not acceptable as they are not supported by the data included in the NDA submission. The labeling claims are discussed in detail in Section IV of this review.

**Background:** According to the Applicant, naloxegol oxalate (study drug NKTR-118), proposed tradename MOVANTIG, is a peripherally-acting mu-opioid receptor antagonist (PAMORA) with the proposed indication for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain. Concerns have arisen regarding the possible association of mu opioid antagonists administered chronically with opioids and the occurrence of cardiac events, based on findings for other similar products. The Applicant has stated that, “Naloxegol has limited capacity to pass through the BBB [blood brain barrier] and thus central opioid antagonism is unlikely.” They concluded that, overall, “there was no evidence of a CNS effect associated with naloxegol.” However, there are mu opioid receptors located in the periphery, and not just the GI tract. The intended mechanism of action of naloxegol is local opioid reversal in the GI, and based on the GI symptoms, this is consistent with the GI symptoms experienced with centrally-mediated opioid reversal. It is unclear whether possible opioid withdrawal symptoms such as diaphoresis, chills, rhinorrhea, and yawning are secondary to the local effects from the GI pain, reflect activity at other peripheral mu receptors, or possibly some central effects.

There were numerous communications between the Sponsor and the Agency during the drug’s development under IND 78,781 and DAAAP provided previous consults to DGIEP for this product. In addition, we have been in ongoing communication with DGIEP in preparation for an Advisory Committee scheduled for March 10-11, 2014, at which time this product will be discussed as part of a class-wide effect of PAMORAs on MACE (Major Adverse Cardiovascular Events).

#### **Pertinent Regulatory History/ Prior Agency Advice:**

- 4/17/13 – DAAAP Consult Response (Under IND 78, 781)  
  
After review of the Sponsor’s submitted materials (preNDA briefing Document: *CV Risk Assessment* dated 3/13/13), DAAAP concluded that, due to flaws in the protocols for the two key Phase 3 Studies 04 and 05, there was limited ability to interpret the Sponsor’s findings. Post-hoc analyses of the data were advised.
- 4/23/13 – At the Type C Meeting to discuss CV and opioid withdrawal symptoms, the Sponsor was informed that additional opioid withdrawal analyses would be required. The specific Agency advice is discussed in Section III of this review.
- 5/7/13 – The Applicant submitted their responses to the Agency request for additional opioid withdrawal analyses with their proposed analysis plan. (See Section III of this review).

- 8/9/13 – The Agency provided clarification comments to the Applicant regarding their planned post-hoc analyses as they requested. (Specific clarifications are discussed in Section III of this review).
- 9/16/13 – NDA 204-760 was submitted which included a section titled, “*Additional Opioid Withdrawal and CV Risk Assessments*” incorporating some Agency advice regarding post-hoc opioid withdrawal analyses (referred to as Analysis 3).
- 10/15/13 – The Sponsor submitted a document to the NDA titled, “*Opioid Withdrawal-CV Risk Assessments*” which was a revised analysis incorporating the Agency’s clarification advice (referred to as Analysis 4).

**Materials Reviewed:** Prior DAAAP consults to DGIEP for this drug under IND 78,781; relevant meeting minutes under IND 78,781 and pertinent sections of the NDA. Throughout this review, study drug may be referred to as naloxegol (NG or NGL) or NKTR-118. Opioid withdrawal syndrome is abbreviated as OWS and may be used interchangeably with drug withdrawal syndrome (DWS).

#### **Review Organization:**

- I) Overview of Applicant’s Phase 3 Protocols
- II) Table of Opioid Withdrawal Safety Assessments Conducted in Phase 3 Trials
- III) Applicant’s Analyses (Section I and Section II)
- IV) Applicant’s Proposed Labeling Claims
- V) DAAAP Conclusions (Responses to DGIEP Questions)
- VI) Appendices

#### **I) Overview of Applicant’s Phase 3 Protocols**

The relevant Phase 3 studies are listed in Table 1 below, with a narrative summary of the key features of the studies following the table.



**Table 1. Applicant's Phase 3 Studies Conducted during Drug Development**

Phase III studies	
D3820C0004	
No. and type of randomized patients:	652 patients were randomized with confirmed OIC and on stable opioid regimen, and received the following treatment: naloxegol 12.5 mg n=217, 25 mg n=218 and placebo n= 217.
Doses and duration of treatment:	Naloxegol tablet 12.5 mg or 25 mg once daily, 12 weeks
Primary objective:	Compare the efficacy of naloxegol 12.5 and 25 mg with placebo in the treatment of patients with OIC
D3820C0005	
No. and type of randomized patients:	700 patients were randomized with confirmed OIC and on stable opioid regimen, and received the following treatment: naloxegol 12.5 mg n=233, 25 mg n=234 and placebo n= 233
Doses and duration of treatment:	Naloxegol tablet 12.5 mg or 25 mg once daily, 12 weeks
Primary objective:	Compare the efficacy of naloxegol 12.5 and 25 mg with placebo in the treatment of patients with OIC
D3820C0007	
No and type of randomized patients:	302 patients rolled over from Study 04 and continued to receive the following treatments as originally assigned in Study 04: naloxegol 12.5 mg n=97, 25 mg n=99 and placebo n= 106
Doses and duration of treatment:	Naloxegol tablet 12.5 mg or 25 mg once daily, 12 weeks
Primary objective:	Compare naloxegol 12.5 and 25 mg with placebo regarding long-term (ie, additional 12 weeks) safety and tolerability in the treatment of opioid OIC using descriptive statistics
D3820C0008	
No and type of randomized patients:	844 randomized patients. 84 patients rolled over from Study 05 or Study 07, 760 newly randomized patients.
Doses and duration of treatment:	Randomly-assigned open-label naloxegol tablet 25 mg once daily or Usual Care treatment, 52 weeks
Primary objective:	Assess the long-term (ie, 52-week) safety and tolerability of naloxegol 25 mg.

(Applicant's table, Clinical Overview, pages 11-12)

Studies D3820C00004 (04) and D3820C00005 (05) (identical)

**Title:** Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of NKTR-118 in Patients with Non-Cancer Related Pain and Opioid- Induced Constipation (OIC).

**Population:** The studies were conducted in patients who were to have been receiving a stable maintenance opioid regimen consisting of a total daily dose of 30 mg to 1000 mg of oral morphine or morphine-equivalent amounts of one or more opioid product for noncancer- related pain and who reported a history of fewer than three spontaneous bowel movements (SBMs) per week and at least one OIC-associated symptom at screening.

*Study Overview:* Patients were to have been randomized to one of three treatment arms: Study drug NKTR-118 (naloxegol) 12.5mg, naloxegol 25 mg, or placebo for a treatment period of 12 weeks. The primary efficacy variable was response (responder/nonresponder) to study drug during Weeks 1-12, where a responder was defined as patients having at least 3 spontaneous bowel movements (SBMs/week) with at least 1 SBM/week increase over baseline, for at least 9 of the 12 weeks, and at least 3 of the last 4 weeks.

*Safety Outcomes (Opioid Withdrawal Related):* Pain (NRS), mean daily opioid dose and opioid withdrawal scores using the modified Himmelsbach Opioid Withdrawal Scale (mHS) were considered safety variables. The pain scores were to have been obtained daily with a safety analysis performed on change from baseline in the mean NRS pain score for Weeks 1 to 4 and 1 to 12. The opioid doses and use of rescue medication were to have been recorded daily. Patients were disqualified from randomization if they consumed >4 opioid doses for breakthrough pain per day for more than 3 days during the 2-week OIC confirmation period or if their maintenance opioid dosing regimen was modified during that time. The mHS was to have been analyzed for observed values and change from baseline in composite score two hours after first dose and at Weeks 1, 4 and 12. The studies were not designed to control for multiplicity. Treatment-emergent AEs that could potentially be indicative of centrally mediated opioid withdrawal were to have been identified prior to unblinding and summarized by treatment group.

#### Study D3820C00007 (07)

*Title:* A Randomized, Double-Blind, Placebo-Controlled 12-Week Extension Study to Assess the Safety and Tolerability of NKTR-118 in Patients with Non-Cancer-Related Pain and Opioid-Induced Constipation.

*Study Overview:* This was a 12-week extension of Study 04. Patients were to continue on their randomized dose of NKTR-118 from Study 04. Patients who successfully completed the 12-week extension study were eligible to participate in a 52-week long term safety extension study (Study 08). Opioid withdrawal-related safety outcome variables included change from baseline in NRS pain score and change from baseline in mean daily prescribed opioid dose. The mHS was to have been administered at Visit 1 (which would have been enrollment data obtained at the Visit 8 of previous roll-over Study 04) and Visit 4 (Week 12). The Applicant considered this study to be suitable for supportive data and was not pooled with the 12-week studies (04 and 05) and the 52-week Study 08, which they considered primary data for the analysis of clinical safety.

#### Study D3820C00008 (08)

*Title:* An Open-Label 52-week Study to Assess the Long-Term Safety of NKTR-118 in Opioid-Induced Constipation (OIC) in Patients with Non-Cancer- Related Pain.

*Study overview:* This was a Phase 3, open-label, randomized, parallel group safety and tolerability study. Eligible patients were to have been randomized in a 2:1 ratio to receive either NKTR-118 25mg daily (QD) or Usual Care treatment for OIC. Participants

may have included patients who completed 12 weeks of treatment in Study 05, the 3-month safety extension (Study 07), or patients not previously treated with NKTR-118 (“new” patients). Safety outcome variables were change from baseline in NRS pain score, mean daily prescribed opioid dose and observed values and change from baseline in composite score of the mHS.

## II) Opioid Withdrawal-Related Safety Assessments in Phase 3 Naloxegol Studies

Table 2 below shows the opioid-withdrawal related safety assessments conducted in the Phase 3 trials.

**Table 2. Opioid Withdrawal Related Safety Assessments**

Safety Parameter	Frequency of Assessment
Studies 04/05	
NRS	Ongoing via eDiary
Δ Mean Daily Opioid Dose	All visits (Weeks 0, 1, 2, 4, 8, 12 and Follow-up)
Opioid Withdrawal Symptoms (mHS)	W0 (baseline and 2 hours post 1 <sup>st</sup> dose), W1, 4, 12
Study 07	
NRS	W4, 8, 12
Δ Mean Daily Opioid Dose	All visits (W4, 8, 12 and follow-up)
Opioid Withdrawal Symptoms (mHS)	W12
Study 08	
NRS	W0, 1,2; M1, 3, 6, 9; Follow-up
Δ Mean Daily Opioid Dose	All visits (W0, 1, 2, M1-12; Follow up)
Opioid Withdrawal Symptoms (mHS)	W0, 1; M1, 3, 6, 9, 12

(Table, reviewer) mHS=modified Himmelsbach; W=week; M=month

Limitations of the studies with regard to determining opioid withdrawal include the following: 1) the studies did not include a subjective measure of opioid withdrawal (such as the subjective Opioid Withdrawal Scale [SOWS]) 2) the mHS was not conducted frequently enough to adequately capture potential opioid withdrawal cases (i.e., in Studies 04 and 05 assessments were obtained at baseline, two hours post 1<sup>st</sup> dose, week 1 and not again until week 4 and 3) the mHS opioid withdrawal scale does not include opioid withdrawal GI-related preferred terms nor does it provide a total composite score which assigns a degree of severity. In contrast, the Clinical Opioid Withdrawal Scale (COWS) provides a total composite score for assigning withdrawal severity (i.e., 5-12=mild; 13-24=moderate; 25-36=moderately severe; >36=severe). The Applicant reported that, “based upon consultation with external subject matter experts, in the absence of published or established thresholds for a clinically important change in the composite mHS score, a change in total score of ≥3 from baseline was a conservative and appropriate cutoff for identifying patients with potential withdrawal symptoms.” While this rationale may be reasonable in some clinical settings, there is no scientific evidence supporting this approach for use in a clinical trial.

**III) Applicant's Analyses:** Data regarding opioid withdrawal were analyzed by the Applicant in five different ways in the NDA, three of which were in response to Agency requests (see Regulatory History).

**A) Review Section I: Analyses Conducted by Applicant Prior to Agency Advice**

**Analysis 1:** The reference document is found in *Module 5.3.5 Individual CSR Studies 04, 05, 07, and 08*. Data from the Individual Clinical Study reports were analyzed by the Applicant for key opioid withdrawal (OW) parameters of prespecified AEs of interest, NRS (numeric rating scale) scores, mean daily opioid use and mHS. Other opioid-related outcome parameters analyzed by the Applicant were pain-related AEs, suspected abuse liability events, and PK (exposure). For this review, the key OW parameters are opioid withdrawal-related AEs, NRS scores, mean maintenance and breakthrough opioid use and mHS (modified Himmelsbach Scale) scores, as these are most informative regarding withdrawal and the effect of naloxegol on analgesia.

**a) Prespecified AEs of Interest**

**Applicant's Methods:** In the individual Clinical Study Reports for Studies 04, 05, 07, and 08, AEs potentially related to opioid withdrawal were identified as a special interest AE. As predefined in the SAP, the AE preferred terms included the following: Drug withdrawal convulsions, Drug withdrawal headache, DWS, DWS neonatal, Rebound effect, Steroid withdrawal syndrome, Withdrawal arrhythmia, Withdrawal syndrome, Drug withdrawal maintenance therapy, Drug rehabilitation).

**Applicant's Results:** In Analysis 1, the Applicant found that across all studies, one placebo and 12 naloxegol-treated patients were coded by the investigator with the MedDRA term of DWS. Table 3 below shows the number (%) of patients with opioid withdrawal related AEs coded as DWS, treatment period only or post-treatment follow up, in the safety analysis set.

**Table 3. Number (%) Of Patients with AEs of Opioid Withdrawal, Treatment Period Only or Post-treatment Follow-up (Safety Analysis Set)**

<b>N Identified by Investigator as MedDRA DWS /total number (%)</b>			
	Placebo	NG 12.5mg	NG 25mg
Study 04	1/213 (0.5)	1/211 (0.5)	1/214 (0.5)
Study 05	0/231	1/230 (0.4)	4/231 (1.7)
Study 07	0/100	1/94 (1.1)	1/97 (1.0)
Study 08	N/A	N/A	3/534 (0.6)

(Table, reviewer)

Based upon review of the narratives for the 12 NG cases, six cases did not appear to have any confounding factors that would explain the withdrawal adverse events, five were confounded and one had insufficient information. However, all cases are considered by this reviewer to be possible OWS cases regardless of confounders.

There were no consistent patterns seen in mHS scores or NRS associated with the events. Major findings from the narratives are presented below in Table 4.

**Table 4. Narratives for Patients Identified by Investigator as DWS**

Patient ID	AE Terms	Onset <sup>1</sup>	Opioid	Comments
<b>Study 04</b>				
E4066015 25mg	DWS (Diarrhea, piloerection, sweating, shakiness, anxiety, increased pain, nasal congestion, dilated pupils)	Day 1	Methadone	Possible DWS with possible causality; discontinued. mHS scores were 0 at all assessments.
E4074023 12.5mg	DWS (Yawning, teariness, runny nose, and flushing ["feeling hot"])	Day 3	Oxycodone	Possible DWS with possible causality. mHS scores were 0 at all assessments.
<b>Study 05</b>				
E5239005 25mg	DWS (Diarrhea, watery eyes, cold sweats; lacrimation, tremor, restlessness)	Day 2	Morphine sulfate ER	Possible DWS with possible causality; discontinued; mHS scores 2, 1 and 3 at assessment periods.
E5267036 25mg	DWS (Vomiting, abdominal pain; tremors, chills, yawning, piloerection, rhinorrhea)	Day 1	Methadone; Tramadol HCL	Possible DWS with possible causality; discontinued; mHS scores were 0 all assessments.
E5267044 25 mg	DWS (Lacrimation, yawning, piloerection, sweating, chills)	Day 1	Methadone	Possible DWS with possible causality; mHS scores 0 at all assessments except post 1 <sup>st</sup> dose (5.0)
E5267047 25mg	DWS (Yawning, tremors, piloerection, lacrimation)	Day 1	Methadone	Possible DWS with possible causality; DAE and SAE; mHS scores 0 at all assessments except post 1 <sup>st</sup> dose (8.0) and Study Day 8 (1.0)
E5220021	DWS (Diarrhea, restless/nervous, nasal	Day 83	Oxycodone	Confounded: The patient ran out of oxycodone 2 days

12.5mg	stiffness, piloerection)			before the 85 day study visit. mHS 0 at all assessments except Day 85 (3.0)
<b>Study 07</b>				
E4053048 12.5mg	DWS (Shakiness, anxious, breathing hard, fast heart rate, jitters, hot and cold flashes, sweatiness)	Day 101	Hydrocodone	Confounded: The patient stopped taking maintenance opioid three days before DWS. SAEs of diarrhea and DWS. Discontinued. mHS scores 1.0, 0.0, 4.0 (day 112)
E4078015 25mg	DWS (Mental status change, pyrexia)	Day 153	Morphine sulfate	Confounded: The patient was hospitalized for altered mental status thought due to opiates and was given naloxone while in the hospital. SAE of mental status change which led to discontinuation. mHS scores 0; max score 1.0 (Day 175)
<b>Study 08</b>				
E8877007	DWS (specific AE terms not provided)	Day 365	Morphine sulfate	Insufficient information. Maximum mHS score was 2.0 (predose)
E8904001	DWS; abdominal pain upper, diarrhea	Day 11	Morphine sulfate	Confounded. The patient tapered her maintenance opioid. Maximum mHS scores was 3.0 (predose)
E8922022	DWS (other specific AE terms not provided)	Day 34	Percocet	Confounded. The patient ran out of his maintenance opioid medication. Discontinued. Maximum mHS score 1.0 (post 1 <sup>st</sup> dose)

(Table, reviewer) <sup>1</sup> Day of onset of opioid withdrawal related AEs in relation to study drug use. mHS=modified Himmelsbach Scale

### ***b) Numeric Rating Scale (NRS) Scores***

Applicant's Methods: Mean daily average pain scores and mean worst pain scores were summarized in the individual CSRs. Daily pain was rated by patients based on the 11-point NRS for pain ranging from 0 (no pain) to 10 (worst imaginable pain). In Studies 04 and 05, both average (over previous 24 hours) and worst (over previous 24 hours) NRS scores were recorded daily (eDiary). The mean daily NRS for an interval was calculated as the sum of daily values for the interval divided by the number of days

within the interval. Change from baseline in mean daily NRS values was calculated for Weeks 1 to 4 and 1 to 12 as the post-baseline value minus the baseline value, where baseline is the mean daily NRS values recorded during the OIC confirmation period. Negative changes from baseline indicate improvement (i.e., less pain). In Studies 07 and 08, patients reported only their average pain during the seven days prior to study visits.

Applicant's Results: In all studies, the scores (average and worst pain) were similar between treatment groups with little variability (an approximately 0.1 difference between groups for change from baseline on average) in Weeks 1 to 4 and Weeks 1 to 12. Tables 5 below shows the summary of change from baseline in NRS Pain Score average for Study 04.

**Table 5. Summary of Change from Baseline in NRS Pain Score (Average), Study 04, Safety Analysis Set**

Week	Statistics	Placebo (N = 213)		NKTR-118 12.5 mg (N = 211)		NKTR-118 25 mg (N = 214)	
		Observed	Change from baseline	Observed	Change from baseline	Observed	Change from baseline
Baseline	n	212		211		214	
	Mean	4.5		4.8		4.7	
	SD	1.85		1.67		1.59	
	Q1	3		4		4	
	Median	4.7		5.0		4.6	
	Q3	6		6		6	
	Min	0		0		0	
	Max	8		9		10	
Week 1 to 4	n	212	212	211	211	212	212
	Mean	4.4	-0.1	4.6	-0.2	4.6	-0.1
	SD	1.97	0.95	1.86	0.84	1.74	0.73
	Q1	3	-1	3	-1	3	0
	Median	4.5	-0.1	4.8	-0.1	4.5	0.0
	Q3	6	0	6	0	6	0
	Min	0	-6	0	-4	0	-4
	Max	8	6	10	4	10	2
Week 1 to 12	n	212	212	211	211	213	213
	Mean	4.3	-0.2	4.6	-0.3	4.5	-0.2
	SD	1.99	1.07	1.93	1.05	1.76	0.95
	Q1	3	-1	3	-1	3	0
	Median	4.4	-0.1	4.6	-0.1	4.5	0.0
	Q3	6	0	6	0	6	0
	Min	0	-6	0	-5	0	-5
	Max	8	6	10	4	10	2

Note: NRS pain score consists of an integer scale from 0 (no pain) to 10 (worst imaginable pain)

Note: The negative changes indicate improvement (ie, less pain).

NRS Numeric Rating Scale; Q1 25<sup>th</sup> percentile; Q3 75<sup>th</sup> percentile; SD standard deviation.

(CSR 04, pages 145-146)

### c) Mean Daily Opioid Dose

Applicant's Methods: Daily opioid dose in morphine equivalent units (MEU) /day was calculated using the equivalence as per the SAP (Statistical Analysis Plan). The total



opioid dose was calculated as the sum of the maintenance and breakthrough opioid use. In addition, mean daily opioid dose was calculated using repeated measures analysis of change from baseline.

Applicant's Results: Mean daily opioid dose was generally stable during the study. Over both Weeks 1 to 4 and Weeks 1 to 12, the mean, upper and lower quartiles for the mean daily opioid dose were similar with no statistically significant differences between the groups.

Results for Study 04 are shown in Tables 6 and 7 below. Findings were similar across all controlled studies and Study 08.

**Table 6. Summary of Change from Baseline in Daily Opioid Use (Study 04)**

Week	Statistics	Placebo (N = 213)		NKTR-118 12.5 mg (N = 211)		NKTR-118 25 mg (N = 214)	
		Observed	Change from baseline	Observed	Change from baseline	Observed	Change from baseline
Week 1 to 12	n	213	213	211	211	214	214
	Mean	133.8	-1.8	137.4	-2.3	143.6	0.4
	SD	140.94	30.19	166.72	20.52	150.47	13.01
	Q1	45.0	0.0	45.0	0.0	45.0	0.0
	Median	75.0	0.0	79.8	0.0	90.0	0.0
	Q3	173.4	0.0	165.0	0.0	184.2	0.0
	Min	15	-426	2	-227	18	-93
	Max	955	62	1280	43	1080	66

Note: Daily opioid use is the sum of the maintenance and break-through opioid medication. The mean daily opioid dose (mg/day) is the sum of daily opioid doses (mg/day) divided by the number of days in the interval while patient remains on treatment.

Q1 25<sup>th</sup> percentile; Q3 75<sup>th</sup> percentile; SD standard deviation.

(CSR 04, p. 150)

Although the Applicant states that there were no statistically significant differences in change from baseline in mean daily opioid dose between either of the NG groups and placebo over Weeks 1 to 4 and Weeks 1 to 12, the study was designed to analyze change from baseline in daily opioid use as a safety variable, as descriptive statistics were used to summarize safety outcomes.

**Table 7. Repeated Measures Analysis of Change from Baseline in Daily Opioid Use (Study 04)**

Time point	Treatment Group	n	LS Means (SEM)	Difference versus Placebo <sup>a</sup>		
				LS Mean	95% CI	p-value
Weeks 1 to 4	Placebo	213	-2.25 (1.91)	NA	NA	NA
	NKTR-118 12.5 mg	211	-2.17 (1.93)	0.08	(-4.25, 4.41)	0.972
	NKTR-118 25 mg	214	0.27 (1.93)	2.51	(-1.82, 6.85)	0.256
Weeks 1 to 12	Placebo	213	-2.75 (1.88)	NA	NA	NA
	NKTR-118 12.5 mg	211	-3.51 (1.90)	-0.76	(-4.98, 3.46)	0.724
	NKTR-118 25 mg	214	0.09 (1.90)	2.84	(-1.39, 7.07)	0.188

<sup>a</sup> Analysis via MMRM with fixed effects for baseline, baseline laxative response, treatment and treatment time interaction. Study pooled center is included as a random effect.

Note: Patient is included in the repeat statement, and a compound symmetry covariance matrix has been assumed.

Note: Baseline value assumed in calculating LS Means: 139.51.

Note: All patients with evaluable data at both baseline and at least 1 post-baseline week are included in the analysis.

CI confidence interval; LS Mean Least-Squares Mean, estimated via the contrast statement in PROC MIXED; MMRM mixed model for repeated measures; NA not applicable; SEM standard error of the mean.

(CSR 04, p. 150-151).

#### **d) Opioid Withdrawal Scale Assessment (Modified Himmelsbach scale) [mHS]**

**Applicant's Methods:** Patients were rated upon examination by a clinician for signs of opioid withdrawal using the mHS with respect to the following eight signs as observed at the time of the assessment: yawning, lacrimation, rhinorrhea, perspiration, tremor, mydriasis, piloerection, and restlessness. These signs were quantified on a scale of 0 to 3, with 0=none, 1=mild, 2=moderate, 3=severe. The limitations of the mHS have been discussed earlier.

**Applicant's Results:** The number of patients with mHS scores  $\geq 3$  (severe) was small and nearly equal in the NG 25mg and placebo for maximum on treatment scores.

Table 8 displays the categories of changes from baseline in mHS. Findings were generally similar across all studies.

**Table 8. Categories of Changes from Baseline in mHS scores (Study 04)**

Assessment	Category	Placebo (N = 213)	NKTR-118 12.5 mg (N = 211)	NKTR-118 25 mg (N = 214)
2 hours post-dose	n	212	210	213
	≤0	200 (94.3)	201 (95.7)	196 (92.0)
	≥1	12 (5.7)	9 (4.3)	17 (8.0)
	≥2	5 (2.4)	3 (1.4)	5 (2.3)
	≥3	3 (1.4)	1 (0.5)	0
Maximum on treatment	n	213	211	213
	≤0	166 (77.9)	179 (84.8)	169 (79.3)
	≥1	47 (22.1)	32 (15.2)	44 (20.7)
	≥2	22 (10.3)	14 (6.6)	19 (8.9)
	≥3	8 (3.8)	3 (1.4)	7 (3.3)

Note: Percentages are based on the number of patients with non-missing baseline and post-baseline modified Himmelsbach Scale score in each treatment group at each assessment.

Note: Last on treatment visit is the latest assessment on or before the last day IP was taken.  
IP investigational product.

(CSR 04, p. 153)

### Applicant's Conclusions (Analysis 1)

1. Predefined AEs of interest: These results are consistent with historical data suggesting that the incidence rate of opioid withdrawal symptoms in patients maintained on a stable opioid regimen for chronic pain in clinical trials of oral opioid analgesics, in the absence of opioid antagonists, ranges from 0% to 4%. In a review article of 11 controlled studies of oral opioid treatment for chronic noncancer pain<sup>1</sup>, nine studies either did not mention withdrawal symptoms or reported that no signs of withdrawal were seen. The highest rate (4% [2 patients]) was reported for patients taking morphine<sup>2</sup>.
2. NRS: In the controlled studies, over both intervals (Weeks 1 to 4 and Weeks 1 to 12) the mean and upper and lower quartiles for the average NRS pain score were generally similar between treatment groups and results for worst pain score were also consistent with these findings.

<sup>1</sup> Kalso E, Edwards JE, Moore RA and McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. Pain 2004;112:372-80.

<sup>2</sup> Maier C, Hildebrandt J, Klingerc R, Henrich-Eberld C. Lindenad G. Morphine responsiveness, efficacy and tolerability in patients with chronic non-tumor associated pain – results of a double-blind placebo-controlled trial (MONTAS). Pain 2002;97:223-33.

3. Mean Daily Opioid Dose: No clinically meaningful trends were identified. Mean daily opioid dose was generally stable during the study. Over both Weeks 1 to 4 and Weeks 1 to 12, the mean, upper and lower quartiles for the mean daily opioid dose were similar with no statistically significant differences between the groups.
4. mHS: No clinically meaningful trends were identified. Few patients had scores  $\geq 3$  on maximum treatment.

**Reviewer's comments:** Overall, I agree with the Applicant's interpretation of the NRS, mean daily opioid dose, and mHS findings, within the limitations discussed earlier. With regard to the cases of opioid withdrawal in the Applicant's cited literature, the referenced articles were limited as follows: 1) the two cases of withdrawal cited in the Mair review<sup>3</sup> occurred in the placebo group described as follows: "The two cases of diarrhea under placebo in the second week were possibly attributable to morphine withdrawal", as the study (conducted in Germany) was designed for patients to receive morphine the first week and placebo in the second week and 2) the articles do not describe whether there is an imbalance in withdrawal AEs between subjects receiving treatment and placebo.

**Analysis 2:** The reference document is found In *Module 2.7.4 Clinical Summary and Module 5 Integrated Summary of Safety (ISS)*. This analysis is essentially the Applicant's Integrated Summary of Safety analysis of the key opioid withdrawal outcomes. In addition, a post-hoc assessment of preferred terms (PTs) related to the modified Himmelsbach (mHS) was conducted.

#### **a) Prespecified AEs of Interest (SMQ):**

**Methods:** Drug Withdrawal analyses were conducted by the Applicant for pre-specified AEs of opioid withdrawal by analyzing the incidence of AEs of opioid withdrawal in the controlled and uncontrolled studies based on the drug withdrawal SMQ PTs (MedDRA version 15.1) terms: drug withdrawal convulsions, drug withdrawal headache, DWS, DWS neonatal, rebound effect, steroid withdrawal syndrome, withdrawal arrhythmia, withdrawal syndrome, drug withdrawal maintenance therapy and drug rehabilitation.

**Results:** Ten patients were identified with DWS across all studies during treatment. Table 9 below represents those patients coded with the PT DWS during treatment only. Although the numbers and percentages are small, a larger proportion of patients receiving naloxegol were identified with DWS. These patients are the same cases as those identified in Analysis 1. No new cases were reported in this analysis.

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<sup>3</sup> Ibid.

**Table 9. Number (%) of Patients with Pre-Specified AEs of OW During Treatment Period (Placebo-controlled pool and Study 08)**

	Placebo-controlled pool (Studies 04/07 and 05)			52-week safety study (Study 08)	
	Placebo (N=444)	NGL 12.5 mg (N=441)	NGL 25 mg (N=446)	Usual care (N=270)	NGL 25 mg (N=534)
Any PT	1 (0.2)	2 (0.5)	6 (1.3)	0	2 (0.4)
Drug withdrawal syndrome	1 (0.2)	2 (0.5)	6 (1.3)	0	2 (0.4)
Any PT and no concurrent interruption of opioid treatment or treatment with a central opioid antagonist	1 (0.2)	1 (0.2)	5 (1.1) <sup>a</sup>	0	0

Note: PTs prospectively identified as AEs of opioid withdrawal were: Drug withdrawal convulsions, Drug withdrawal headache, Drug withdrawal syndrome, Drug withdrawal syndrome neonatal, Rebound effect, Steroid withdrawal syndrome, Withdrawal arrhythmia, Withdrawal syndrome, Drug withdrawal maintenance therapy, Drug rehabilitation.

<sup>a</sup> All 5 of these patients had concurrent gastrointestinal AEs. Four were on methadone.

(SCS, p. 83)

**b) Pain Assessment (Numeric Rating Scale) [NRS]:**

Methods: In Analysis 2, the Applicant used a cut off of  $\geq 2$  point change increase as clinically notable. (See Applicant's rationale Appendix C of review) as compared to a cut off of change in one point in Analysis 1.

Results: The proportion of patients with increases of  $\geq 2$  points in 1) average score and 2) worst score was similar across treatment groups in the 12-week pool. Pooled results from Studies 04 and 05 are shown below in Table 10. In general, the results are similar between the NG 25 mg and placebo treatment arms for worst pain. NG 12.5 mg had fewer subjects who experienced  $\geq 2$  point increase in average or worst NRS scores. The clinical significance of that is not clear.

**Table 10. Summary of Patients with Increases of  $\geq 2$  Points in NRS Pain Scores (12-week pool) Studies 04 and 05**

	Placebo n/N (%)	NGL 12.5 mg n/N (%)	NGL 25 mg n/N (%)
<b>Average daily pain</b>			
Week 1	8/443 (1.8)	3/437 (0.7)	7/439 (1.6)
Maximum on treatment	37/443 (8.4)	35/438 (8.0)	43/442 (9.7)
<b>Worst pain</b>			
Week 1	9/443 (2.0)	2/437 (0.5)	6/439 (1.4)
Maximum on treatment	38/443 (8.6)	29/438 (6.6)	36/442 (8.1)

n Number of patients meeting criterion; N Total number of patients with non-missing baseline and post-baseline NRS scores; NGL Naloxegol; NRS Numeric rating scale.

(SCS, p. 79)

### c) Opioid Withdrawal Scale Assessment (modified Himmelsbach) [mHS]

Methods: Pooled data for the 12-week controlled studies and Study 08 were analyzed.

Results: The pooled findings were similar to those reported in Analysis 1 and shown below in Table 11. The proportion of patients with a change in total score of  $\geq 3$  from baseline to two hours post first dose assessment was  $<1\%$  in each treatment group. In the 12-week controlled pool, for patients on treatment, a slightly greater percentage of patients had a change in total mHS  $\geq 3$  in the NG 25mg (4%) group compared to NG 12.5mg (2%) and Placebo (3%) groups.

**Table 11. Summary of Modified Himmelsbach Scale Results (12-week pool and Study 08)**

	12-week pool (Studies 04 and 05)			52-week safety study (Study 08)	
	Placebo (N=444)	NGL 12.5 mg (N=441)	NGL 25 mg (N=446)	Usual care (N=270)	NGL 25 mg (N=534)
<b>Mean (SD) change from baseline in the modified Himmelsbach scale</b>					
2 hours post-first-dose <sup>a</sup>	Study 04: 0.04 (0.532) Study 05: 0.00 (0.493)	Study 04: 0.03 (0.425) Study 05: -0.06 (0.763)	Study 04: 0.07 (0.440) Study 05: 0.14 (0.978)	0.0 (0.52)	0.0 (0.65)
Last on treatment	Study 04: -0.01 (0.626) Study 05: -0.01 (0.852)	Study 04: -0.02 (0.553) Study 05: -0.15 (1.098)	Study 04: 0.00 (0.662) Study 05: -0.09 (0.978)	-0.1 (0.91)	-0.1 (0.84)
<b>n/N (%) of patients with a change of <math>\geq 3</math> in the modified Himmelsbach scale from baseline</b>					
2 hours post-first-dose <sup>a</sup>	3/443 (0.7)	1/438 (0.2)	4/442 (0.9)	1/225 (0.4)	2/480 (0.4)
On treatment	13/444 (2.9)	9/440 (2.0)	16/445 (3.6)	10/262 (3.8)	23/534 (4.3)

<sup>a</sup> The results shown for the 2 hours post-first dose assessment in Study 08 are for the newly randomized patients only.

Scale: 0=none, 1=mild, 2=moderate, 3=severe.

n: Number of patients meeting criterion; N: Total number of patients with non-missing baseline and post-baseline mHS scores; NA: Not available; NGL: Naloxegol; SD: Standard deviation.

(Applicant's table, SCS, p. 83)

### d) Modified Himmelsbach (mHS) Terms Potentially related to OW

Post-hoc analysis of preferred terms potentially related to OW using only the terms of the mHS revealed that overall, the treatment arms were similar for the occurrence of most terms except for hyperhidrosis, which occurred in 3% of the NG 25 mg group compared to  $<1\%$  in the NG 12.5mg and placebo groups. The high incidence of this isolated term may be due to causes other than OWS (i.e., pain associated with bowel movements), however, there is no data available to confirm this. Also, the term was matched to the preferred terms night sweats and cold sweats which may contribute to the higher incidence. Table 12 below displays the number of patients with AEs related to mHS signs.

**Table 12. Number (%) of patients with AEs Related to mHS Signs During Treatment Period (12-Week Pool and Study 08)**

	12-week pool (Studies 04 and 05)			52-week safety study (Study 08)	
	Placebo (N=444)	NGL 12.5 mg (N=441)	NGL 25 mg (N=446)	Usual care (N=270)	NGL 25 mg (N=534)
Any sign <sup>a</sup>	4 (0.9)	8 (1.8)	22 (4.9)	4 (1.5)	25 (4.7)
Hyperhidrosis	2 (0.5)	2 (0.5)	13 (2.9)	1 (0.4)	17 (3.2)
Tremor	3 (0.7)	4 (0.9)	5 (1.1)	1 (0.4)	3 (0.6)
Rhinorrhoea	0	1 (0.2)	3 (0.7)	1 (0.4)	4 (0.7)
Yawning	1 (0.2)	0	2 (0.4)	0	3 (0.6)
Lacrimation	0	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)
increased					
Piloerection	0	0	1 (0.2)	0	0
Restlessness	1 (0.2)	0	0	0	5 (0.9)
Mydriasis	0	0	0	0	0

<sup>a</sup> The sign Hyperhidrosis was matched to the preferred terms hyperhidrosis, night sweats, and cold sweats. The sign tremor was matched to the preferred terms tremor and feeling jittery. The sign restlessness was matched to the preferred terms restlessness and akathisia. All other signs were matched directly to MedDRA preferred terms.  
 AE Adverse event; MedDRA Medical Dictionary for Regulatory Activities; mHS Modified Himmelsbach scale; N Number of patients in safety population; NGL Naloxegol.

(SCS, p. 85)

### Applicant's Interpretation of Analysis 2

1. All five patients on naloxegol 25mg with an AE of DWS had concurrent GI AEs and four were receiving methadone as their maintenance opioid medication.
2. In the analysis with mHS terms, the higher incidence in the naloxegol 25mg group in the controlled studies and uncontrolled study was driven primarily by the term hyperhidrosis.
3. A recommended cutoff for PCI (potentially clinically important) changes for the NRS in the setting of concurrent use of an opioid receptor antagonist has not been established. Using external consultant advice and literature, a cut off of an increase of  $\geq 2$  point change from baseline was considered PCI.

**Reviewer's Comments:** Although there were cases of possible DWS in patients receiving methadone maintenance, there were also possible cases of DWS which occurred in patients on other maintenance opioids.

While the excess number of reports in the naloxegol treatment group was driven by hyperhidrosis, and this may have been due to the GI effect of naloxegol, there are no data available to confirm this. There were no new cases of DWS identified in Analysis 2 which were not already reported in analysis 1.



## **B) Review Section 2: Analyses Conducted by Applicant after Agency Advice**

The description of the Applicant's post-hoc analyses and their supporting reference documents are shown below:

- Analysis 3: This analysis was to include additional, potentially opioid withdrawal-related, preferred terms (with and without GI terms). In *Module 5 Additional Opioid Withdrawal and CV Risk Assessments*, 8/5/13, an analysis which used an expanded list of preferred opioid withdrawal non-GI terms from OOWS, COWS, SOWS, DSM-IV and other terms agreed to by the Agency was to be performed. (see Appendix A of this review for the preferred terms). However, despite Agency advice, the Applicant performed Analysis 3 excluding selected GI preferred terms. Therefore, Analysis 4 was requested.
- Analysis 4: The reference supporting document for this analysis is *Response to Query Regarding Opioid Withdrawal and CV Risk Assessment*, 10/8/13 which included analyses with and without GI preferred terms using the expanded list (see Appendix B of this review) as well as additional analyses conducted by the Applicant in response to the Agency's clarification (as requested by the Applicant).
- Analysis 5: This was an analysis in response to Clinical IR sent 12/19/13.

This review presents the Agency's advice (bold font), the Applicant's response (italics) and methods/results (regular font) where applicable. All Agency advice, clarification advice, and IR requests are listed, however, only those results which differ from Analysis 1 or 2 or which add information not previously identified are discussed in detail.

### **1. Agency Advice: Display weekly average opioid use (maintenance and breakthrough morphine equivalent doses) along with pain scores and withdrawal symptoms by treatment group for each study.**

*As outlined in the SAPs for the individual studies within the Phase III program, mean daily morphine equivalent dose per week (maintenance and break through pain medication) is summarized along with pain score. The modified Himmelsbach composite score (assessing withdrawal symptoms) are summarized at each time point via summary statistics and histograms.*

Reviewer's comments: This analysis resulted in no new information and supported the findings of Analyses 1 and 2.

### **2. Agency Advice: In graphic or tabular form, display information regarding mean weekly opioid dose, mean weekly pain scores, and withdrawal assessments for all patients (as mean scores) and individually for the subjects who experienced an AE of withdrawal by week of treatment in order to compare opioid use and pain scores in patients who experienced a withdrawal AE with the study population as a whole.**

AstraZeneca proposes including a listing of these parameters (weekly opioid dose, pain score and indicator of withdrawal occurrence time) within a single listing for patients experiencing an adverse event potentially related to opioid withdrawal, as outlined above and in the appendix. [Reference Appendix B of this review].

## Results

Table 13 below summarizes the change from baseline of the weekly mean opioid dose, weekly NRS, and mHS score change from baseline at any time during the study for Studies 04 and 05 pooled for all patients (Analysis 4), and includes GI terms. When analyzing all treatment groups, the NG 25 mg group had a slightly higher incidence of increase in mean weekly opioid dose, mean weekly average pain scores, and increase in mHS scores compared to placebo or NG 12.5mg. This may indicate an increased risk for the occurrence of withdrawal in this dosing group.

**Table 13. Number (%) of Patients in the Overall Safety Population, by Category Mean Weekly Opioid Dose Change, Mean Weekly NRS Average Pain Score and mHS Score Change (12-week Pool)**

	Placebo (N=444)	Naloxegol 12.5 mg (N=441)	Naloxegol 25 mg (N=446)
≥10% increase from baseline in mean weekly opioid dose during the study	51 (11.5)	51 (11.6)	58 (13.0)
≥30% increase from baseline in mean weekly opioid dose during the study	24 ( 5.4)	17 ( 3.9)	28 ( 6.3)
≥2 point increase from baseline in mean weekly NRS average pain at any time during the study	37 ( 8.3)	35 ( 7.9)	43 ( 9.6)
≥3 point increase from baseline in mHS score at any time during the study	13 ( 2.9)	14 ( 3.2)	16 ( 3.6)

Note: Percentages are based on the number of patients in the safety set for each treatment group.

Mean weekly opioid dose includes maintenance plus breakthrough opioids.

AE Adverse event; mHS Modified Himmelsbach Scale; N Number of patients in safety analysis set; NRS Numeric Rating Scale.

(Source: Sponsor's table, 10/8/13 Response Document, p. 13)

In pooled data from Studies 04 and 05, the Applicant found that 84 (19%) of the placebo group, 106 (24%) of the NG 12.5mg group, and 150 (34%) of the NG 25mg group experienced at least one AE potentially related to OWS including specified GI-related AEs as summarized in Table 14, below.

**Table 14. Number (%) of patients with any PT potentially related to OWS during the treatment period, including GI PTs for the 12-week pool.**

	Placebo (N=444)	Naloxegol 12.5 mg (N=441)	Naloxegol 25 mg (N=446)
Patients with any PT potentially related to opioid withdrawal syndrome, including selected GI PTs <sup>a</sup>	84 (18.9)	106 (24.0)	150 (33.6)
<u>Patients with at least 1 of these PTs and:</u>			
≥10% increase from baseline in mean weekly opioid dose within 2 weeks of an event	6 ( 1.4)	9 ( 2.0)	16 ( 3.6)
≥30% increase from baseline in mean weekly opioid dose within 2 weeks of an event	4 ( 0.9)	4 ( 0.9)	8 ( 1.8)
≥2 point increase from baseline in mean weekly NRS average pain at any time during the study	9 ( 2.0)	11 ( 2.5)	21 ( 4.7)
≥2 point increase from baseline in weekly average NRS pain score within 2 weeks of an event	7 ( 1.6)	5 ( 1.1)	11 ( 2.5)
≥3 point increase from baseline in mHS score at any time during the study	4 ( 0.9)	6 ( 1.4)	9 ( 2.0)
≥1 reported PT potentially related to opioid withdrawal syndrome, excluding GI PTs, at any time <sup>b</sup>	12 ( 2.7)	17 ( 3.9)	40 ( 9.0)
≥1 other reported PT potentially related to opioid withdrawal, excluding GI PTs, that started within 2 weeks of the GI PT	8 ( 1.8)	14 ( 3.2)	35 ( 7.8)
≥2 other reported PT potentially related to opioid withdrawal, excluding GI PTs, that started within 2 weeks of the GI PT	1 ( 0.2)	2 ( 0.5)	11 ( 2.5)
<p>Note: Percentages are based on the number of patients in the safety set for each treatment group, not on the number of patients with a selected GI PT. For AEs, 'within 2 weeks' = within 14 days prior to or after the start day of a qualifying GI event.</p> <p><sup>a</sup> Abdominal pain, abdominal pain upper, abdominal pain lower, diarrhea, nausea, or vomiting.</p> <p><sup>b</sup> Any PT potentially related to opioid withdrawal syndrome that started on or after the first dose of Investigational Product through the end of the study is included. Patients with &gt;1 event in the same category/subcategory are counted once in that category/subcategory. Patients with events in &gt;1 category/subcategory are counted once in each category/subcategory.</p> <p>AE Adverse event; GI Gastrointestinal; mHS Modified Himmelsbach Scale; N Number of patients in safety analysis set; NRS Numeric Rating Scale; PT preferred term.</p>			

(10/8/13 document, p. 14)

This analysis also resulted in the Applicant's identification of seven patients with ≥30% increase from baseline in mean weekly opioid dose within 2 weeks of the onset of a selected GI PT in the naloxegol 25mg treatment group. The narratives for these subjects were reviewed. No specific trends could be identified.

**3. Agency Advice: Provide a graph of weekly pain scores over time for patients with AE of drug withdrawal compared to all patients by treatment group in order to assess changes in pain over time for all subjects, without using a cutoff of an increase of at least 2 points in the pain score.**

*AstraZeneca proposes patient line plots of pain scores for patients with an adverse event potentially related to opioid withdrawal, as outlined above and in the appendix, by*

*treatment arm, with box plots of the overall mean scores in the overall population superimposed.*

Reviewer's comments: No new information was identified with this analysis and the findings support Analyses 1 and 2.

**4. Agency Advice: Provide an analysis of breakthrough/rescue analgesic use by treatment group that includes opioid and non-opioid rescue. Agency Clarification: When providing a summary of morphine equivalent units of breakthrough opioid pain medication and non-opioid concomitant medications used for pain, provide the timing of administration of these medications in relation to the last dose of study drug.**

*Within the Summary of Clinical Safety, AstraZeneca proposes to include summaries of MEUs of breakthrough opioid pain medications, by timepoint. Separately, AstraZeneca proposes to produce a summary of concomitant non-opioid medications recorded in the concomitant medications CRF, which were started after randomization and were for a pain indication.*

Results: The use of breakthrough opioid and non-opioid analgesics was similar across the treatment groups. According to the Applicant, because naloxegol was taken once daily in an outpatient setting, with the exception of the first day that the study treatment was dosed, details around the dosing time were not collected. Non-opioid pain medication use was recorded on a general concomitant medication case report form with only the start and stop dates (not dosing times). Therefore, the detailed analysis regarding the timing of administration in relation to the last dose could not be conducted because the data was not available.

**5. Agency Advice: Include additional preferred term events in the post hoc analysis of adverse events potentially related to opioid withdrawal that include signs and symptoms of withdrawal noted in the DSM- IV Opioid Withdrawal Diagnostic Criteria, COWS, OOWS and other clinical terms associated with opioid withdrawal. Clarification: The Applicant was again advised to conduct the analyses with and without GI AEs.**

*AstraZeneca will include all of the non-GI AEs which are outlined above. AstraZeneca continues to believe that given the underlying action of the drug, patients exhibiting GI AEs only, in the absence of other non-GI AEs potentially related to withdrawal, do not constitute potential opioid withdrawal cases.*

Methods: The Applicant submitted the material as outlined above (Analysis 3 without GI terms and Analysis 4 with GI terms).

Results: Excluding GI preferred terms, the PTs reported for  $\geq 2$  patients in any treatment group showed that the overall incidence of preferred terms was similar among treatment groups, except for the term hyperhidrosis which occurred with an incidence of approximately 12% in the NG 25 mg group compared to 6% and 7% for the placebo and NG 12.5mg groups, respectively, in the Studies 04 and 05.

When GI terms are included, the highest incidence of GI PTs occurred in the NG 25 mg group with abdominal pain at a frequency of almost 10%, followed by diarrhea and nausea, both at >5% incidence.

The Applicant also analyzed patients with potential “clusters” of PTs occurring in temporal proximity (suggesting a more clinically relevant picture of patients who may be experiencing a constellation of signs/symptoms consistent with opioid withdrawal). The Applicant searched in the naloxegol 25mg group for those patients with  $\geq 1$  selected GI PT AND  $\geq 2$  non-GI AEs potentially related to opioid withdrawal syndrome (provided at least one of the non-GI AEs was reported within 2 weeks of the GI AE) in the 12-week pool and identified nine patients in the naloxegol 25mg group with a “cluster” of AEs potentially related to opioid withdrawal syndrome. Narratives were provided and reviewed for these nine patients. Three of these cases resulted in DAEs (discontinuation adverse event) and one occurred in a patient who experienced an SAE (serious adverse event).

The nine cases identified by the Applicant represent all cases with even one PT potentially related to OW. In order to provide more meaningful clinical context, these cases were reviewed using the criteria of all PTs occurring on the same day. After review of the nine narratives, five additional cases of possible OWS were identified, with one case adjudicated as a possible CV event. Key findings from the nine cases are shown below in Tables 15 and 16, with the possible CV event described in more detail.

**Table 15. Patients with “Clusters” of PTS Potentially Related to Opioid Withdrawal (Studies 04 and 05) Meeting Criteria of  $\geq 3$  PTs, Not All GI, Occurring in the Same Event**

Study ID	AE Terms	Onset	Maintenance	Comments
E4074011 25mg	Abdominal pain upper, rhinorrhea, yawning	Day 2	Hydromorphone HCL	Patient discontinued Day 3; withdrew Day 18
E5206010 25mg	Abdominal pain, chills, diarrhea, hyperhidrosis (sweats)	Day 3	Oxycodone HCL	Patient discontinued day 4 (withdrew Day 15). mHS scores 0 all visits except Day 15 (1.0)
E5243001 25mg	Diarrhea, irritability, hyperhidrosis	Day 27	Oxycodone HCL	Patient discontinued Day 47; mHS scores 0 all visits
E5283018 25mg	Abdominal pain, cold sweats, tremor	Day 6	Fentanyl	SAE of wound infection Day 72. mHS scores 2.0, 4.0 (day 9), 1.0, 1.0

E4089004 (SAE) Adjudicated as CV event  25mg	AEs: Diarrhea, nausea, vomiting (onset Day 2); hyperhidrosis, nausea, and palpitations (onset Day 58) 49-year-old female with mild AEs noted above. Hyperhidrosis, nausea and palpitations onset on Day 58 and resolved on Day 58. The patient was also reported to have AE of cellulitis, serious adverse event (SAE) of non-cardiac chest pain, AEs of peptic ulcer disease, and shortness of breath on Day 58. The patient's history was significant for musculoskeletal chest pain, myocardial infarction, and peptic ulcer, but she had no prior documented history of palpitations. Acute coronary syndrome was ruled out by negative serial troponins. The patient refused a nuclear stress test and was discharged from the hospital on no CV medications. The patient continued in the study. Although ≥3 PTs of interest occurred on Day 2, they were all GI terms. The events on Day 58 were adjudicated as a CV event. Underlying viral gastroenteritis (day 31) and cellulitis (day 58) confound the case. Methadone and Oxycodone+APAP were maintenance opioids; mHS scores were 0 at all visits except Study Day 10 when the score was 1.0.
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(Table, reviewer)

**Table 16. Patients with “Clusters” of PTS Potentially Related to Opioid Withdrawal (Studies 04 and 05) Not Consistent with Possible OWS**

E4023040 25mg	Hyperhidrosis, cold sweat, nausea occurred on separate days. The case was also confounded as the patient tested positive for amphetamines at Visit 8.
E4089005 25mg	Hyperhidrosis (day 1); anxiety and nausea (Day 2). All three terms did not occur on the same day.
E5215007 25mg	Abdominal pain (day 1), insomnia and anxiety (Day 3). All PTs did not occur on the same day.
E5218017 25mg	Myalgia (Day 2), insomnia and nausea (Day 9). All PTs did not occur on the same day.

(Table, reviewer)

Reviewer's comments: Of the nine patients identified by the Applicant with ≥1 selected GI PT AND ≥2 non-GI AEs potentially related to opioid withdrawal syndrome (provided at least one of the non-GI AEs was reported within 2 weeks of the GI AE), only five of these patients had narratives which supported a clinical presentation of possible opioid withdrawal syndrome using a criteria of ≥3 PTs potentially related to OWS occurring on the same day.

**Agency Clinical IR: Provide a summary table for the controlled naloxegol clinical trials (04 and 05) for patients who experienced ≥ 3 opioid-withdrawal symptoms by study and treatment arm over the 12-week treatment period not separated by GI or non-GI preferred terms and not restricted by the other opioid withdrawal outcome parameters of ≥2 point increase in NRS, ≥10 or 30% increase in mean weekly opioid dose and ≥3 point increase from baseline in mHS.**

Results: Using the criteria of ≥ 3 opioid-withdrawal symptoms without upper limit cut offs, including GI terms and not assigning causality, the number of patients with ≥3 PTs

potentially related to OWS was higher in the naloxegol 25mg treatment group compared with placebo (5, 2, and 2% in Study 4 and 9, 3, and 1% in Study 5 for the naloxegol 25mg, 12.5mg and placebo treatment groups, respectively). The cases were further sub-divided by the Applicant into the following GI vs non-GI PTs categories: a)  $\geq 3$  non-GI PTs, b) two non-GI and  $\geq 1$  GI PTs, c) no non-GI and  $\geq 3$  GI PTs based on the presence or absence of GI symptoms. Overall, the distribution of types of GI vs. non-GI symptoms was fairly even except for a higher percentage of patients in the NG 25 mg group in Studies 04 and 05 who experienced all combinations of terms. Table 17 below summarizes the total number of patients who were identified as having  $\geq 3$  potential OW terms at any time during Studies 04 and 05.

**Table 17. Summary of Patients with  $\geq 3$  PTs Potentially Related to OWS During the Treatment Period, Studies 04 and 05**

Study : D3820C00004

Category	Treatment		
	Placebo (N=213) n ( % )	NGL-118 12.5 mg (N=211) n ( % )	NGL-118 25 mg (N=214) n ( % )
Patients with $\geq 3$ PTs	5 ( 2.3)	4 ( 1.9)	10 ( 4.7)
Patients with $\geq 3$ non-GI PTs	2 ( 0.9)	1 ( 0.5)	2 ( 0.9)
Patients with 2 non-GI and $\geq 1$ GI PTs	0 ( )	0 ( )	4 ( 1.9)
Patients with 1 non-GI and $\geq 2$ GI PTs	2 ( 0.9)	1 ( 0.5)	2 ( 0.9)
Patients with no non-GI and $\geq 3$ GI PTs	1 ( 0.5)	2 ( 0.9)	2 ( 0.9)

Study : D3820C00005

Category	Treatment		
	Placebo (N=231) n ( % )	NGL-118 12.5 mg (N=230) n ( % )	NGL-118 25 mg (N=232) n ( % )
Patients with $\geq 3$ PTs	3 ( 1.3)	7 ( 3.0)	20 ( 8.6)
Patients with $\geq 3$ non-GI PTs	0 ( )	0 ( )	1 ( 0.4)
Patients with 2 non-GI and $\geq 1$ GI PTs	0 ( )	2 ( 0.9)	5 ( 2.2)
Patients with 1 non-GI and $\geq 2$ GI PTs	2 ( 0.9)	2 ( 0.9)	9 ( 3.9)
Patients with no non-GI and $\geq 3$ GI PTs	1 ( 0.4)	3 ( 1.3)	5 ( 2.2)

(12/31/13 Document, p. 12 and 13)

The table above (and the Applicant's analysis) identified patients with  $\geq 3$  PTs potentially related to OWS. However, not all of these cases were consistent with a clinical criteria of possible OWS (i.e.,  $\geq 3$  potential OW PTs occurring on the same day). Therefore, to further identify potential cases of clinical OWS, using the criteria of  $\geq 3$  PTs potentially related to opioid withdrawal (not all three terms GI only) and occurring on the same day, individual line listings for the above patients were reviewed. Of the 15 cases in the NG 12.5 group in Study 04 and 27 cases in the NG group in Study 05, applying a stricter clinical criteria yielded six additional cases of possible OWS in the naloxegol treatment arm which had not previously been identified using one of the other analyses already discussed, as shown in Table 18 below.

**Table 18. Cases of Potential OWS Not Previously Identified (Using Clinical Criteria) Studies 04 and 05**

	Study 04
E4026026 12.5mg	Anxiety, heart rate increased, feeling jittery (Day 3); oxycodone maintenance; mHS 0 at all assessments
E4840016 25mg	Lacrimation increased, yawning, rhinorrhea (Day 21); hydromorphone maintenance; [narrative not provided; identified



	by line listing review]
	<b>Study 05</b>
E5218009 12.5mg	Diarrhea, nausea, vomiting, cold sweats (Day 2); oxycodone and fentanyl maintenance; [narrative not provided; identified by line listing review]
E5267032 12.5mg	Abdominal pain, nausea, anxiety (Day 1); maintenance morphine sulfate; mHS scores were 0 at all assessments except post 1 <sup>st</sup> dose=2.0
E5218010 25mg	Abdominal pain, myoclonus, nausea (Day 1); hydrocodone maintenance; [narrative not provided; identified by line listing review]
E5267051 25mg	Hyperhidrosis, abdominal pain, diarrhea (Day 1); morphine sulfate maintenance; [narrative not provided; identified by line listing review]

(Table, reviewer)

There were two cases that did not meet the clinical criteria of  $\geq 3$  PTs potentially related to OWS but had a PT potentially related to a cardiac event (i.e., palpitations). These cases are included here in Table 19 to be comprehensive.

**Table 19. Cases Identified  $\geq 3$  PTs Potentially Related to OW; Not Meeting Criteria of Possible OWS but with At Least One Cardiac Preferred Term**

E5218011 12.5mg	Abdominal pain, flushing (Day 1), palpitations (Day 17)
E5526005 25mg	Abdominal pain (Day 11), palpitations (Day 43), diarrhea (Day 54)

(Table, reviewer)

Reviewer's comments: Although considerably more patients were identified using the criteria of patients who experienced  $\geq 3$  opioid-withdrawal symptoms over the 12-week treatment period not separated by GI or non-GI preferred terms and not restricted by the other opioid withdrawal outcome parameters of  $\geq 2$  point increase in NRS,  $\geq 10$  or 30% increase in mean weekly opioid dose and  $\geq 3$  point increase from baseline in mHS, this identification of isolated AE terms alone does not effectively capture only those patients who more likely experienced clinical OWS. Therefore, expanding the criteria yields an overall higher number of patients with potential OW (high sensitivity) but lacks more robust clinical criteria for possible OWS (low specificity).

**8. Agency Advice: Perform a post-hoc analysis of drop-outs (discontinuations) due to AEs potentially related to opioid withdrawal during each treatment period by treatment group.**

*AstraZeneca proposes to conduct a post-hoc summary by treatment group of DAEs potentially related to opioid withdrawal using the broad definition of terms outlined above and in the appendix.*

**Results**

Discontinuation AEs Terms (DAEs):

*Analysis excluding GI terms:* In the 12-week pool (Studies 04 and 05), the only non-GI DAEs potentially related to opioid withdrawal that were reported for  $\geq 2$  patients in any treatment group were hyperhidrosis and myalgia (reported for 4/446 and 2/446 patients, respectively, in the naloxegol 25 mg group). All six of these events were reported as recovered/resolved.

In the 52-week study (Study 08), the only non-GI DAEs potentially related to opioid withdrawal reported for  $\geq 2$  patients in the naloxegol 25 mg group were hyperhidrosis, chills, and arthralgia (reported for 3/534, 3/534, and 2/534 patients, respectively). Except for one case of arthralgia, these eight events were reported as recovered/resolved. There were also two cases of depression reported in the 52-week study. In the 12-week extension of Study 04 (Study 07), there were no DAEs potentially related to opioid withdrawal.

*Analysis including GI terms:* GI preferred terms of diarrhea and abdominal pain were seen more frequently ( $>2\%$ ) in those who discontinued in naloxegol 25mg compared to naloxegol 12.5 mg and placebo. The percentage of patients with at least one DAE potentially related to Opioid Withdrawal Syndrome in the pooled studies and Study 08 are shown in table 20 below.

**Table 20. Number (%) of Patients with a DAEs Potentially Related to Opioid Withdrawal (12-week pool and Study 08) [GI terms Excluded and Included]**

	12 Week Pool			52-week OL Study	
	PLA N=444 (%)	NG 12.5 mg N=441 (%)	NG 25 mg N=446 (%)	Usual Care N=270 (%)	NG 25 mg N=534 (%)
Any DAE <sup>1</sup>	24 (5)	21 (5)	46 (10)	N/A	56 (10)
Any OW DAE <sup>2</sup>	6 (1)	0	9 (2)	N/A	10 (2)
Any OW DAE <sup>3</sup>	10 (2)	10 (2)	29 (6)		29 (5)
Non-GI DAE	6 (1)	1 (<1)	10 (2)		13 (2)
Hyperhidrosis	1 (<1)	0	4 (<1)		3 (<1)
Myalgia	0	0	2 (<1)		1 (<1)
Depression	0	1 (<1)	1 (<1)		2 (<1)
Chills	0	0	1 (<1)		3 (<1)
Arthralgia	0	0	0		2 (<1)
GI DAE	5 (<1)	9 (2)	25 (6)		17 (3)
Diarrhea	3 (<1)	4 (<1)	14 (3)		11 (2)
Abdominal pain	1 (<1)	4 (<1)	13 (3)		9 (2)
Nausea	1 (<1)	5 (<1)	5 (<1)		3 (<1)
Abdominal pain (upper)	0	0	5 (<1)		2 (<1)
Vomiting	1 (<1)	2 (<1)	4 (<1)		5 (<1)
Abdominal pain (lower)	0	0	0		2 (<1)

(Table, reviewer, Applicant's tables 3 page 14, 8/5/13 document and 10/8/13 documents) <sup>1</sup> Any DAE (safety population; all causes); <sup>2</sup> DAEs with GI PTs excluded; <sup>3</sup> DAEs with/without GI PTs

**Agency Clinical IR: Provide a separate table for those patients who experienced ≥ 3 opioid withdrawal term adverse events and also had a serious adverse event or discontinued.**

#### DAEs

Using the Applicant's analysis, there were thirteen naloxegol-treated patients in the pooled 12-week studies who met the criteria of ≥3 PTs potentially related to OWS and who discontinued compared to two placebo cases who met the criteria and discontinued.

Using the clinical criteria of ≥3 PTs potentially related to OWS, occurring on the same day, with GI+ non-GI, (GI only excluded), there were eight cases identified as follow:

- Study 04: there were no discontinuations in the NG 12.5mg group and two in the NG 25mg group.
- Study 05: there were no discontinuations in the 12.5mg group and six in the NG 25mg group. Case E5267047 was also an SAE. The only discontinuation case

which was not previously identified was case E5241042, whose mini-narrative is described below in Table 21.

**Table 21. Mini-narrative of DAE Case Not Previously Identified Meeting Criteria of Possible OWS**

E5241042 25mg	Abdominal pain, diarrhea, feeling jittery (onset Day 2). Study drug was discontinued Day 2 and the subject withdrew on Day 22. Maintenance opioid was morphine. mHS scores 1.0 at all assessments.
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(Table, reviewer)

DAE Summary: Of the total 19 cases identified in Studies 04 and 05 as possible OWS (using clinical criteria), eight led to study discontinuation.

### SAEs

Using the Applicant's analysis, there were five naloxegol-treated patients in the pooled 12-week studies who met the criteria of  $\geq 3$  PTs potentially related to OWS and who experienced an SAE. There were no SAEs in the placebo group.

The DAEs and SAEs using the analysis of  $\geq 3$  PTs and an SAE or DAE for Studies 04 and 05 are summarized in table 22 below.

**Table 22. DAEs and SAEs, Applicant's Analysis  $\geq 3$  PTs Potentially Related to OW During the 12-Week Treatment Period (Studies 04 and 05)**

Study : D3820C00004

Category	Treatment		
	Placebo (N=213) n ( % )	NGL-118 12.5 mg (N=211) n ( % )	NGL-118 25 mg (N=214) n ( % )
Patients with $\geq 3$ PTs	5 ( 2.3 )	4 ( 1.9 )	10 ( 4.7 )
Patients with any SAE (a)	0 ( )	1 ( 0.5 )	2 ( 0.9 )
Patients who discontinued the study	2 ( 0.9 )	1 ( 0.5 )	2 ( 0.9 )
Adverse Event	2 ( 0.9 )	0 ( )	2 ( 0.9 )
Withdrawal By Subject	0 ( )	1 ( 0.5 )	0 ( )

Study : D3820C00005

Category	Treatment		
	Placebo (N=231) n ( % )	NGL-118 12.5 mg (N=230) n ( % )	NGL-118 25 mg (N=232) n ( % )
Patients with $\geq 3$ PTs	3 ( 1.3 )	7 ( 3.0 )	20 ( 8.6 )
Patients with any SAE (a)	0 ( )	0 ( )	2 ( 0.9 )
Patients who discontinued the study	0 ( )	2 ( 0.9 )	8 ( 3.4 )
Adverse Event	0 ( )	2 ( 0.9 )	7 ( 3.0 )
Withdrawal By Subject	0 ( )	0 ( )	1 ( 0.4 )

(12/31/13 Document, pages 14-15)

SAE Summary: Using the clinical criteria described previously, of the total 19 cases identified in Studies 04 and 05 with possible OWS, two cases were identified in which patients experienced an SAE. These narratives have already been included in this review.

### Studies 07 and 08 Analyses

For Study 07, the Applicant identified four (4%) patients in the placebo group, nine (10%) in the NG 12.5 mg group, and 14 (14%) patients in the NG 24 mg group with at least one AE potentially related to OWS, as shown in Table 23 below.

**Table 23: Patients with at Least One AE Potentially Related to OW, Study 07**

Category Preferred term	Number (%) of patients		
	Placebo (N=100)	NKTR-118 12.5 mg (N=94)	NKTR-118 25 mg (N=97)
Number of pts with at least 1 AE potentially related to Opioid Withdrawal including specific GI-related AEs	4 ( 4.0 )	9 ( 9.6 )	14 ( 14.4 )

(10/8/13 Document, p. 80)

For Study 08, the Applicant identified 70 (26%) Usual Care and 253 (47%) of patients who experienced at least one AE potentially related to OW, as shown in Table 24 below.

**Table 24: Patients with at Least One AE Potentially Related to OW, Study 08**

Category Preferred term	Number (%) of patients	
	Usual Care (N=270)	NKTR-118 25 mg (N=534)
Number of pts with at least 1 AE potentially related to Opioid Withdrawal including specific GI-related AEs	70 ( 25.9)	253 ( 47.4)

(10/8/13 Document, p. 440)

The groups above, for Studies 07 and 08, identify all patients with even one AE potentially related to OW which does not provide clinically meaningful context. Therefore, the data were further analyzed to identify patients with  $\geq 3$  PTs potentially related to OWS, occurring on the same day and not all GI.

The following information for Studies 07 and 08 is based upon an internal analysis.

#### Study 07

There were no new cases of potential OWS identified. The two cases of DWS that were SAEs and led to discontinuation have been identified earlier in this review.

#### Study 08

There were 50 patients identified in Study 08 with  $\geq 3$  PTs potentially related to OWS in the NG group compared to nine in the Usual Care group. Of these 50 NG-treated cases, 37 were excluded because they did not meet the criteria of  $\geq 3$  potential opioid withdrawal terms which occurred in the same event (i.e., same day).

Of the 13 cases remaining, seven were identified (not previously identified) who met the criteria of  $\geq 3$  PTs potentially related to OW occurring the same day. Of these seven cases, there was one case in which the PTs were all GI and one all non-GI with the remainder a combination of GI and non-GI.

No new patients were identified who met the criteria of OWS and experienced an SAE in Study 08. There were a total of three patients who experienced potential OWS and led to study discontinuation in Study 08. There was one patient not previously identified who discontinued (GI + non-GI terms).

The internal analysis of Studies 04 and 05 generally support the Applicant's analysis for these studies.

**7. Agency Advice: In order to understand the association of CV AEs and AEs due to withdrawal, include the type and timing (relative to dosing) of the CV events in a table that also includes the withdrawal AEs for those patients identified in the**

**studies as having both types of AEs. In addition, provide narratives for these patients.**

*AstraZeneca proposes a listing and patient narratives for any patient that had both CV-related AE and AE potentially related to opioid withdrawal as noted above.*

**Methods:** The Applicant's submission included a listing of patients in the placebo-controlled Phase 3 studies (04, 05 and 07) and the long-term safety study (08) with a cardiovascular (CV) AE (i.e., in the MedDRA Cardiac Disorders System Organ Class or Vascular Disorders SOC and/or a reported PT potentially related to opioid withdrawal syndrome, including selected GI PTs (abdominal pain, abdominal pain upper, abdominal pain lower, diarrhea, nausea and vomiting).

**Results:** In each listing, reported episode terms, PT, onset relative to treatment start and end dates, seriousness, severity, and outcome were presented for all CV AEs and PTs potentially related to opioid withdrawal syndrome with onset during the study period.

The Applicant found that the proportion of patients with CV PTs was higher in the naloxegol treatment groups compared to the placebo groups in the controlled studies. Study 08 also showed a higher proportion of patients in the NG group who experienced a CV event. The findings from the controlled 12-week pool are shown in Table 25 below.

While the numbers of reports are small, there does appear to be a dose-response relationship for CV events.

**Table 25. Number (%) of Patients with Both a Selected GI PT and a CV PT During Treatment (12-week pool)**

	Placebo (N=444)	Naloxegol 12.5 mg (N=441)	Naloxegol 25 mg (N=446)
Patients with a selected GI PT <sup>a</sup>	62 (14.0)	86 (19.5)	127 (28.5)
<u>Patients with at least 1 selected GI PT and:</u>			
A CV PT <sup>b</sup> at any time	5 ( 1.1)	8 ( 1.8)	12 ( 2.7)
A CV PT within 2 weeks of the selected GI PT <sup>c</sup>	2 ( 0.5)	7 ( 1.6)	8 ( 1.8)

Note: Percentages are based on the number of patients in the safety set for each treatment group.  
MedDRA version 15.1.

<sup>a</sup> Abdominal pain, abdominal pain upper, abdominal pain lower, diarrhea, nausea, or vomiting.

<sup>b</sup> Any PT in the MedDRA Cardiac Disorders or Vascular Disorders system organ class.

<sup>c</sup> The AE started within 14 days prior to or after the start day of a qualifying event.

CV Cardiovascular; GI Gastrointestinal; MedDRA Medical Dictionary for Regulatory Activities; N Number of patients in safety analysis set; PT preferred term.

(Applicant's table, Opioid Withdrawal 10/8/13 document, p. 25)

Of the cases discussed in this review, six cases had at least one PT potentially related to possible OW and at least one CV term (E8705022, E881008, E8873020, E8731002,



E5218011, E5526005). Patient E4089004 met the criteria for possible OWS, experienced an SAE and was an adjudicated CV case.

Refer to Dr. Preston Dunnmon's review in the Division of CardioRenal Products for the discussion of the Applicant's CV analysis.

### Applicant's Conclusions (All analyses)

There is no definitive evidence of opioid withdrawal syndrome associated with naloxegol in clinical trials of up to 52 weeks in duration with nearly 1500 unique OIC patients exposed, whether or not GI events are included in the assessment.

### Reviewer's Summary

For controlled studies 04 and 05, the results of all analyses (total) of those patients who met the clinical criteria determined by this reviewer to represent possible clinically meaningful OWS:  $\geq 3$  PTs potentially related to OWS (excluding cases with PTs which were all GI) occurring the same day regardless of whether the cases were confounded are summarized in Table 26 below. Study 07 yielded no additional cases from Analysis 1. Study 08 resulted in 3/270 (<1%) Usual Care and 10/534 (2%) NG 25mg with possible OWS.

**Table 26 . Cases Identified as Possible OWS, Pooled Controlled Studies 04 and 05**

Placebo N=444 (%)	12.5mg N=441(%)	25mg N=446 (%)
Pooled Total (All Analyses Combined) Studies 04 and 05		
1/444 (<1)	5/441 (1)	14/446 (3)

(Table, reviewer)

## IV) Applicant's Proposed Labeling Claims

### Proposed Label

#### 5.3 Concurrent Methadone Use

Patients receiving methadone as primary therapy for their pain condition were observed in clinical trials to have a higher frequency of gastrointestinal adverse events (such as abdominal pain and diarrhea) than patients not receiving methadone. In a few cases, symptoms suggestive of opioid withdrawal when receiving naloxegol 25 mg were observed in patients receiving methadone for their pain condition [see *Patient Counseling Information* (17.4)].

*Reviewer's comment: This proposed labeling is not acceptable, as there were possible cases of opioid withdrawal syndrome seen in patients receiving other opioid products for their pain condition. Consideration should be given to including language that also reflects those findings.*

#### Section 10. Overdosage

If a patient on opioid therapy receives an overdose of naloxegol, the patient should be monitored closely for potential evidence of opioid withdrawal

symptoms or reversal of central analgesic effect. In cases of known or suspected overdose of naloxegol, symptomatic treatment as well as monitoring of vital functions should be performed.

*Reviewer's comment: This proposed language appears unacceptable. The proposed wording is as follows: If a patient on opioid therapy receives an overdose of naloxegol, the patient should be monitored closely for potential evidence of opioid withdrawal symptoms such as chills, rhinorrhea, diaphoresis or reversal of central analgesic effect. Base treatment on the degree of opioid withdrawal symptoms, including changes in blood pressure and heart rate, and on the need for analgesia.*

#### Section 14. Clinical Studies

There were no clinically relevant differences between naloxegol 12.5 mg, 25 mg, and placebo groups in average pain intensity, daily opioid dose, or in opioid withdrawal scores over the 12-week study. (Annotation 2.5 Clinical Overview, Section 5.4.3.1; 2.7.4 Summary of Clinical Safety Section, Sections 4.4.1 and 4.4.2)

*Reviewer's comment: DAAAP would not consider this language appropriate for labeling. The analyses of pain intensity and opioid dose were descriptive in nature, and the studies were not designed to assess these endpoints in a valid statistical manner. Additionally, there was evidence of opioid withdrawal in study subjects receiving naloxegol.*

**Reviewer's Conclusions:** See discussion below in DAAAP's response to the DGIEP questions.

**V) DAAAP Responses to DGIEP Questions:** (DGIEP question is in regular font and DAAAP response is bolded font)

1. For Studies 04 and 05, is there evidence of opioid withdrawal in study drug compared to placebo?

**DAAAP Response: Yes, based upon all analyses, there is evidence of possible opioid-withdrawal related AEs which occurred in the controlled 12-week Studies 04 and 05.**

- **While the overall incidence was generally low, possible opioid withdrawal symptoms occurred with a higher frequency in patients taking naloxegol (2%) compared to placebo (<1%) and occurred with a greater incidence in the naloxegol 25mg group (14/446=3%) than the naloxegol 12.5mg group (5/441=1%).**
- **Analyzing the data using expanded terms from DSM-IV, COWS, SOWS, OOWS and other relevant terms including GI terms resulted in the identification of a higher number of cases with potential opioid withdrawal terms but not all cases met the criteria of clinically meaningful possible OWS.**

- When analyzing preferred terms potentially related to opioid withdrawal, the most frequently occurring AE term was hyperhidrosis, which occurred more frequently in naloxegol-treated patients than placebo. This term, however, may also be associated with mechanical straining from bowel movements. Making a determination of opioid withdrawal is challenging since opioid withdrawal syndrome may mimic other clinical presentations. We do not have adequate data to make definitive determinations of causality of the clinical manifestations reported.
- No trends with regard to demographics were identified in those patients who experienced possible opioid withdrawal symptoms.
- Five cases (out of 19 cases total) of possible DWS were reported in patients using methadone as their opioid maintenance. The other possible cases involved maintenance opioids other than methadone.

2. Does naloxegol appear to have an effect on analgesia?

**Naloxegol does not appear to have a negative effect on analgesia based upon the NRS (Numeric Rating Scale) scores and mean opioid use which appeared generally stable among the three treatment arms across all analyses, including the analysis without a  $\geq 2$  point cut off.**

3. Provide comments regarding opioid withdrawal and analgesic outcomes for Studies 07 and 08.

**In general, the findings for Studies 07 and 08 were similar to Studies 04 and 05.**

- **Opioid Withdrawal**
  - For Study 07, a slightly higher incidence of possible OWS was seen in naloxegol-treated (NG 12.5mg 6/535 [1%] and NG 25mg 15/543 [3%] compared to placebo <1%) when Study 07 is pooled with the other placebo-controlled Studies 04 and 05.
  - For Study 08, there were 10/534 (2%) NG-treated compared to 3/270 (<1) Usual Care who were identified as experiencing possible OWS.
- **Analgesic Outcomes**
  - The analgesic outcomes for Studies 07 and 08 were similar to those for Studies 04 and 05.

4. Additional comments

- **Labeling Claims:**
  - a. **Concurrent methadone use:** This proposed labeling is not acceptable, as there were cases of opioid withdrawal syndrome seen in patients receiving other opioid maintenance. Consideration should be given to including language that also reflects those findings.
  - b. **Overdosage:** This proposed language appears unacceptable. DAAAP proposes the following language: If a patient on opioid therapy receives an overdose of naloxegol, the patient should be monitored closely for potential evidence of opioid withdrawal

**symptoms such as chills, rhinorrhea, diaphoresis or reversal of central analgesic effect. Base treatment on the degree of opioid withdrawal symptoms, including changes in blood pressure and heart rate, and on the need for analgesia.**

- c. Effect on analgesia: The Applicant's proposed labeling claims regarding effect on analgesia are not acceptable, as this data is merely descriptive, and the studies were not designed to adequately assess these opioid withdrawal outcomes. Additionally, there was evidence of opioid withdrawal in study subjects receiving naloxegol.**
- The relationship of naloxegol and CV events is being evaluated by the Division of CardioRenal Products.**

## Appendix A: Applicant's List of Potentially Opioid-Related Preferred Terms

Source	Symptom or opioid withdrawal scale item	Preferred term
MedDRA SMQ Drug Withdrawal	NA	Drug withdrawal convulsions
	NA	Drug withdrawal headache
	NA	Drug withdrawal syndrome
	NA	Drug withdrawal syndrome neonatal
	NA	Rebound effect
	NA	Steroid withdrawal syndrome
	NA	Withdrawal arrhythmia
	NA	Withdrawal syndrome
	NA	Drug withdrawal maintenance therapy
	NA	Drug rehabilitation
Modified Himmelsbach Scale (mHS)	Yawning	Yawning
	Lacrimation	Lacrimation increased
	Rhinorrhea	Rhinorrhoea, Rhinitis
	Perspiration	Hyperhidrosis; Night sweats, Cold sweat
	Tremor	Tremor; Feeling Jittery
	Mydriasis	Mydriasis
	Piloerection	Piloerection
	Restlessness	Restlessness; Akathisia
Clinical Opiate Withdrawal Scale (COWS)	Resting pulse rate	Heart rate increased; Palpitations; Tachycardia; Sinus tachycardia
	Sweating	Hyperhidrosis, Night sweats, Cold sweat
	Restlessness	Restlessness; Akathisia
	Pupil size	Mydriasis
	Bone or Joint aches	Bone pain; Arthralgia
	GI upset (stomach cramps, nausea, vomiting, diarrhea)	Abdominal pain upper; Nausea; Vomiting; Diarrhoea <sup>a</sup>
	Tremor	Tremor; Feeling jittery
	Yawning	Yawning
	Anxiety or Irritability	Anxiety; Irritability; Agitation; Anxiety disorder
	Gooseflesh skin	Piloerection
	Runny nose or tearing	Rhinorrhoea; Lacrimation increased, Rhinitis

Subjective Opiate Withdrawal Scale (SOWS)	"I feel anxious"	Anxiety; Irritability; Agitation; Anxiety disorder
	"I feel like yawning"	Yawning
	"I am perspiring"	Hyperhidrosis; Night sweats; Cold sweat
	"My eyes are teary"	Lacrimation increased
	"My nose is running"	Rhinorrhoea, Rhinitis
	"I have goosebumps"	Piloerection
	"I am shaking"	Tremor; Feeling jittery
	"I have hot flashes"	Hot flush; Feeling hot; Flushing
	"I have cold flashes"	Chills, Feeling Cold
	"My bones and muscles ache"	Bone pain; Myalgia
	"I feel restless"	Restlessness; Akathisia
	"I feel nauseous"	Nausea <sup>a</sup>
	"I feel like vomiting"	Vomiting <sup>a</sup>
	"My muscles twitch"	Muscle twitching; Muscle spasms; Myoclonus
	"I have stomach cramps"	Abdominal pain upper <sup>a</sup>
	"I feel like using now"	Drug abuse; Drug dependence; Drug effect decreased

Objective Opioid Withdrawal Scale (OOWS)	Yawning	Yawning
	Rhinorrhea	Rhinorrhoea, Rhinitis
	Piloerection (observed arm)	Piloerection
	Perspiration	Hyperhidrosis; Night sweats; Cold sweat
	Lacrimation	Lacrimation increased
	Tremor	Tremor; Feeling jittery
	Mydriasis	Mydriasis
	Hot and cold flushes	Hot flush; Feeling hot; Flushing
	Restlessness	Restlessness; Akathisia
	Vomiting	Vomiting <sup>a</sup>
	Muscle twitches	Muscle twitching; Muscle spasms; Myoclonus
	Abdominal cramps	Abdominal pain upper <sup>a</sup>
	Anxiety	Anxiety; Irritability; Agitation; Anxiety disorder
FDA Clinical Review of alvimopan with respect to the topic of opioid withdrawal <sup>b</sup>	Insomnia	Insomnia, Initial insomnia
	Return of pain	Drug effect decreased
	Sneezing	Sneezing

Note: PTs related to the DSM-IV criteria for opioid withdrawal, other than fever and dysphoric moods, are included in the table under another heading or headings: MedDRA SMQ, mHS, COWS, SOWS, OOWs, or FDA Clinical Review of alvimopan.

- <sup>a</sup> Gastrointestinal adverse events were excluded because of the potential to confound the assessment of opioid withdrawal. These events may be associated with the intended action of naloxegol and in the absence of other events potentially related to withdrawal, they do not constitute opioid withdrawal per se.
- <sup>b</sup> Terms from the FDA Clinical Review of alvimopan are included here only if they are not already included in the list.
- MedDRA Medical Dictionary for Regulatory Activities; NA Not applicable; SMQ Standardized MedDRA Query.

(Source: 8/5/13 Document, Applicant's table, Appendix A, Additional Opioid Withdrawal and CV Risk, pages 20-22)

**Appendix B:** Appendix B reflects all of the terms in Appendix A with GI terms included. Additionally, two terms in DSM-IV were included.

**Appendix B. Updated Comprehensive List of MedDRA Preferred Terms Potentially Related to Opioid Withdrawal Syndrome (GI Terms included)**

Source	Symptom or opioid withdrawal scale item	Preferred term
DSM-IV <sup>c</sup>	Fever	Pyrexia
	Dysphoric moods	Agitated depression; Depressed mood; Depression; Dysphoria; and Depressive symptom

Note: PTs related to the DSM-IV criteria for opioid withdrawal, other than fever and dysphoric moods, are included in the table under another heading or headings: MedDRA SMQ, mHS, COWS, SOWS, OOWS, or FDA Clinical Review of alvimopan

<sup>a</sup> In the "Additional opioid withdrawal and cardiovascular (CV) risk assessments" document in Module 5.3.5.3, gastrointestinal adverse events were excluded because of the potential to confound the assessment of opioid withdrawal. These events may be associated with the intended action of naloxegol and in the absence of other events potentially related to withdrawal, they do not constitute opioid withdrawal per se. They are included in the assessments presented in this document. Note that abdominal pain and abdominal pain lower were not in the original table but have been added to be as comprehensive as possible.

<sup>b</sup> Terms from the FDA Clinical Review of alvimopan are included here only if they are not already included in the list.

<sup>c</sup> Terms related to the DSM-IV criteria for opioid withdrawal were inadvertently omitted from the comprehensive list used in "Additional opioid withdrawal and cardiovascular (CV) risk assessments" document in Module 5.3.5.3. They are included in the assessments presented in this document. Terms based on the DSM-IV criteria are included here only if they are not already included in the list.

DSM Diagnostic and Statistical Manual of Mental Disorders; MedDRA Medical Dictionary for Regulatory Activities; NA Not applicable; SMQ Standardized MedDRA Query.

(10/8/13 Document, p. 38-40)



## Appendix C: AstraZeneca's Rationale for the Determination of Clinical Relevance for Cut-Offs Used for Opioid Dose, NRs and mHS

### This information is taken verbatim from the Applicant's submission:

AstraZeneca recognized that patients may have minor fluctuations from day-to-day in NRS pain score, number of doses of breakthrough opioid pain medication, and minor changes in individual signs in the modified Himmelsbach scale which may not be viewed as clinically significant. As such, an attempt to identify threshold values reflecting clinically relevant changes was made. In response to the 19 December 2013 clarification request regarding determination of clinical relevance for cut-offs used for opioid dose, NRS and mHS, AstraZeneca considers these clinically relevant for the following reasons:

- **≥10% or ≥30% increase from baseline in mean weekly opioid dose during the study:** The ≥30% increase in opioid dose was selected, as it was used as a proxy in other studies to identify significant increases in opioid dose. It also corresponds with the recommendation by Dworkin et al 2005 (reference provided in the original NDA submission) as the 30% increase in pain being clinically significant. As an example, in the Phase III studies, the mean baseline opioid dose was about 100 morphine equivalent units (meu), and thus a 10% increase in dose corresponds to an approximately 10 meu increase, and a 30% increase in dose corresponds to an approximately 30 meu increase. The selection of 30% increase in pain being clinically significant was further substantiated via consultation with external experts. In addition, we also provided the analysis for the ≥10%, a more conservative cut-off.
- **≥2 point increase in Numeric Rating Scale:** At an individual patient level, an increase of ≥2 in NRS score relative to baseline was selected based on Dworkin et al 2005 and further substantiated via consultation with external experts as an appropriate cut-off for identifying potentially clinically important increases in pain. The ≥2 point increase in Numeric Rating Scale cut-off was used for both average pain scores and worst pain scores measured in the studies. At the study level, a difference of 1-point in the least-square mean NRS pain score versus placebo was pre-defined in the SAP as the smallest difference which would be considered clinically relevant. See also Section 1.1.4.1 in Module 2.7.4 Summary of Clinical Safety.
- **≥3 point increase in mHS:** This threshold was chosen by AstraZeneca because there was no published or established threshold for a clinically important change in the total mHS. As an example, in the naloxegol program, most patients had scores of 0 on a 0-24 scale at baseline, corresponding to a complete absence of signs included in the scale. An increase of 3 points could represent going from "not present" to severe for an individual sign OR for 3 separate signs going from not present to mild. The change of ≥3 was considered, in consultation with external subject matter experts, to be an appropriate cut-off for identifying patients with potential withdrawal symptoms. See also Section 4.4.3.1 in Module 2.7.4 Summary of Clinical Safety. In addition, the "2 week window" between the initial reported date of the first and temporally last preferred terms occurring was chosen to ensure all patients with potential opioid withdrawal syndrome cluster of symptoms were identified. Based on the definition of opioid withdrawal, characterized by ≥3 separate symptoms occurring together, the symptoms of withdrawal would be expected to overlap temporally and emerge either instantaneously (antagonist administration) or evolve over few days (opioid cessation), American Psychiatric Association 2013 as documented in DSM-5. As stated in the *Response to Query*

*Regarding Opioid Withdrawal and CV Risk Assessment, dated 8 October 2013* criteria used to define these potential indicators of opioid withdrawal syndrome were chosen, in consultation with external experts in opioid withdrawal, as clinically relevant criteria for identifying patients who may have experienced generalized opioid withdrawal.

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/s/  
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ELIZABETH M KILGORE  
01/29/2014

ELLEN W FIELDS  
01/30/2014

SHARON H HERTZ  
01/30/2014

BOB A RAPPAPORT  
01/30/2014