CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204760Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 16, 2014
From	Anil Rajpal, MD, MPH, Clinical Team Leader Division of Gastroenterology and Inborn Errors Products
Subject	Cross-Discipline Team Leader Review
NDA/ BLA Supplement #	NDA 204760
Applicant	Astra Zeneca
Date of Submission	September 16, 2013
PDUFA Goal Date	September 16, 2014
Proprietary Name / Established (USAN) names	Movantik / naloxegol
Dosage forms / Strength	Tablets (12.5 mg and 25 mg)
Proposed Indication	opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain
Recommended Action:	Approval

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1 Introduction

This submission, received September 16, 2013, is the initial New Drug Application (NDA) for Movantik (naloxegol). When administered at the recommended dose levels, naloxegol functions as a peripherally-acting mu-opioid receptor antagonist in tissues such as the gastrointestinal tract, thereby decreasing the constipating effects of opioids.

The Applicant proposes the following indication for opioid-induced constipation (OIC):

- "… for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain."

2 Background

2.1 Opioid-Induced Constipation

Opioid-induced constipation (OIC) is a frequent complication of chronic opioid use. Opioids tend to inhibit gastric emptying, increase absorption and decrease secretion in both the large and small intestines, delay small intestinal and colonic transit, and increase internal anal sphincter tone. Some of the signs and symptoms related to this effect are constipation, dry hard stools, incomplete evacuation, straining at stool and abdominal distension.

2.2 Current Treatments

Currently, there are two approved drugs for the treatment of OIC, Amitiza (lubiprostone) and Relistor (methylnaltrexone). Amitiza, a chloride channel activator, was approved in April 2013 for an OIC indication in adults with chronic non-cancer pain. Relistor, an opioid antagonist, was approved in April 2008 for an OIC indication in patients who are receiving palliative care.

In addition, there exists a wide variety of over-the-counter and prescription products that are used to treat constipation including stool softeners (docusate), bulk-forming laxatives (psyllium, methylcellulose, polycarbophil), stimulant laxatives (bisacodyl, senna, and castor oil), saline osmotic laxatives (sodium phosphate, magnesium citrate, and magnesium hydroxide), osmotic laxatives (lactulose and sorbitol), lubricants (mineral oil, glycerin), and other osmotic agents like polyethylene glycol (PEG)-3350 (with and without electrolytes).

2.3 Regulatory History - Naloxegol

The table below provides a summary of the pertinent regulatory activity of naloxegol prior to submission of the NDA.

Table 1. Pertinent Regulatory History of Naloxegol (NDA 204760)*

Date	Event
October 22, 2007	Initial IND submission for naloxegol
January 10, 2008	Advice Letter: ▪ Clinical Pharmacology comments were sent notifying the sponsor that information such as the following may be needed with their NDA: ➢ Drug-drug interactions ➢ QT prolongation potential ➢ PK characterization in special populations (e.g, hepatic impairment, renal impairment, elderly patients) ➢ Bridging study (if formulation used in the clinical trials differs from the To-Be-Marketed Product (TBMP)) ➢ Exposure-response relationship for efficacy and adverse events (AEs)
May 6, 2009	Advice Letter: ▪ Pharmacology/Toxicology comments were sent providing recommendations for the dosing regimens for a mouse carcinogenicity study.
January 26, 2010	End of Phase 2 Meeting: ▪ Key Clinical Pharmacology recommendations to the sponsor included the following: ➢ In vitro and in vivo data and rationale for conducting or not conducting certain drug interaction studies should be provided in the NDA submission. ➢ Exposure-response analysis for efficacy and AEs should be conducted. ▪ Key Clinical recommendations included the following: ➢ The study population definition should use a criterion of < 3 spontaneous bowel movements (SBMs)/week. ➢ The Division stated the sponsor's proposal to perform stratified analyses [using definitions of laxative adequate responders (LAR), laxative inadequate responders (LIR), and laxative unknown responders (LUR)] was reasonable; however, objective and rigorous definitions for classification of these subgroups would be needed for statements in the Clinical Studies section of labeling. See additional discussion below. ➢ The primary endpoint should be based on a responder analysis rather than change in bowel frequency; the Division agreed that meeting criteria for 3 out of 4 weeks of absolute number of ≥ 3 SBM/week and increase in ≥1SBM/week was an acceptable primary endpoint definition. ➢ Because there have been reports of bowel perforation in patients administered opioid antagonists for OIC, there should be special attention to the potential for this AE.

Date	Event
April 27, 2010	Advice Letter: ▪ Key recommendations from the Controlled Substances Staff (CSS) sent to the sponsor included the following: ➢ As a derivative of thebaine, naloxegol is a Schedule II controlled substance under the Federal Controlled Substances Act (CSA); the sponsor should consult the Drug Enforcement Administration (DEA) to ensure that they are in compliance with the current regulations that apply to Schedule II controlled substances, and to determine the procedures that need to be followed for possible rescheduling or decontrol of naloxegol from the CSA, providing that criteria for rescheduling or decontrol can be satisfied. ➢ The Sponsor needs to assess possible opioid agonist effects of naloxegol. ➢ Nonclinical studies to evaluate abuse potential and dependence-producing properties should be conducted including in vitro studies to characterize functional effects of naloxegol, dose-response study of analgesic and gastrointestinal transit effects of naloxegol, drug discrimination study evaluating potential stimulus generalization to morphine, self-administration study to evaluate the possible reinforcing effects of naloxegol, and a physical dependence study evaluating for spontaneous and precipitated withdrawal following long-term exposure to naloxegol. ➢ Should the nonclinical studies suggest that naloxegol has opioid agonist or partial agonist activity, a human abuse potential study will be required to support possible rescheduling. ➢ The sponsor was requested to provide data from clinical studies related to abuse liability assessment including diversion and overdose potential is needed; specific requests included AEs from Phase 3 studies and dose-escalation/dose-ranging studies, and narratives of abuse/overuse/overdose or lost/stolen/missing/unaccounted for drug.

Date	Event
June 23, 2011	Type C Meeting: ▪ Key Clinical recommendations for the proposed OIC in patients with non-cancer pain development program included the following: ➢ The Division did not agree with the sponsor's proposed baseline laxative response definitions (LIR, LAR, LUR) which are based on laxative use over the past 2 weeks, number of days laxatives were used, severity of OIC symptoms, and side effects from the laxative. The Division especially questioned the relevance of side effects to a range of different types of laxatives in the definitions. The sponsor agreed to reconsider these definitions (particularly the LIR definition), and to further justify or reconsider the appropriateness of a 2-week recall period. See additional discussion below. ➢ The Division advised the sponsor that our current standard for OIC is to demonstrate efficacy over 12 weeks, and that therefore, we expect that the sponsor's key secondary endpoint (12-week responder analysis) will also demonstrate statistical significance; the Division also recommended that the sponsor modify their secondary endpoint to also require that response must not only occur in 9 out of 12 weeks, but also must include 3 of the last 4 weeks for a patient to be considered a responder. See additional discussion below.
October 18, 2011	Type C Meeting (included CSS): ▪ Key recommendations included the following: ▪ A human abuse liability study is not needed (based on information provided), but this determination may be re-evaluated if after reviewing all studies a signal indicative of abuse potential is detected. ▪ FDA agreed with the sponsor's approach to submit the petition to decontrol naloxegol to the DEA.
January 24, 2012	Type C meeting: ▪ Key recommendations included the following: ▪ The Sponsor should conduct qualitative research to address concerns about the stool symptom screener instrument including the following: – Evidence to support content validity – Justification of the two-week recall period ▪ The Sponsor should perform sensitivity analyses including: – Assessment of treatment effect in LIR and non-LIR subgroups – Unadjusted analysis of overall ITT population See additional discussion below.
March 14, 2012	TQT study submitted

Date	Event
October 8, 2012[#]	Preliminary Comments for Type C Pre-NDA Meeting:[#] ▪ In addition to a number of content and format recommendations, the Division communicated the following concerns: ➢ The effects of opioid withdrawal on the autonomic nervous system, including changes in hemodynamic parameters, are known to increase the risk of cardiovascular AEs. ➢ Signs and symptoms consistent with opioid withdrawal have been reported in patients exposed to this class of drugs. ➢ Another peripheral μ-opioid antagonist (Entereg) has been associated with a higher number of ischemic cardiovascular events compared to placebo in a 12-month trial in patients with OIC.[†] ▪ The Division notified the sponsor that we would like to discuss the following at the next Pre-NDA meeting: ➢ Evaluation of the incidence of the signs/symptoms of opioid withdrawal including cardiovascular events. ➢ Cardiovascular events of particular interest include myocardial infarction, cerebrovascular accident, and death; we are also interested in cases of chest pain. ➢ In patients with cardiovascular events and/or chest pain, narratives should be provided that include information on any withdrawal symptoms. ➢ Evaluation of potential risk factors for the development of opioid withdrawal, including evaluation of a PK/PD relationship for withdrawal, impact of concomitant opioid dose, and other elements deemed important to assess these risks. ▪ The Division advised the sponsor of the possible need for a randomized controlled clinical trial designed to rule out a specific upper bound of a hazard ratio for major adverse cardiovascular events.
October 29, 2012	The sponsor submitted a Proposed Pediatric Study Request (PPSR).
January 23, 2013	Type C Meeting ▪ This meeting focused on a possible (b) (4) [redacted] ▪ The Division advised the sponsor of the following: ➢ The sponsor would need to (b) (4) [redacted] ➢ The Division's current position is that the indication would specifically state the population studied (b) (4) [redacted] OIC in patients with non-cancer pain) if substantial evidence of efficacy was provided for that population.

Date	Event
April 23, 2013	Type C Pre-NDA meeting: ▪ Discussion related to concern about risk of cardiovascular (CV) events included the following: ➢ Further discussion of the study of another drug in this class (Entereg) with a higher number of ischemic cardiovascular events compared to placebo in a 12-month trial in patients with OIC.† ➢ Withdrawal events were reported for another drug in this class (Relistor). ➢ Opioid withdrawal with precipitation of hemodynamic effects may be the most likely mechanism to explain the possible increase in CV risk, although we cannot exclude other mechanisms. ➢ Additional post-hoc analyses/presentations of the naloxegol data were requested from the sponsor pertaining to: – possible association with opioid withdrawal (including weekly average opioid dose, weekly average pain scores, and assessments of withdrawal signs/symptoms) – possible association of opioid withdrawal with CV AE's (including narratives/tables summarizing type and timing of CV AE's and opioid withdrawal AE's relative to dosing in patients experiencing both types of AE's)
August 9, 2013	Advice/Information Request Letter: ▪ Comments were sent to the sponsor providing: ➢ Additional details of request for post hoc analyses/presentations regarding opioid withdrawal syndrome and cardiovascular (CV) risk assessments – most notably, the sponsor was requested to not exclude gastrointestinal AE's from analyses of opioid withdrawal data.
September 16, 2013	NDA 204,760 submitted

*IND 78781
#Preliminary Comments sent October 8, 2012 (the meeting scheduled for October 10, 2012 was cancelled).
† Meeting Materials for Gastrointestinal Drugs Advisory Committee for Entereg (alvimopan) dated January 23, 2008 available at the following link: http://www.fda.gov/ohrms/dockets/ac/cder08.html#gdac

In the clinical protocols (Study 004 and Study 005), the assessment of laxative responsiveness status was initially based on the following four assessments:

(i) Laxative use over the past 2 weeks (yes/no)
(ii) At least 4 days of laxative use over the past 2 weeks (yes/no)
(iii) At least 1 of the 4 symptoms questions is scored moderate, severe, or very severe (yes/no)
(iv) Laxative side effects (yes/no)

The clinical protocols (Study 004 and Study 005) were amended (on November 2, 2011) so that the question regarding laxative side effects would no longer be used to determine laxative responsiveness status; patients were reclassified based on the revised criteria using their electronic Case Report Form (eCRF) data for the purpose of all data analyses. (See Appendix 1 Baseline Laxative Response Status Questionnaire; and Appendix 2 Definitions of LIR, LAR, and LUR.)

The clinical protocols (Study 004 and Study 005) were amended (on November 2, 2011) so that the primary efficacy endpoint was changed to response to study drug during Weeks 1 to 12 (instead of Weeks 1 to 4); response during Weeks 1 to 4 was moved to an additional secondary efficacy variable (see definitions of the primary and secondary endpoints in Section 7.3 of this CDTL Review).

See the Clinical Review by Aisha Peterson Johnson for additional details of the naloxegol regulatory history.

2.4 Current Application

The application was submitted on September 16, 2013. It was classified as a Standard submission with a PDUFA deadline of September 16, 2014.

2.4.1 Advisory Committee

There was not a specific matters Advisory Committee meeting for this application.

However, on June 11-12, 2014, there was a general matters meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) to discuss:

- the potential cardiovascular (CV) 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 OIC in patients taking opioids for chronic pain.

In addition to Movantik (naloxegol), the specific products discussed at the AADPAC included Entereg (alvimopan) and Relistor (methylnaltrexone).

The issues and the corresponding recommendations were as follows:

- CV safety signal: The committee was split on whether the totality of the data (for the class of peripherally active mu opioid receptor antagonists (PAMORAs)) suggest a CV safety signal. Among those that did believe there was a signal, there was consensus that the signal was weak (but could not be ignored); their concern was primarily driven by the Entereg 12-month controlled trial. There was consensus that there is not sufficient data to implicate specific biologic mechanisms for the signal.
- Feasibility of conducting a CV outcomes trial: There was consensus that conducting a CV outcomes trial is feasible, but there are challenges that include anticipated high dropout rates and large sample sizes required (if not enriched with patients at high CV risk); the committee recommended a compressed time frame may eliminate some of the challenges. A few committee members considered a 2-fold increase in risk to be necessary to be excluded in a CV outcomes trial.
- CV outcomes trial requirement (all PAMORAs vs. specific PAMORAs vs. no requirement): Of the 24 total members, seven (7) voted that CV outcomes trials should be required for *all* PAMORAs, five (5) voted that they should be required for *specific* PAMORAs, and 12 voted that they should *not* be required for PAMORAs. However, five (5) members of the 12 who voted that CV outcomes trials should be required for *all* or *specific* PAMORAs explained that they had intended to vote that CV outcomes trials

should not be required for PAMORAs, but thought the question was asking about observational studies (rather than randomized controlled trials). Of the seven (7) members who did intend to vote that CV outcomes trials should be required for *all* or *specific* PAMORAs, the majority would like to see a controlled clinical trial for Entereg.

- Requirement for CV outcomes trial (pre-approval vs. post-marketing vs. combination): Summarized along with the next item below.
- Requirement for longer term pre-approval controlled clinical trial (if a CV outcomes trial is not required): The consensus of the committee was that pre-approval general safety trials should be of sufficient duration to assess long term outcomes (e.g., 12 months). Also, post-marketing observational studies may also be conducted; appropriate measures should be taken to enrich them with high CV risk patients.

2.4.2 Review Documents

The relevant review disciplines have all written review documents.

The primary review documents relied upon were the following:

(1) Clinical Review by Aisha Peterson Johnson dated May 11, 2014, and Addendum (Clinical Investigator Financial Disclosure Review Template) dated September 9, 2014
(2) Statistics Review by Wen-Jen Chen, dated June 20, 2014
(3) ONDQA Biopharmaceutics Review by Kareen Riviere, dated May 16, 2014, and Addendum dated July 8, 2014
(4) Clinical Pharmacology Review by Sandhya Apparaju, dated May 14, 2014, and Addendum by Elizabeth Shang, dated September 5, 2014
(5) Pharmacology/Toxicology Review by Yuk-Chow Ng, dated May 15, 2014 and Secondary Pharmacology/Toxicology Review by David Joseph, dated June 5, 2014.
(6) Quality Review by Bogdan Kurtyka, dated June 12, 2014, and Addendum dated September 12, 2014
(7) Microbiology Quality Review by Stephen Langille, dated June 6, 2014
(8) Consult Reviews:
    (a) Division of Cardiovascular and Renal Products (DCRP) Consult Review (Naloxegol) by Preston Dunnmon dated March 10, 2014 and DCRP Review (CV Safety of Opioid Receptor Antagonists) dated April 15, 2014
    (b) Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) Consult Review by Elizabeth Kilgore dated January 30, 2014
    (c) QT Interdisciplinary Review Team (QT-IRT) Consult Review by Janice Brodsky, dated July 9, 2013 (filed under IND 78,781)
    (d) Controlled Substance Staff (CSS) Review by Katherine Bonson, dated June 3, 2014
    (e) Pediatric and Maternal Health Staff (PMHS) Consult Review (Pediatric Review) by Ethan Hausman, dated April 4, 2014
    (f) Pediatric and Maternal Health Staff (PMHS) Consult Review (Maternal Health Review) by Carrie Ceresa, dated May 14, 2014
    (g) OSI Clinical Inspection Summary by Susan Leibenhaut, dated May 7, 2014
    (h) Risk Evaluation and Mitigation Strategy (REMS) Review by Nyedra Booker, dated June 10, 2014

(i) Division of Neurology Products Consult Review by Heather Fitter dated September 9, 2014
(j) Qualitative Research Study Consult Review by Shelly Harris dated August 18, 2014

(9) Labeling Reviews:
(a) Division of Medication Error Prevention and Analysis (DMEPA) Label, Labeling and Packaging Review by Monica Calderon, dated November 7, 2013
(b) DMEPA Proprietary Name Review by Lisa Khosla, dated October 31, 2013
(c) Office of Professional Drug Promotion (OPDP) Review of Package Insert (PI) and Medication Guide (MG) by Meeta Patel, dated August 20, 2014
(d) Division of Medical Policy Programs (DMPP) Patient Labeling Review by Matthew Barlow, dated August 18, 2014

The reviews should be consulted for more specific details of the current application.

3 CMC

The reader is referred to the Quality Review by Bogdan Kurtyka, dated June 12, 2014, and the Microbiology Quality Review by Stephen Langille, dated June 6, 2014.

3.1 Drug Substance (DS)

Overview:
The Quality Reviewer noted the following regarding the drug substance (DS):

- The proposed drug substance naloxegol oxalate is a new molecular entity.
- It is a white to off-white (b) (4) powder, highly soluble in water in pH range 1 to 7.5.
- It is manufactured in (b) (4).

Impurities:

- The sponsor proposed to control multiple potential and observed impurities through in-process controls and specification. The sponsor proposed not to control some impurities and polymorphic forms.
- *Quality Reviewer's Conclusion: Based on the knowledge of manufacturing process and batch data obtained so far, the sponsor demonstrated that the risk of such impurities being present in drug substance is negligible. This approach is acceptable.*

Organic and Genotoxic Impurities:

- The drug substance specification includes description, identification, assay, organic impurities, a specified genotoxic impurity (b) (4) and (b) (4).
- *Quality Reviewer's Conclusion: The limits for organic and genotoxic impurities were found adequate by the pharmacology/toxicology reviewer (see Nonclinical Review) and the specification is deemed satisfactory.*

Container System:

- Drug substance is packaged in (b) (4) (b) (4)

- [redacted]
- *Quality Reviewer's Conclusion: The container system is deemed satisfactory.*

24-Month Re-Test Period:

- The sponsor provided the results of up to 12 months long-term stability studies, and proposed a [redacted] retest period.
- *Quality Reviewer's Conclusion: The [redacted] retest period is justified by the submitted data.*

3.2 Drug Product (DP)

Overview:

- The drug product is an immediate release tablet.
- The inactive ingredients of the formulation are commonly used in oral drug products.
- The drug product is manufactured by [redacted].
- The sponsor proposed its establishment in Södertälje, Sweden as the manufacturing site.

Drug Product Specification:

- The drug product specification includes: description, identification, assays of drug substance [redacted], degradation products, dissolution, uniformity of dosage units, and [redacted]
- [redacted] content is tested on annual bases.
- *Quality Reviewer's Conclusion: The test attributes, acceptance criteria, analytical methods and their validation are deemed satisfactory.*

Container Closure Systems:

- Three container closure systems are proposed: HDPE bottle, aluminum/aluminum blister, and aluminum bag for bulk storage.
- *Quality Reviewer's Conclusion: The information included in the application demonstrates that the proposed container/closure systems are suitable for drug product.*

Stability:

- The sponsor provided the results of up to 12 months long-term stability studies, and proposed a 24-month expiration dating period for all packaging presentations under the controlled room temperature conditions.
- *Quality Reviewer's Conclusion: The requested expiration dating periods are granted for all the packaging configurations.*

Environmental Assessment:

- The applicant claimed categorical exclusion from the Environmental Assessment based on 21CFR 25.31(a) or (b).

- *Quality Reviewer's Comment: The review of the Environmental Assessment was documented on 18-Jul-2014, with the determination that the application qualifies for the categorical exclusion claimed by the sponsor.*

Method Validation:

- Method validation request has been sent to DPA for assay and selected impurities procedures.
- *Quality Reviewer's Comment: On 25-Aug-2014, Method Validation was documented for the following methods: (1) (b) (4) test by LC; (2) Assay by UHPLC; (3) Assay by HPLC; and (4) (b) (4) by LC. The report found all methods acceptable for the quality control urposes.*

3.3 Product Microbiology

Overview:

- The product is a coated tablet (b) (4) .

Microbial Limits Testing at Product Release:

- The applicant has asked for a waiver of microbial limits testing at product release because there is little microbiological risk associated with this product. The Applicant's justification is that input material, packaging material, and the manufacturing process are controlled to ensure the microbiological quality of the drug product; and high risk excipients such as magnesium stearate and microcrystalline cellulose are monitored for microbiological quality as specified by their compendial monographs.
- *Quality Microbiology Reviewer's Conclusion: The applicant has provided an adequate justification for not having a microbial limit specification.*

Microbial Limits Testing as Part of the Stability Protocol:

- The applicant will conduct microbial limits testing as part of the stability protocol (i.e., the applicant will perform microbial limits testing at the initial stability testing time point).
- The results of microbial limits testing on a number of stability batches were provided.
- *Quality Microbiology Reviewer's Comment: The stability commitment and results regarding microbial limits testing are satisfactory.*

3.4 Recommendation

Quality:

The Quality Reviewer concluded that the applicant has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. The Office of Compliance issued an overall "Acceptable" recommendation for establishments; this is documented in the Addendum to the Quality Review dated September 12, 2014.

The Quality Reviewer concluded that, from the ONDQA perspective, this NDA is recommended for approval with an expiration dating period of 24-month for all packaging configurations.

Quality Microbiology:

An Approval Action is the recommendation by the Quality Microbiology discipline.

4 Nonclinical Pharmacology/Toxicology

The reader is referred to the Nonclinical Pharmacology/Toxicology Review by Yuk-Chow Ng, dated May 15, 2014, for complete information.

4.1 Overview

The Nonclinical Reviewer noted that naloxegol
- is a PEGylated derivative of naloxone;
- acts as an antagonist at the μ- and δ-opioid receptors, and is a weak partial agonist at κ-opioid receptors, with the highest binding affinity at μ-opioid receptors;
- is a substrate of the P-glycoprotein (P-gp) transporter, which reduces its ability to cross the blood-brain barrier;
- thus, naloxegol functions as a μ-opioid receptor antagonist in the gastrointestinal tract with reduced CNS effects.

4.2 Issues

The Nonclinical Reviewer focused on the following:
A. Potential CNS Effects
B. Carcinogenicity Study Results
C. Potential for the formation of EG, DEG and metabolites:

Each of these issues and the Nonclinical Reviewer's conclusion are summarized below.

A. Potential CNS Effects

The Nonclinical Reviewer noted the following:
- Pharmacokinetic studies demonstrated that distribution of naloxegol-related radioactivity into the rat brain and spinal cord was low compared to other tissues, suggesting relatively low CNS penetration of naloxegol in rats.
- A single time-point brain perfusion study in rats showed that the penetration of naloxegol was approximately 15 times slower than that of naloxone.

- However, in pharmacology studies, naloxegol produced a dose-dependent reduction in the centrally-mediated effects of morphine at plasma levels 15- to 112-times the human Cmax at the Maximum Recommended Human Dose (MRHD).
- In addition, a comparison of the effects of naloxegol and naloxone on GI transit and analgesia showed that there was only a minimal separation between the dose-response curves for the peripheral and central antagonist effects for naloxegol; there was no separation between the central and peripheral antagonist effects for naloxone.

The Nonclinical Reviewer concluded that the results from these nonclinical studies suggested that naloxegol at high doses has considerable CNS effects.

B. Carcinogenicity Study Results

The Nonclinical Reviewer noted the following:

- In the 2-year oral carcinogenicity study in rats, a dose-dependent increase in the incidence of benign interstitial (Leydig) cell adenoma of the testis was noted (statistically significant in trend test). A pair-wise comparison showed a statistically significant increase in the incidence of Leydig cell adenoma in the 400 mg/kg/day males. In addition, there was a significant increase in the incidence of Leydig cell hyperplasia in the 120 mg/kg/day males.
- The Sponsor examined the possibility that the naloxegol-induced increase in the incidence of benign Leydig cell tumors in rats was due to chronic exposure to elevated levels of plasma luteinizing hormone. It was demonstrated that plasma LH increased significantly after intravenous infusion of naloxegol. Plasma levels of testosterone also increased, but to a lesser extent.

The Nonclinical Reviewer concluded that the results support the proposal that the observed drug-related increase in the incidence of benign Leydig cell adenoma and hyperplasia in rats was likely due to naloxegol-induced centrally mediated hormonal changes (i.e. elevated LH levels). The Nonclinical Reviewer noted that such a mechanism in tumor formation is common in rats. Given that the drug-induced increase in Leydig cell adenoma incidence was statistically significant only at 400 mg/kg/day (818 times the human AUC at the MHRD), the Nonclinical Reviewer concluded that this effect is unlikely to be relevant to humans.

C. Potential for the formation of EG, DEG and metabolites

The Nonclinical Reviewer noted the following:

- One of the metabolic pathways for naloxegol involves sequential shortening of the PEG chain moiety. As a result, ethylene glycol (EG) and diethylene glycol (DEG) are by-products of naloxegol metabolism. EG and DEG are known toxicants in animals and humans. Thus, potential exposure to EG and DEG in naloxegol-treated patients needs to be evaluated. An Information Request was sent to the sponsor from the Clinical Pharmacology team stating: "The proposed metabolism of naloxegol, a PEGylated product, is described as formation of partially shortened PEG chain products. Address the potential for the formation and systemic accumulation of ethylene glycol, diethylene glycol as well as their toxic metabolites as by-products of this metabolism."
- In their response, the Sponsor presented two assessments of the potential exposure to EG and DEG.

- In the first assessment, the sponsor assumed the entire 16.6 mg of PEG in a naloxegol oxalate tablet was fully metabolized to EG, DEG, or oxalic acid. The maximum theoretical doses for EG, DEG, and oxalic acid was 0.332, 0.244, and 0.483 mg/kg, respectively. The Sponsor indicated that these levels are significantly lower than the EPA Reference Doses of 2 and 1.6 mg/kg/day for EG and DEG, respectively, and are, therefore, considered safe. However, the cited Reference Doses are significantly higher than the Permitted Daily Exposure (PDE) of 6.2 mg per day for EG, as stated in ICH guidance Q3C.
- In the second assessment, potential exposure to EG and DEG was calculated based on metabolic profiles obtained from the clinical studies. Based on the relative abundance of the detected metabolites, which have varying PEG lengths, an administered naloxegol dose of 25 mg, or 38.3 µmoles, may potentially release 27.3 µmoles (1.7 mg) of EG or 10.8 µmoles (1.14 mg) of DEG. To account for the 12% of the metabolites in the excreta that could not be identified in the clinical studies, the Sponsor's worst case scenario assumed that all 7 EG subunits in the PEG moiety were released as EG. This produces an additional 32.2 µmoles (2.0 mg) per day of EG for a possible total exposure of 3.7 mg EG per day. Under similar assumptions, a possible daily exposure of 2.6 mg DEG was estimated. These levels are less than the PDE of 6.2 mg per day for EG. It is noted that diethylene glycol is considered to have similar toxicity to that observed for ethylene glycol.

The Nonclinical Reviewer considers the estimation based on metabolic profiles to represent the most realistic assessment. The Nonclinical Reviewer concluded that the Sponsor's assessments, taken together, provide a reasonable assurance of safety for the potential exposure to EG and DEG as metabolites of naloxegol.

The Nonclinical Reviewer recommends an Approval action based on the non-clinical review of the information submitted in the NDA. The Nonclinical Reviewer additionally recommends that the proposed labeling be revised to include the revisions shown below.

4.3 Recommended Label Revisions

The recommended label revisions from the Nonclinical Reviewer are summarized below by section.

A. Section 8.1 of Label (Pregnancy)

Wording in the Pregnancy section should be revised to:

"**8.1 Pregnancy**

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with Movantik in pregnant women. The use of Movantik during pregnancy may precipitate opioid withdrawal in a fetus

due to the undeveloped fetal blood brain barrier. No effects on embryo-fetal development were observed following administration of naloxegol in pregnant rats during the period of organogenesis at doses up to 1452 times the human AUC (area under the curve) at the maximum recommended human dose. No effects on embryo-fetal development were observed following administration of naloxegol in pregnant rabbits during the period of organogenesis at doses up to 409 times the human AUC at the maximum recommended human dose. Movantik should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

Oral administration of up to 750 mg/kg/day naloxegol in rats (1452 times the human AUC at the maximum recommended human dose) and 450 mg/kg/day naloxegol in rabbits (409 times the human AUC at the maximum recommended human dose) during the period of organogenesis produced no adverse effects on embryo-fetal development. Oral administration of up to 500 mg/kg/day in rats (195 times the maximum recommended human dose based on body surface area) during the period of organogenesis through lactation produced no adverse effects on parturition or the offspring."

B. Section 12.1 of Label (Mechanism of Action)

Wording in the Mechanism of Action section should be revised to:

"12.1 Mechanism of Action

(b) (4)

CDTL Comment: The Nonclinical Reviewer and Team Leader have proposed revised wording for Section 12.1 of the label since the time of the Nonclinical Review; the final wording agreed upon with the Applicant is provided in Section 12.3 of this CDTL Review.

C. Section 13.1 of Label (Carcinogenesis, Mutagenesis, and Impairment of Fertility)

Wording in the Carcinogenesis, Mutagenesis, and Impairment of Fertility section should be revised to:

"**13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility**

Carcinogenesis

In a 104-week carcinogenicity study in CD-1 mice, naloxegol was not tumorigenic at oral doses up to 100 mg/kg/day in males and 160 mg/kg/day in females (43 and 27 times the human AUC at the maximum recommended human dose for male and female mice, respectively). In a carcinogenicity study in Sprague-Dawley rats, naloxegol was administered orally at doses of 40, 120, and 400 mg/kg/day for at least 93 weeks. Naloxegol did not cause an increase in tumors in female rats. In male rats, an increase in interstitial (Leydig) cell adenomas in testes was observed at 400 mg/kg/day (818 times the human AUC at the maximum recommended human dose). The no observed effect level for increased tumor incidence was 120 mg/kg/day in male and 400 mg/kg/day in female rats (246 and 1030 times the human AUC at the maximum recommended human dose for male and female rats, respectively. The Leydig cell neoplasms in rats are considered to be unlikely relevant to humans.

Mutagenesis

Naloxegol was not genotoxic in the *in vitro* bacterial reverse mutation (Ames)assay, mouse lymphoma $TK^{+/-}$ mutation assay, or the *in vivo* mouse micronucleus assay.

Impairment of Fertility

Naloxegol was found to have no effect on fertility or reproductive performance in male and female rats at oral doses up to 1000 mg/kg/day (greater than 1000 times the human AUC at the maximum recommended human dose)."

D. Section 13.2 of Label (Animal Toxicology and/or Pharmacology)

The Nonclinical Reviewer concluded that (b) (4) is not required and should be deleted.

4.4 Recommendation

An Approval Action is the recommendation by the Nonclinical Pharmacology/Toxicology discipline provided the labeling revisions described above are made.

5 Clinical Pharmacology/Biopharmaceutics

The reader is referred to the Biopharmaceutics Review by Kareen Riviere, and the Clinical Pharmacology Review by Sandhya Apparaju, for complete information. The following is summarized from the Biopharmaceutics and Clinical Pharmacology Reviews.

5.1 Issues

5.1.1 Biopharmaceutics

The Biopharmaceutics review focused on the following:

A. the BE data bridging the Phase 3 formulation and the commercial formulation,
B. the proposed dissolution methodology,
C. the proposed dissolution acceptance criterion,
D. the dissolution data supporting a biowaiver for the 12.5 mg strength tablet, and
E. the dissolution data bridging the tablets containing drug substance with different (b) (4)
F. the dissolution data supporting formulation flexibility.

Each of these issues and the Biopharmaceutics Reviewer's conclusion are summarized below.

A. BE Study Bridging the Phase 3 and Commercial Formulations

The Applicant conducted an *in vivo* BE Study D3820C00018 with the primary objective to demonstrate bioequivalence between the following two formulations:

- commercial naloxegol film-coated tablet 25 mg (as naloxegol oxalate) and
- naloxegol film coated tablet 25 mg (as free base) used in the Phase 3 study

The BE study demonstrated that the 90% CI for the test/reference ratio for Cmax and AUC fell within FDA's BE criterion of 80-125%. Thus, the Biopharmaceutics Reviewer concluded that the commercial formulation is bioequivalent to the Phase 3 formulation.

In the Addendum to the Biopharmaceutics Review, the Biopharmaceutics Reviewer cited the OSI inspection report for Study D3820C00018 (dated June 27, 2014) which stated "The data generated by Quintiles Drug Research Unit (clinical site) and (b) (4) (analytical site) were found to be reliable. Therefore, these reviewers recommend that data generated at these sites should be accepted for Agency review."

B. Dissolution Method

The proposed dissolution method shown below was deemed acceptable by the Biopharmaeutics Reviewer:

- USP Apparatus: 2
- Rotation Speed: 50 rpm
- Media Volume: 500 mL
- Temp: 37 °C
- Medium: 0.1 M HCl buffer

C. Dissolution Acceptance Criterion

The proposed acceptance criterion of Q = (b) (4)% at 30 minutes was deemed acceptable by the Biopharmaeutics Reviewer.

D. Biowaiver for 12.5 mg Strength

The Applicant provided multi-point dissolution profile data comparing the 12.5 mg and 25 mg strengths in pH 1.2, pH 4.5, and pH 6.8 dissolution media. The Biopharmaceutics Reviewer concluded that these data demonstrate that the dissolution profiles of the two strengths are similar in all three media; thus, a biowaiver is granted for the 12.5 mg strength.

E. Dissolution Data Bridging the Tablets Containing Drug Substance Manufactured with (b) (4)

The Applicant provided multi-point dissolution profile data comparing the following in pH (b) (4) dissolution media:

- tablets containing drug substance manufactured (b) (4)
- tablets containing drug substance manufactured (b) (4).

The Biopharmaceutics Reviewer concluded that these data demonstrate that the dissolution profiles of the tablets containing drug substance manufactured with (b) (4)

F. Formulation Design Space

(b) (4)

5.1.2 Clinical Pharmacology

The Clinical Pharmacology Review focused on the following:

A. dose/exposure-response findings,
B. pharmacokinetics,
C. specific populations, and
D. drug-drug interactions

Each of these issues and the Clinical Pharmacology Reviewer's conclusion are summarized below.

A. Dose/Exposure-Response Findings

Phase 2b trial: Dose-response in terms of efficacy and safety was assessed in a Phase 2b clinical trial in OIC patients (5 mg *qd*, 25 mg *qd*, 50 mg *qd* vs. placebo); due to the absence of significant efficacy outcomes, the 5 mg *qd* dose was not evaluated further in the phase 3 trials, while the 50 mg *qd* dose was also not carried into phase 3 due to increased abdominal AEs and discontinuations at this dose level.

Phase 3 trials: The phase 3 pivotal efficacy and safety trials evaluated two doses of naloxegol (12.5 mg *qd* and 25 mg *qd*) against placebo allowing exploration of dose-response. The primary efficacy endpoint was percentage responders during the 12 week treatment period relative to placebo. The Clinical Pharmacology Reviewer's conclusions were as follows:

- Dose-Response (Efficacy): Based on the applicant's primary efficacy analysis, there is a trend in dose-response for the efficacy of naloxegol with modest increase in response rates between 12.5 and 25 mg dose groups. Response rates for the primary endpoint in study 04 are 29.4%, *40.8%, *44.4% for placebo, 12.5 and 25 mg arms. Response rates for the replicate study 05 are 29.3%, 34.9%, *39.7% for placebo, 12.5 and 25 mg arms (* denotes statistical significance indicating that the lower dose of 12.5 mg did not meet the statistical significance in trial 05). The 25 mg dose is most effective and the efficacy conclusions are consistent across all secondary endpoints.
- Exposure-Response (Efficacy): Exposure-response analysis for the primary efficacy endpoint showed a significant relationship between exposures and response which is consistent with the dose response, suggesting that higher exposures lead to better response. The significant exposure-response analysis provides supportive evidence of effectiveness for the naloxegol in the treatment of opioid induced constipation. Moreover, the shallow exposure-response analysis also indicates that lower exposures compared to that observed with 25 mg may not result in a meaningful loss of efficacy.
- Dose- and Exposure-Response (Safety): Dose- and exposure-response relationships were also evident for gastrointestinal AEs. In particular abdominal pain was evaluated by severity, and relationships for moderate and severe and severe AEs were considered to be shallow. Dose-response was also apparent for discontinuations due to opioid withdrawal events. Discontinuations were 2-fold higher for the 25 mg compared to 12.5 mg dose group, due to AEs. However, the drug was fairly well tolerated overall with < 20% of patients discontinuing in the 25 mg group due to AEs.

Dosing Recommendations: The Clinical Pharmacology Reviewer commented that the sponsor's proposed dose of 25 mg appears reasonable for those that can tolerate it (>85% of patients in phase 3 studies 04 and 05). However, the Clinical Pharmacology Reviewer noted the following:

- Because of the numerical trend in dose response and shallow exposure response relationships for efficacy, the question arises as to whether patients who cannot tolerate the 25 mg dose would benefit from the 12.5 mg dose.
- Because patients who did not tolerate the 25 mg dose did not receive 12.5 mg subsequently in the registration trials, the question was asked: Do patients with abdominal pain have a different response compared to those who do not? This question was driven by two pharmacological aspects:

1) abdominal pain may be a symptom of opioid withdrawal;
2) abdominal pain may also be an indicator of efficacy.

- Both the primary and secondary endpoints were evaluated with regards to the occurrence of abdominal pain; in general, patients with abdominal pain AEs had consistently higher response rates for both the primary and secondary endpoints. Based on this observation in combination with a shallow exposure-response relationship and apparent dose-response in both studies, the Clinical Pharmacology Reviewer recommended that patients who cannot tolerate the drug due to abdominal pain, to reduce their dose to 12.5 mg prior to discontinuing the drug.

QT prolongation potential: The Clinical Pharmacology Reviewer noted that while there is an apparent exposure-response relationship for naloxegol effect on the QT interval, the IRT concluded there was no significant QTc prolongation effect of naloxegol in the TQT study. The largest upper bound of the 2-sided 90% CI's for the mean differences between 150 mg naloxegol (supra-therapeutic dose) and placebo was below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines.

Potential for formation of naloxone: The Clinical Pharmacology Reviewer noted that because naloxegol is PEGylated naloxone, formation of naloxone by complete separation of the 7-pegylated side chain is a theoretical possibility. Based on the information available from phase 1 trials and in vitro studies, the Clinical Pharmacology Reviewer noted that naloxone concentrations ≥ 0.25 ng/mL (LLOQ for the assay) can be ruled-out. The Clinical Pharmacology Reviewer noted that neither the presence of naloxone at concentrations below 0.25 ng/mL nor the clinical relevance of such low concentrations in causing central opioid antagonism is known.

Potential for the formation of EG, DEG and metabolites: Because of the PEGylated side-chain on naloxegol and metabolism by sequential removal of ethoxy units, it was considered whether there is a likelihood for the formation of ethylene glycol (EG) and diethylene glycol (DEG) and their toxic metabolites such as glycolic acid, oxalic acid etc. The Clinical Pharmacology Reviewer noted that the likelihood that significant amounts of such toxic metabolites are formed after naloxegol administration and accumulate to toxic levels after naloxegol administration is low. The Clinical Pharmacology Reviewer noted that even when assuming the worst-case scenario (i.e., all PEG in naloxegol was metabolized to EG, DEG, or OA) which, based on metabolic profiling is a significant overestimation, the metabolite concentrations after daily dosing would still be below the reported safe or minimally toxic daily doses in humans. The Pharmacology/Toxicology reviewers for the NDA also concur with the sponsor's estimations in this regard (see Section 4.2 of this CDTL Review).

B. Pharmacokinetics

The Clinical Pharmacology Reviewer noted that naloxegol PK is dose- and time-independent, with dose proportional increases in AUC and slightly more than dose proportional increases in Cmax, that PK variability was moderate (27- 55 %), and that daily dosing results in minimal accumulation. In addition, the Clinical Pharmacology Reviewer noted the following regarding PK:

- Absorption: Absorption occurs after oral dosing with a median Tmax of 1 to 1.5 h. Double peaks are seen in most individuals. The reason for this observation is unclear. Food increases naloxegol Cmax and AUC (by 47 % and 55 %, respectively, for the Phase 3 formulation and by 30 % and 46 % respectively, for the commercial formulation) However phase 3 trials were conducted in fasted conditions and hence the labeling proposes dosing on an empty stomach as well. Absolute bioavailability was not evaluated for this drug.
- Distribution: The mean apparent volume of distribution during the terminal phase (Vz/F) in healthy volunteers ranged from 968 to 2140 L. The plasma protein binding of naloxegol is low (4.2 %). There is no concentration-dependent effect on protein binding.
- Metabolism: Based on in vitro studies, CYP3A4/5 appear to be the major isoforms for the metabolism of naloxegol, while CYP2D6 appears to have minor contribution. Based on all the information available (including mass balance and drug interaction data), metabolism appears to be the predominant route of clearance. Metabolism of naloxegol occurs by partial removal of ethoxy units from the PEG side-chain as well as other oxidative reactions. There were no major metabolites (i.e. > 10 %) for naloxegol. Naloxegol glucuronide was below detection in plasma at clinically relevant doses.
- Excretion: The terminal elimination half-life across phase 1 studies was variable, ranging from 6-11 hours. Half-life of naloxegol in patients was somewhat longer at steady-state (14 h) vs. those noted in healthy volunteer PK studies. In a mass balance study in healthy volunteers, naloxegol had an average recovery of 84 %. 16 % of radioactivity dose was found in urine, with 10 % as unchanged drug and 6 % as metabolites. In feces, ~ 68 % of radioactivity dose was found; 58 % of fecal radioactivity was characterized, with 16 % noted to be unchanged drug and remaining as metabolites. A biliary excretion component for naloxegol may be suggested by the appearance of secondary peak in the PK profile suggestive of enterohepatic recirculation, but this was not formally assessed.
- PK in patients vs. healthy volunteers:
  - Cross-study comparisons (Phase 2b PK sub-study vs. healthy volunteers receiving naloxegol alone in Phase 1 drug-drug interaction study): Based on cross-study comparisons, mean Cmax and mean AUC values in OIC patients (Phase 2b PK sub-study; n=9-12) were observed to be roughly twice those noted in healthy volunteers (dosed with naloxegol alone across the various phase 1 drug-drug interaction studies; n = ~22). The Clinical Pharmacology Reviewer noted that there was substantial PK variability in both sets of data (coefficient of variation of up to 52%) and small sample size in the Phase 2b PK sub-study; thus, the Clinical Pharmacology Reviewer concluded that it is difficult to determine if the observed differences in mean Cmax and mean AUC represent true differences.
  - Cross-study comparisons (Phase 2b PK sub-study vs. Phase 1 renal and hepatic PK studies): Based on cross-study comparisons, mean Cmax and mean AUC values in OIC patients in the Phase 2b PK sub-study were similar to those noted in control groups of phase 1 renal and hepatic PK studies (n=6 healthy volunteers in the renal PK study; n=8 healthy volunteers in the hepatic PK study).
  - Population PK analysis (Phase 3 vs. Phase 1 data): The population PK analysis suggested a 30% lower AUC in OIC patients in the Phase 3 trials compared to healthy subjects in the Phase 1 trials (see Figure 8 of the Clinical Pharmacology Review on Page 64).

Even if there is higher exposure (as suggested by the first cross-study comparison above) in the OIC patients studied compared to healthy volunteers, all the safety information generated from the Phase 3 trials will be at this higher exposure; the safety profile was acceptable based on what was found in the Phase 3 clinical trials with the 25 mg dose and 12.5 mg dose (see Section 8 of this CDTL Review).

C. Specific Populations

The Clinical Pharmacology Reviewer noted the following regarding specific populations:

- Race: Caucasians appear to have modestly higher systemic naloxegol exposure (20 %) and lower clearance values compared to Japanese or African-Americans based on a cross-study comparison in small sample size populations.
- Age: In a Japanese PK study, elderly volunteers on average had ~ 30 % and 45 % higher naloxegol Cmax and AUC_{tau} at steady-state compared to younger subjects. In clinical trials of naloxegol, elderly (> 65 years) represented ~ 11 % of the trial population. No dosage adjustment is proposed for the elderly, however safety in elderly in general needs to be monitored due to potential for increased exposure, as well as reduced renal function (which in turn may have effects on metabolism and transport processes; note some individuals with unusually high exposures in the renal PK study) and increased sensitivity to some medications in the elderly.
- Hepatic Impairment: Although naloxegol appears to be extensively metabolized, there was no impact of mild to moderate hepatic impairment on the pharmacokinetics of naloxegol. There are no PK, efficacy or safety data in subjects with severe hepatic impairment.
- Renal Impairment: Renal clearance appears to be a minor pathway for naloxegol based on overall information summarized below.
  - In a PK study in moderate (n= 8), severe (n = 4), and ESRD patients not yet on dialysis (n =4), there was an average increase of 70 %, 131 %, and 98 %, respectively, for AUC and an average increase of 18 %, 86 %, and 107 %, respectively, for Cmax in these renal impairment subgroups compared to the control group.
  - The study also included ESRD subjects on dialysis (n = 8) who had systemic exposures comparable to that of the control subjects; however, very little drug was removed by dialysis (based on pre-and post-dialysis measurements of plasma concentrations of naloxegol).
  - Four individuals belonging to the moderate, severe, or ESRD (not yet on dialysis) groups appeared to drive up the averages with individual increases of up to 5-fold increase over normal group in Cmax and up to 8.4-fold for AUC; these differences in exposure could not be attributed to any particular factor based on available demographic, disease and concomitant medication history of these subjects and as such subjects could not be ruled out as outliers in this small sample size study.

  Based on the four individuals with significantly higher exposures than the control group, the Clinical Pharmacology Reviewer concluded that it would be advisable to start patients with renal impairment (moderate, severe or ESRD) on a lower dose of naloxegol (e.g., 12.5 mg qd); the dose may be increased by the healthcare provider if adequate efficacy was not noted and safety was acceptable at the lower dose.

D. Drug-Drug Interactions

In vitro findings: The Clinical Pharmacology Reviewer noted the following:

- Naloxegol as a substrate: Naloxegol is a substrate for CYP3A drug metabolizing enzyme and P-gp efflux transporter; therefore drugs that are inhibitors or inducers of these systems are likely to modulate naloxegol pharmacokinetics. It does not appear to be a substrate for other major CYP450 enzymes and transporters.
- Naloxegol as an inhibitor or inducer: Naloxegol did not cause inhibition or induction of major CYP enzymes and transporters *in vitro* at clinically relevant concentrations.

In vivo findings: Based on the *in vitro* findings, the *in vivo* drug-drug interaction studies focused on the effects of inhibitors or inducers of CYP3A4 enzyme and/or P-gp transporter on the PK of naloxegol. The Clinical Pharmacology Reviewer noted the following:

- Strong CYP3A4/P-gp Inhibitors: Co-administration with ketoconazole, a strong CYP3A4/P-gp inhibitor, resulted in 11-fold and ~ 12.85-fold increases in Cmax and AUC of naloxegol. Therefore, dosing with such drugs is contraindicated.
- Grapefruit/Grapefruit Juice: Use with grapefruit/grapefruit juice, which can be a strong CYP3A inhibitor, was not formally evaluated but the Clinical Pharmacology Reviewer recommended avoiding concomitant use of naloxegol with such foods due to a potential for increased exposure.
- Moderate CYP3A4/P-gp Inhibitors: Co-administration with moderate CYP3A4 inhibitor diltiazem resulted in 2.86-fold and 3.4-fold increase in Cmax and AUC; dose reduction to 12.5 mg qd was proposed by the sponsor for use with moderate CYP3A4 inhibitors. Considering the potential for increased AEs particularly abdominal AEs, the Clinical Pharmacology Reviewer recommended that concurrent dosing with moderate CYP3A4 inhibitors should be avoided; if dosing with moderate CYP3A4 inhibitor drugs cannot be avoided, then the dose should be reduced to 12.5 mg qd and used with caution.
- P-gp Inhibitors: Co-administration with quinidine, a P-gp inhibitor, resulted in a 2.4-fold and 1.4-fold increase in Cmax and AUC of naloxegol, respectively. The sponsor's proposal for dosing recommendations in the label was to follow the corresponding CYP3A4 inhibitor potential; for example, P-gp inhibitors which are also strong or moderate CYP3A4 inhibitors should follow the dosing recommendations for those inhibitor class of drugs (i.e. contraindication or dose-reduction, respectively), while P-gp inhibitors that are weak CYP3A4 inhibitors do not need dose adjustment; the Clinical Pharmacology Reviewer agreed with the sponsor's proposal.
- CYP3A4/P-gp Inducers: CYP3A4 inducer rifampin reduced naloxegol exposure by 89 % (AUC); therefore, the Clinical Pharmacology Reviewer concluded that use with rifampin should not be recommended due to potential for loss of efficacy.

In addition, the Clinical Pharmacology Reviewer noted that in a study in healthy subjects, naloxegol did not appear to alter the pharmacokinetics of morphine.

5.2 Recommendation

Biopharmaceutics: An Approval Action is the recommendation by the Biopharmaceutics discipline.

Clinical Pharmacology: An Approval Action is the recommendation by the Clinical Pharmacology discipline pending agreement related to the labeling language. In addition, the Clinical Pharmacology discipline recommends that the label (Dosage and Administration section) contain instructions for dose reduction to 12.5 mg if the 25 mg dose is not tolerated due to abdominal pain (see Section 12.3 of this CDTL Review). Finally, the Clinical Pharmacology discipline recommends a postmarketing commitment (see Section 13.6 of this CDTL Review).

6 Clinical Microbiology

Clinical Microbiology considerations do not apply to this application because naloxegol is not an antimicrobial agent.

7 Clinical/Statistical - Efficacy

The reader is referred to the Clinical Review by Aisha Peterson Johnson, and the Statistics Review by Wen Jen Chen for complete information.

7.1 Overview

Proposed Indication

The Applicant proposed the following indication:

> "… for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain."

Overview of Phase 3 Trials

An overview of the two key Phase 3 trials is shown in the table below. The design is described in more detail in Section 7.2 of this CDTL Review.

Table 2. Key Phase 3 Trials

Clinical Trials	Design	Arms	Primary Efficacy Endpoint	N
004	• R, DB, PC	• Randomized 1:1:1 to: ➢ Placebo ➢ Naloxegol 12.5 mg QD ➢ Naloxegol 25 mg QD	• Response* at Wk 12	652
005	• R, DB, PC	• Randomized 1:1:1 to: ➢ Placebo ➢ Naloxegol 12.5 mg QD ➢ Naloxegol 25 mg QD	• Response* at Wk 12	700

R: Randomized; DB: Double-blind; PC: Placebo-controlled
*The primary endpoint was response defined as: ≥3 SBMs per week and a change from baseline of ≥1 SBM per week for at least 9 out of the 12 study weeks *and* 3 out of the last 4 weeks.
Table modified from Clinical Review.

An overview of the key Phase 3 safety studies is shown in the table below. The design is described in more detail in Section 8.1 of this CDTL Review.

Table 3. Key Phase 3 Safety Studies

Clinical Trials	Design	Arms	N
007 (Safety Extension Study)	• 12-week extension of Study 004	• Continuation of blinded treatment (from 004): ➢ Placebo ➢ Naloxegol 12.5 mg QD ➢ Naloxegol 25 mg QD	302
008 (Long-Term Safety and Tolerability Study)	• 52-week, open-label, randomized, parallel group, study[#]	• Randomized 2:1 to: ➢ usual care treatment for OIC* ➢ Naloxegol 25 mg QD	844

*Usual care treatment for OIC as determined by the investigator; excluding peripheral mu-opioid antagonists
[#]Patients from Studies 005 and 007 or new patients could enter Study 008.
Table modified from Clinical Review.

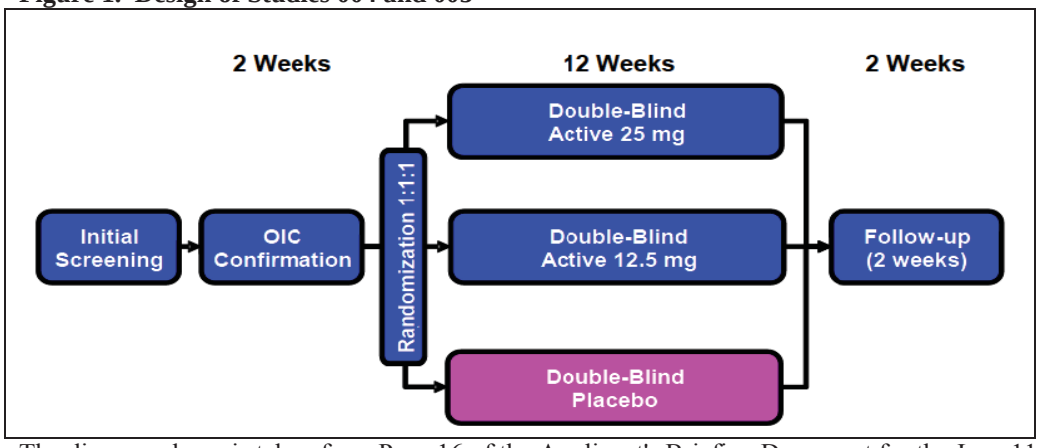
7.2 Design of Key Phase 3 Trials (Studies 004 and 005)

Studies 004 and 005 were replicate trials. The features of the trials are summarized below.

Design:

The design of Studies 004 and 005 is summarized in the figure below.

Figure 1. Design of Studies 004 and 005



The diagram above is taken from Page 16 of the Applicant's Briefing Document for the June 11-12 Advisory Committee.

Key Entry Criteria:

Key Inclusion Criteria: Key inclusion criteria of Studies 004 and 005 were a stable maintenance opioid regimen and opioid-induced constipation.

- *Stable Maintenance Opioid Regimen*: A stable maintenance opioid regimen was defined as the following: (1) morphine equivalent daily dose between 30 and 1,000 mg; and (2) duration of use of at least 4 weeks prior to screening. The opioid regimen was confirmed by a prescription or a clearly labeled medication bottle. Patients were disqualified from randomization if they met either of the following criteria (during the 2-week OIC confirmation period): (1) >4 additional breakthrough pain medication doses/day (for more than 3 days); or (2) long-acting maintenance opioid dose was modified (during this same period).
- *Opioid Induced Constipation*: Opioid induced constipation (OIC) was based on both self-report of OIC symptoms (at screening) and documented confirmation of OIC (during the two-week OIC confirmation period). Self-reported active symptoms of OIC (at screening) were defined as <3 spontaneous bowel movements (SBMs) per week and experiencing ≥1 reported symptom of hard/lumpy stools, straining, or sensation of incomplete evacuation/anorectal obstruction in at least 25% of bowel movements (BMs) over the previous 4 weeks. An SBM was defined as a BM without rescue laxative taken within the past 24 hours. Documented confirmed OIC (during the two-week OIC confirmation period) was defined as <3 SBMs/week on average over the 2-week OIC confirmation period; patients must report in at least 25% of the BMs recorded in the eDiary (during the two-week OIC confirmation period) ≥1 of the following: (1) Bristol Stool Scale stool type 1 or 2 (see Appendix 3 of this CDTL Review); (2) moderate, severe, or very severe straining; and (3) incomplete BM. Patients who have 0 BMs over the 2-week OIC confirmation period, and patients with an uneven distribution of SBMs across the 2-week OIC confirmation period (0 SBMs in 1 week with ≥4 SBMs in the other week) were not randomized.

Key Exclusion Criteria: Key exclusion criteria of Studies 004 and 005 were conditions of the GI tract which could confound interpretation of the results, conditions of the GI tract that

could impose risk to the patient, and conditions that may have affected the permeability of the blood-brain barrier.

- *Conditions of the GI Tract which could Confound Interpretation of the Results*: Patients were excluded if they had conditions and treatments associated with diarrhea, intermittent loose stools, or constipation, which could confound the interpretation of the results, e.g., fecal incontinence or chronic idiopathic constipation. In addition, patients having irritable bowel syndrome (IBS) that had been previously diagnosed by a physician prior to first initiation of opioid therapy and that met the following criteria, would be excluded: (1) absence of a structural or biochemical explanation for the abdominal pain symptom; (2) at least 12 weeks during a period of 12 months, of abdominal discomfort or pain with at least 2 of the following 3 features: (a) Relieved with defecation; (b) Onset associated with a change in frequency of stool; (c) Onset associated with a change in form of stool.
- *Conditions of the GI tract that could Impose Risk to the Patient:* Of the conditions that could impose risk to the patient, there was a special emphasis on conditions that might impair the local or global structural integrity of the GI tract, such as inflammatory bowel disease, intestinal obstruction or pseudo-obstruction, suspected mechanical GI obstruction or previous history of recurrent bowel obstruction, history of >1 episode of diverticulitis (unless treated with surgery) or clinically important active diverticular disease, history of rectal prolapse, history of GI hemorrhage related to ongoing GI pathology (e.g., ulcer), clinically important or severe peptic ulcer disease, GI ostomy, intraperitoneal catheter, history of bowel perforation, history of ischemic bowel disease or ischemic colitis, previous small bowel surgery, history of surgical stenosis, known intra-abdominal adhesions, or previous gastric by-pass surgery.
- *Conditions that may have Affected the Permeability of the Blood-Brain Barrier:* Patients suspected of having clinically important disruptions to the blood-brain barrier were excluded (examples of such conditions in the protocols were: multiple sclerosis, recent brain injury, Alzheimer's disease, and uncontrolled epilepsy).

See additional details of entry criteria in the Clinical Review.

Randomization and Stratification:

Randomization: Patients in Studies 004 and 005 were randomized 1:1:1 to placebo, naloxegol 12.5 mg, or naloxegol 25 mg.

Stratification: Patients were stratified by response to laxatives at baseline (with ≥50% of patients enrolled in the LIR category):

- Laxative inadequate responder (LIR)
- Laxative adequate responder (LAR)
- Laxative unknown responder (LUR)

(See Appendix 1 Baseline Laxative Response Status Questionnaire; and Appendix 2 Definitions of LIR, LAR, and LUR.)

Rescue Laxative Use:

Throughout each of the studies (Studies 004 and 005) (including the two-week run-in period), patients were prohibited from using laxatives other than bisacodyl rescue laxative (if they had not had a BM for 72 hours) and one-time use of an enema (if after 3 doses of bisacodyl, they still did not have a BM).

Endpoints:

The primary and secondary endpoints of Studies 004 and 005 are shown in the table below.

Table 4. Primary and Secondary Endpoints of Studies 004 and 005

Endpoint	Definition
Primary:	Response defined as ≥3 SBMs per week and a change from baseline of ≥1 SBM per week for at least 9 out of the 12 study weeks *and* 3 out of the last 4 weeks. (An SBM was defined as a BM without rescue laxative taken within the past 24 hours.)
1st Ranked Secondary:	Response (as defined above) in the LIR subgroup (see definition of LIR in Appendix 2 of this CDTL Review).
2nd Ranked Secondary:	Time to first-dose SBM without the use of rescue laxatives within the previous 24 hours.
3rd Ranked Secondary:	Mean number of days per week with at least 1 SBM during Weeks 1 to 12 (only days with no more than 3 SBM's in one day are included).*

*Differences between treatment groups will be analyzed using the mixed model repeated measures (MMRM) approach; the MMRM will include the treatment group, the baseline value of the response variable, time (as a class variable for weeks 1 to 12 as applicable) and treatment-time interaction and baseline laxative response as fixed effects, and center as a random effect (Source: Statistical Analysis Plan of each study). See the Statistics Review for additional details.

7.3 Results of Key Phase 3 Trials (Studies 004 and 005)

Baseline Demographics and Disease Characteristics:

Demographics: The three arms of each study were similar with regard to sex, age, race, and BMI. The mean age in each study was 52 years (10% and 13% were ≥ 65 years of age), 61% and 63% were female, and 78% and 80% were Caucasian in Studies 004 and 005, respectively. See table below.

Table 5. Demographics (Studies 004 and 005)

Demographic Subgroup	Study 004 (ITT Population)			Study 005 (ITT Population)		
	Placebo (N=214)	Naloxegol 12.5 mg (N=213)	Naloxegol 25 mg (N=214)	Placebo (N=232)	Naloxegol 12.5 mg (N=232)	Naloxegol 25 mg (N=232)
Sex (n,%)						
Male	74 (34.6)	78 (36.6)	96 (44.9)	87 (37.5)	83 (35.8)	85 (36.6)
Female	140 (65.4)	135 (63.4)	118 (55.1)	145 (62.5)	149 (64.2)	147 (63.4)
Age (n,% and Mean ± SD)						
< 50 years	71 (33.2)	81 (38.0)	73 (34.1)	94 (40.5)	96 (41.4)	84 (36.2)
50 to <65 years	121 (56.5)	113 (53.1)	121 (56.5)	110 (47.4)	110 (47.4)	115 (49.6)
≥ 65 to <75 years	17 (7.9)	17 (7.9)	17 (7.9)	23 (9.9)	19 (8.2)	26 (11.2)
≥ 75 years	5 (2.3)	2 (0.9)	3 (1.4)	2 (2.2)	7 (3.0)	7 (3.0)
Mean ± SD	52.9 ± 9.99	51.9 ± 10.43	52.2 ± 10.29	52.3 ± 11.62	52.0 ± 11.02	51.9 ± 12.11
Race (n,%)						
Caucasian	160 (74.8)	164 (77.0)	173 (80.8)	183 (78.9)	187 (80.6)	189 (81.5)
Black	44 (20.6)	42 (19.7)	38 (17.8)	44 (19.0)	41 (17.7)	40 (17.2)
Asian	4 (1.9)	5 (2.3)	1 (0.5)	0	1 (0.4)	0
AI/AN	2 (0.9)	1 (0.5)	0	2 (0.9)	1 (0.4)	1 (0.4)
Other	4 (1.9)	1 (0.5)	2 (0.9)	3 (1.3)	2 (0.9)	2 (0.9)
BMI (kg/m2)						
<18.5	0	1 (0.5)	1 (0.5)	3 (1.3)	3 (1.3)	2 (0.9)
18.5-<30	108 (50.5)	98 (46.0)	102 (47.7)	118 (50.9)	123 (53.0)	112 (48.3)
≥30	106 (49.5)	114 (53.5)	111 (51.9)	111 (47.8)	106 (45.7)	115 (49.6)

AI/AN: American Indian or Alaska Native
BMI: Body Mass Index
Table above is modified from the Clinical Review. Source is Table 9, p 66 Study 04 CSR and Table 9, p 68 Study 05 CSR

Primary Reason for Opioid Use: The three arms of each study were similar with regard to the primary reason for opioid use. Back pain was the most common reason for pain (56% and 57%); arthritis (10% and 10%) and joint pain (3% and 5%) were other prominent reasons in Studies 004 and 005, respectively. See table below.

Table 6. Primary Reason for Opioid Use (Studies 004 and 005)

Subgroup	Study 004 (ITT Population)			Study 005 (ITT Population)		
	Placebo (N=214)	Naloxegol 12.5 mg (N=213)	Naloxegol 25 mg (N=214)	Placebo (N=232)	Naloxegol 12.5 mg (N=232)	Naloxegol 25 mg (N=232)
Back pain	118 (55.1)	131 (61.5)	110 (51.4)	129 (55.6)	136 (58.6)	130 (56.0)
Joint pain	7 (3.3)	8 (3.8)	7 (3.3)	10 (4.3)	11 (4.7)	16 (6.9)
Fibromyalgia	15 (7.10)	6 (2.8)	9 (4.2)	18 (7.8)	16 (6.9)	11 (4.7)
Headache/migraine	3 (1.4)	1 (0.5)	4 (1.9)	2 (0.9)	1 (0.4)	5 (2.2)
Arthritis	22 (10.3)	20 (9.4)	22 (10.3)	21 (9.1)	20 (8.6)	27 (11.6)
Neuralgia	4 (1.9)	1 (0.5)	8 (3.7)	5 (2.2)	6 (2.6)	7 (3.0)
Pain Syndrome	5 (2.3)	5 (2.3)	7 (3.3)	2 (0.9)	0	3 (1.3)
Other*	39 (18.2)	41 (19.2)	46 (21.5)	44 (19.0)	42 (18.1)	33 (14.2)

*In both studies, in the category of "other", the majority of patients reported localized musculoskeletal pain as their primary type of pain (see Clinical Review).
Table above is modified from the Clinical Review. Source is Study 04 CSR, Table 10 p 67; Study 05 CSR, Table 10, p 69

Baseline Opioid Dose: The three arms of each study were similar with regard to baseline opioid dose. The mean baseline opioid dose was 140 and 136 Morphine Equivalent Units (MEU) per day in Studies 004 and 005, respectively. See table below.

Table 7. Baseline Opioid Dose [Morphine Equivalent Units (MEU) / Day], Studies 004 and 005

	Study 004 (ITT Population)			Study 005 (ITT Population)		
	Placebo (N=213)	Naloxegol 12.5 mg (N=211)	Naloxegol 25 mg (N=214)	Placebo (N=231)	Naloxegol 12.5 mg (N=230)	Naloxegol 25 mg (N=232)
Mean ± SD	135.6 ± 145.8	139.7 ± 167.4	143.2 ± 150.1	119.9 ± 103.8	151.7 ± 153.0	136.4 ± 134.3
Maximum	968	1280	1080	607	990	750
Quartile 3	180.0	178.9	191.3	180.0	195.0	180.0
Median	75.0	87.6	90.0	77.1	90.0	84.6
Quartile 1	45.0	45.0	45.0	45.0	45.0	45.0
Minimum	15	1	18	15	11	15

Table above is modified from the Clinical Review. Source: Study 04 CSR, Table 44, p 150; Study 05, Table 43, p 150

Duration of Current Opioid Use: The three arms of each study were similar with regard to duration of current opioid use. The average duration of current opioid use was 42.8 months (i.e., 3.6 years) and 44.1 months (i.e., 3.7 years) in Studies 004 and 005, respectively. See table below.

Table 8. Duration of Current Opioid Use (Months), Studies 004 and 005

	Study 004 (ITT Population)			Study 005 (ITT Population)		
	Placebo (N=214)	Naloxegol 12.5 mg (N=213)	Naloxegol 25 mg (N=214)	Placebo (N=231)	Naloxegol 12.5 mg (N=232)	Naloxegol 25 mg (N=230)
Mean ± SD	39.5 ± 39.3	44.4 ± 47.3	44.5 ± 47.8	43.0 ± 51.4	48.5 ± 48.7	40.9 ± 41.6
Maximum	192	276	252	432	252	228
Median	24.0	24.0	24.0	24.0	36.0	24.0
Minimum	1	1	1	1	1	1

Source is Study 04 CSR, Table 10 p 67; Study 05 CSR, Table 10, p 69

Prior Laxative Use: The three arms of each study were similar with regard to laxative use reported over the two weeks prior to enrollment and reported over the six months prior to enrollment. Laxative use within the two weeks prior to enrollment was reported by 71% of patients in both Studies 004 and 005; laxative use within the six months prior to enrollment was reported by 85% and 83% of patients in Studies 004 and 005, respectively. See tables below.

Table 9. Laxative Use Reported over Past 2 Weeks and over Past 6 months (n,%), Studies 004 and 005

	Study 004 (ITT Population)			Study 005 (ITT Population)		
Laxative Use Reported over Past:	Placebo (N=214)	Naloxegol 12.5 mg (N=213)	Naloxegol 25 mg (N=214)	Placebo (N=232)	Naloxegol 12.5 mg (N=232)	Naloxegol 25 mg (N=232)
2 weeks (n,%)	151 (70.6)	140 (65.7)	166 (77.6)	173 (74.6)	156 (67.2)	166 (71.6)
6 months (n,%)	177 (82.7)	184 (86.4)	181 (84.6)	197 (84.9)	189 (81.5)	194 (83.6)

Source: Pages 50 and 55 of Summary of Clinical Efficacy

Disposition:

The three arms of each study were similar with regard to percentage of patients that completed the studies (see table below); 80.4% and 73.9% completed Studies 004 and 005, respectively.

In both studies, rates of discontinuation due to AE's were higher in the naloxegol 25 mg group compared to the placebo and naloxegol 12.5 mg groups. In the naloxegol 25 mg group, rates of discontinuation due to AE's were 10.1% and 10.3% in Studies 004 and 005, respectively. In contrast, rates of discontinuation due to AE's were 5.1% and 5.2% (in the placebo group) and 4.1% and 4.7% (in the naloxegol 12.5 mg group) in Studies 004 and 005, respectively (see table below).

Patient Disposition, Studies 04 and 05 (ITT population)

	Study 004			Study 005		
	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg
Randomized	217	217	218	233	233	234
Received Treatment	216 (99.5)	215 (99.1)	218 (100)	232 (99.6)	231 (99.1)	234(100)
Completed Study	177 (81.6)	174 (80.2)	173 (79.4)	187 (80.3)	177 (76.0)	173 (73.9)
Discontinued Early	36 (16.6)	37 (17.1)	41 (18.8)	44 (18.9)	53 (22.7)	59 (25.2)
Patient Request	13 (6.0)	17 (7.8)	6 (2.8)	13 (5.6)	23 (9.9)	20 (8.5)
Did not Meet Eligibility Criteria	1(0.5)	0	0	1(0.4)	0	0
Death	0	1 (0.5)	0	0	0	0
Adverse Event	11 (5.1)	9 (4.1)	22 (10.1)	12 (5.2)	11 (4.7)	24 (10.3)
Severe Protocol violation	2 (0.9)	0	5 (2.3)	2 (0.9)	2 (0.9)	2 (0.9)
Lack of therapeutic response	2 (0.9)	0	0	3 (1.3)	3 (1.3)	0
Development of study-specific withdrawal criteria	2 (0.9)	3 (1.4)	1 (0.5)	3 (1.3)	0	3 (1.3)
Lost to follow-up	4 (1.8)	7 (3.2)	6 (2.8)	9 (3.9)	11 (4.7)	9 (3.8)
Other	1 (0.5)	0	1 (0.5)	1 (0.4)	3 (1.3)	1 (0.4)

Table above is modified from the Clinical Review. Source: CSR Study 04, Table 11.1.1.1, p 182; CSR Study 05, Table 11.1.1.1

Primary Endpoint:

There was a statistically significant difference for the naloxegol 25 mg group versus placebo for the primary endpoint in Study 004 and Study 005 (see table below). Statistical significance for the naloxegol 12.5 mg group versus placebo was observed in Study 004 but not in Study 005 (see table below).

Table 10. Primary Endpoint: Response[#] (Studies 004 and 005)

	Study 004			Study 005		
	Placebo (N = 214)	Naloxegol 12.5 mg (N = 213)	Naloxegol 25 mg (N = 214)	Placebo (N = 214)	Naloxegol 12.5 mg (N = 232)	Naloxegol 25 mg (N = 232)
Patients responding, n (%)	63 (29%)	87 (41%)	95 (44%)	68 (29%)	81 (35%)	92 (40%)
Treatment Difference[†] (95% CI)	--	11.4% (2.4%, 20.4%)	15.0% (5.9%, 24.0%)		5.6% (-2.9%, 14.1%)	10.3% (1.7%, 18.9%)
p-value	--	0.015*	0.001*		0.202	0.021*

Response defined as: ≥3 SBMs per week and a change from baseline of ≥1 SBM per week for at least 9 out of the 12 study weeks *and* 3 out of the last 4 weeks.
[†]Treatment Difference: Naloxegol - Placebo
*Statistically significant after adjustment for multiplicity
Analysis via Cochran Mantel-Haenszel test
CI = confidence interval
Table above is modified from the Clinical Review. Treatment Difference and 95% CI provided by applicant in a Response to Information Request dated August 11, 2014.

Secondary Endpoints:

First Secondary Endpoint: Response in the LIR Subgroup

The first secondary endpoint was response in the LIR subgroup of patients. (See Appendix 1 Baseline Laxative Response Status Questionnaire; and Appendix 2 Definitions of LIR, LAR, and LUR.)

Fifty-five percent (55%) of patients in Study 004 and 53% of patients in Study 005 were in this subgroup.

The most commonly used laxatives reported over the last two weeks in the LIR subgroup were stimulants, stool softeners, polyethylene glycol, and lubricants (see Appendix 4 Prior Laxative Class Usage Reported in the LIR Subgroup).

In Study 004, a statistically significantly higher percentage of patients in this subgroup responded with naloxegol 12.5 mg compared to placebo (43% vs. 29%; p=0.03) and with naloxegol 25 mg compared to placebo (49% vs. 29%; p=0.002). See table below.

In Study 005, a statistically significant difference in response between naloxegol 25 mg and placebo in this subgroup was demonstrated (47% vs. 31%; p=0.01). This secondary endpoint was not tested for naloxegol 12.5 mg versus placebo in Study 005 because the primary endpoint was not statistically significant for this comparison. See table below.

Table 11. First Secondary Endpoint: Response[#] in the LIR Subgroup (Studies 004 and 005)

	Study 004			Study 005		
	Placebo (N = 118)	Naloxegol 12.5 mg (N = 115)	Naloxegol 25 mg (N = 117)	Placebo (N = 121)	Naloxegol 12.5 mg (N = 125)	Naloxegol 25 mg (N = 124)
Patients responding, n (%)	34 (28.8)	49 (42.6)	57 (48.7)	38 (31.4)	53 (42.4)	58 (46.8)
Relative risk[†]		1.48	1.69		1.35	1.49
95% CI		1.04, 2.11	1.20, 2.37		0.97, 1.88	1.08, 2.06
p-value		0.028*	0.002*		NT	0.014*

[#]Response defined as: ≥3 SBMs per week and a change from baseline of ≥1 SBM per week for at least 9 out of the 12 study weeks *and* 3 out of the last 4 weeks.
*Statistically significant under multiple testing procedure
[†]Relative Risk: Naloxegol/Placebo
Analysis via Chi-squared test
NT = Not tested. In Study 005, secondary endpoints were not tested for naloxegol 12.5 mg versus placebo because the primary endpoint was not statistically significant for this comparison.
CI=confidence interval.
Table above is modified from the Clinical Review. Source is Page 68 of the Summary of Clinical Efficacy.

Key issues with this endpoint include the following

- There are concerns about the acceptability of identifying "Laxative Inadequate Responders" using the Applicant's investigator-administered instrument. The applicant provided a qualitative study report/protocol for the investigator-administered questionnaire (as requested in a pre-submission meeting on January 24, 2012) (see Section 2.3 of this CDTL Review). A consult was requested for the review of this qualitative study report/protocol (see Section 11.4 of this CDTL Review).
- There are concerns with use of the term "laxative inadequate responders" to describe the subgroup identified because the use of laxatives for at least 4 out of 14 days may not be an adequate trial of laxatives in this population
- The types/number/and frequency of dosing of drugs patients report to have taken may not reflect a group of patients taking significant laxative therapy.

Although there remain concerns about the instrument such as recall bias which could influence the accuracy of the patient's responses (see Section 11.4) as well as the other concerns listed above, it seems reasonable to provide the results in this subgroup in the label if it is clear how the subgroup was identified (i.e., investigator-administered questionnaire; reported use of laxatives ≥4 out of 14 days) and what laxative classes (or combinations of laxative classes) were reported to have been used most frequently anytime during the 14-day period and on a daily basis. See Section 12.3 of this CDTL Review.

Second Secondary Endpoint: Time to First Post-Dose SBM

The second secondary endpoint was time to first post-dose SBM. The median time to first post-dose SBM was significantly shorter with naloxegol 25 mg compared to placebo in both Study 004 (6 vs. 36 hours; $p < 0.001$) and Study 005 (12 vs. 37 hours; $p < 0.001$), and for naloxegol 12.5 mg as compared to placebo in Study 004 (20 vs. 36 hours; $p < 0.001$). This secondary endpoint was not tested for naloxegol 12.5 mg versus placebo in Study 005 because the primary endpoint was not statistically significant. See table below.

Table 12. Time to First Post-dose SBM (Studies 004 and 005)

	Study 004			Study 005		
	Placebo (N = 214)	Naloxegol 12.5 mg (N = 213)	Naloxegol 25 mg (N = 214)	Placebo (N = 232)	Naloxegol 12.5 mg (N = 232)	Naloxegol 25 mg (N = 232)
Number of patients (%) with post-dose SBM	209 (97.7)	211 (99.1)	213 (99.5)	228 (98.3)	228 (98.3)	227 (97.8)
Median time (hours) to first SBM	35.8	20.4	5.9	37.2	19.3	12.0
Hazard Ratio†		1.61	2.38		1.590	1.58
95% CI		1.32, 1.96	1.93, 2.9		1.31, 1.93	1.30, 1.91
p-value		<0.001*	<0.001*		NT	<0.001*

Analysis conducted via log-rank test stratified by baseline laxative group
*Statistically significant after adjustment for multiplicity
†Hazard Ratio: Naloxegol/Placebo
NT = Not tested In Study 005, secondary endpoints were not tested for naloxegol 12.5 mg versus placebo because the primary endpoint was not statistically significant for this comparison.
CI = Confidence Interval
Table above is modified from the Clinical Review. Source is Summary of Clinical Efficacy Page 70.

Third Secondary Endpoint: Mean Number of Days Per Week with at least 1 SBM but no more than 3 SBM's

The third secondary endpoint was mean number of days per week with at least one SBM but no more than 3 SBMs in one day (analyzed via MMRM; see Section 7.2). Baseline mean number of days per week with at least one SBM but no more than 3 SBM's was 1.3 days in Study 004 and 1.4 days in Study 005, and was similar across the three arms of each study (see table below). There was a statistically significant change from baseline in the mean number of days per week with at least one SBM for naloxegol 25 mg compared to placebo in both Study 004 (2.5 vs. 1.7 days; $p<0.001$) and Study 005 (2.4 vs. 1.7 days; $p<0.001$), and for naloxegol 12.5 mg compared to placebo in Study 004 (2.2 vs. 1.7 days; $p<0.001$). This secondary endpoint was not tested for naloxegol 12.5 mg versus placebo in Study 005 because the primary endpoint was not statistically significant. See table below.

Table 13. Repeated Measures Analysis of Mean Number of Days Per Week with at Least 1 SBM (but no more than 3) over Weeks 1 to 12 –Studies 004 and 005 (ITT analysis set)

	Study 004			Study 005		
	Placebo (N = 213)	Naloxegol 12.5 mg (N = 213)	Naloxegol 25 mg (N = 214)	Placebo (N = 232)	Naloxegol 12.5 mg (N = 232)	Naloxegol 25 mg (N = 232)
Baseline, Mean (SD)	1.3 (0.85)	1.4 (0.81)	1.2 (0.94)	1.4 (0.89)	1.5 (0.86)	1.3 (0.84)
Change from baseline, LS mean (SE)	1.66 (0.13)	2.21 (0.13)	2.48 (0.13)	1.73 (0.12)	2.12 (0.12)	2.41 (0.13)
Difference vs Placebo LS mean		0.55	0.82		0.39	0.68
95% CI		0.24, 0.86	0.51, 1.13		0.09, 0.69	0.37, 0.98
p-value		<0.001*	<0.001*		NT	<0.001*

Analysis via Mixed Model for Repeated Measures (MMRM).
*Statistically significant after adjustment for multiplicity.
NT = Not Tested. In Study 005, secondary endpoints were not tested for naloxegol 12.5 mg versus placebo because the primary endpoint was not statistically significant.
Source is Summary of Clinical Efficacy Page 73.

7.4 Recommendation

An Approval Action is the final recommendation from a Clinical/Statistical standpoint.

Both the Clinical Reviewer and the Statistical Reviewer agreed that efficacy was demonstrated for the naloxegol 25 mg dose. The Statistical Reviewer commented that substantial evidence of efficacy for the 12.5 mg dose was not demonstrated because naloxegol 12.5 mg was not shown to be superior to placebo in Study 005. The Clinical Reviewer also noted this point, and recommended that only the 25 mg dose be approved because of the lack of serious safety concerns with the 25 mg dose (see Section 8.3 of this CDTL Review). However, the Clinical Reviewer also commented that the recommendation from the Clinical Pharmacology discipline that the label (Dosage and Administration section) contain instructions for dose reduction to 12.5 mg if the 25 mg dose is not tolerated due to abdominal pain should be considered (see Section 5.2 of this CDTL Review). The Clinical Reviewer noted that the 12.5 mg dose will be available on the market for special populations; thus, providing instructions on how and when to use the 12.5 mg dose may be appropriate. The Statistical Reviewer did not specifically comment on the dose reduction recommendation by the Clinical Pharmacology discipline. This Reviewer agrees with the dose reduction recommendation by the Clinical Pharmacology discipline; patients unable to tolerate the 25 mg dose may benefit from a decrease in the dose to 12.5 mg because the exposure-response analysis for efficacy indicated that response was similar over the range of 12.5 mg to 25 mg once a day (see Section 5.1.2 of this CDTL Review).

See Section 12.3 of this CDTL Review for a summary of the main revisions to the Applicant's proposed Dosage and Administration, and Clinical Studies sections of the label.

8 Safety

The reader is referred to the Clinical Review by Aisha Peterson Johnson for complete information.

8.1 Overview of Data Evaluated for Safety

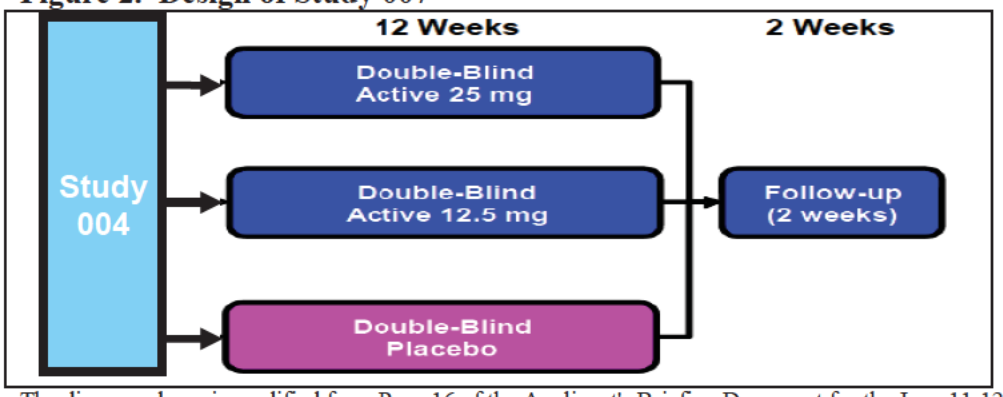
Analysis Populations

Three primary analysis sets were used for the review of safety:
(1) the 12-week pool (Studies 004 and 005),
(2) the placebo-controlled safety pool (Studies 004, 005, and 007), and
(3) the 52-week pool (Study 008).

Design of Studies 007, and 008

Study 007: The design of Study 007 is summarized in the figure below. Patients who completed Study 004 had the option of continuation of blinded treatment in Study 007.

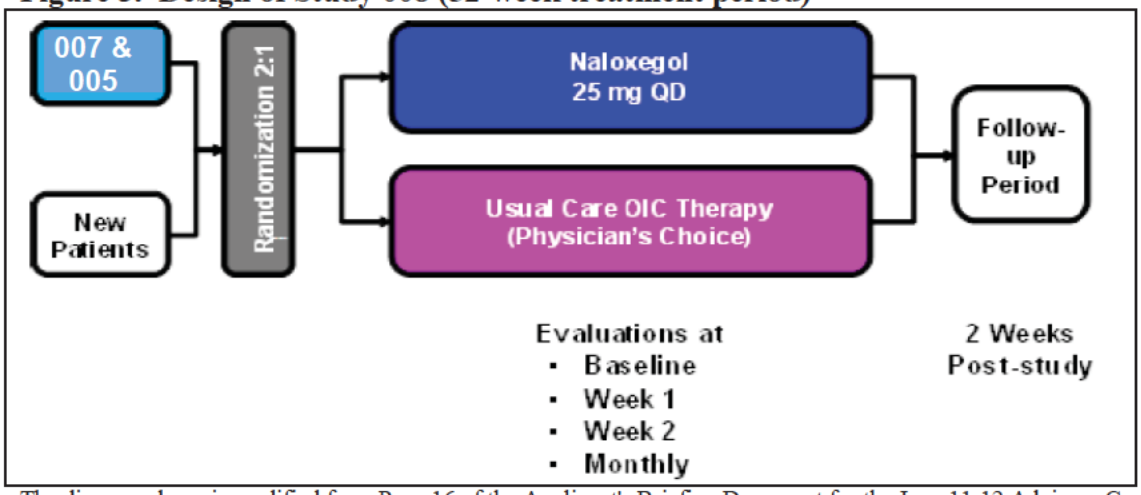
Figure 2. Design of Study 007



The diagram above is modified from Page 16 of the Applicant's Briefing Document for the June 11-12 Advisory Committee.

Study 008: The design of Study 008 is summarized in the figure below.

Figure 3. Design of Study 008 (52-week treatment period)



The diagram above is modified from Page 16 of the Applicant's Briefing Document for the June 11-12 Advisory Committee.

Entry into Studies 007 and 008

The rollover of patients from Study 004 to Study 007, from Study 005 to Study 008, and from Study 007 to Study 008, is summarized in the figure below.

Figure 4. Rollover of Patients from Study 004 to Study 007, from Study0 05 to Study 008, and from Study 007 to Study 008

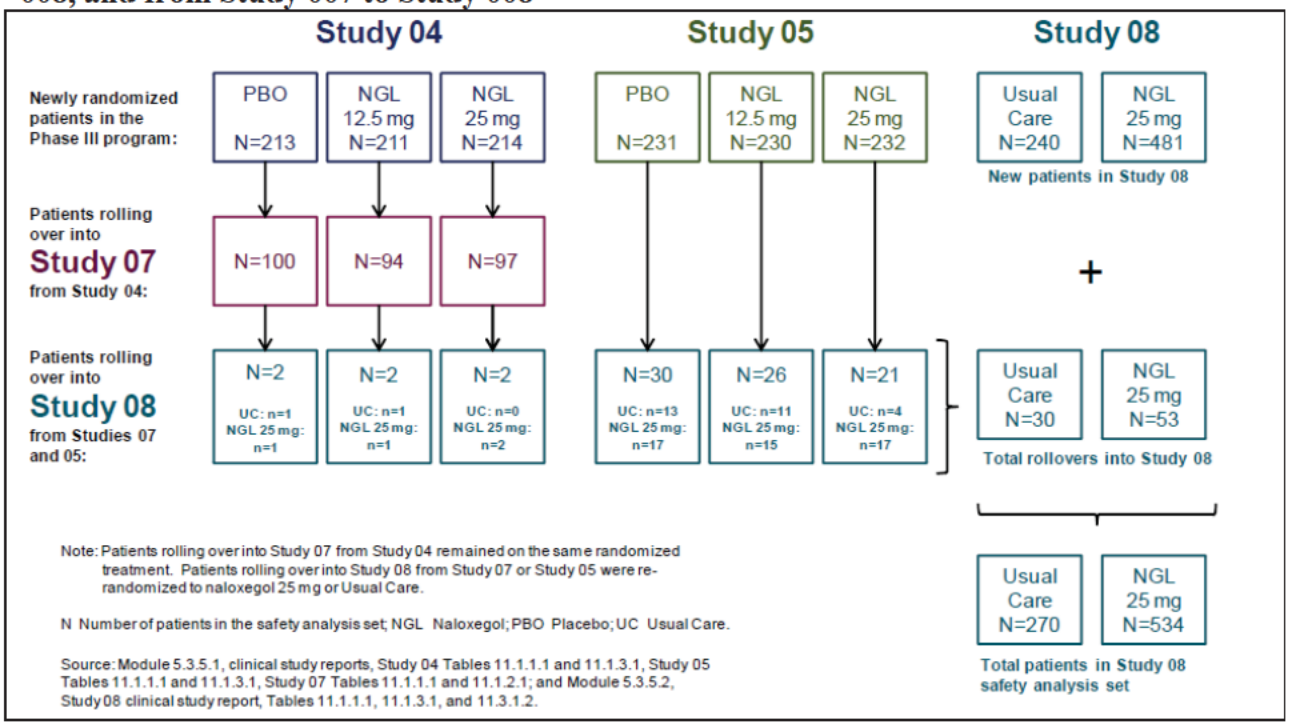


Figure above is taken from the Clinical Review

Disposition of Studies 007, and 008

Study 007: Of the 99 on naloxegol 25 mg, 82 (83%) completed. Of the 97 on naloxegol 12.5 mg, 77 (79%) completed. Of the 106 enrolled on placebo, 86 (81%) completed. (Source: Page 43 of the CSR for Study 007).

Study 008: Of the 534 enrolled on Naloxegol, 327 (61%) completed. Of the 270 on usual care, 189 (70%) completed. . (Source: Page 137 of the CSR for Study 008).

8.2 Exposure

Studies 004, 005, and 007 (Placebo-Controlled Pool):

The exposure in patient years was 115.8 patient years on Placebo, 112.3 patient years on naloxegol 12.5 mg, and 110.2 patient years on naloxegol 25 mg. See the table below.

Table 14. Duration of Exposure to Double-Blind Treatment (Placebo-controlled Pool) [Studies 004, 005, and 007])

	Placebo (N=444)	NGL 12.5 mg (N=441)	NGL 25 mg (N=446)
Duration (days)[a]			
Mean (SD)	95.3 (44.61)	93.0 (43.44)	90.3 (47.10)
Median	85	85	85
Range (min, max)	(1-189)	(1-184)	(1-183)
Total patient years[b]	115.8	112.3	110.2
Duration category: n (%)			
≥1 day	444 (100.0)	441 (100.0)	446 (100.0)
≥1 week	436 (98.2)	432 (98.0)	425 (95.3)
≥2 weeks	426 (95.9)	423 (95.9)	408 (91.5)
≥3 weeks	414 (93.2)	407 (92.3)	398 (89.2)
≥4 weeks	411 (92.6)	405 (91.8)	396 (88.8)
≥5 weeks	399 (89.9)	399 (90.5)	382 (85.7)
≥6 weeks	397 (89.4)	396 (89.8)	376 (84.3)
≥7 weeks	394 (88.7)	392 (88.9)	372 (83.4)
≥8 weeks	392 (88.3)	390 (88.4)	369 (82.7)
≥12 weeks	330 (74.3)	324 (73.5)	323 (72.4)
≥24 weeks	77 (17.3)	72 (16.3)	71 (15.9)

[a] The duration of exposure is calculated as the total number of days that the patient was prescribed double-blind study medication, from the randomized treatment start day to treatment end day.
[b] The total patient years is calculated as the sum of the duration of treatment exposure in years for all patients in the safety analysis set.
N Total number of patients; n Number of patients in category; NGL Naloxegol; SD Standard deviation.
Table from Clinical Review. Source is Summary of Clinical Safety p. 37.

Study 008:

The exposure in patient years was 219.3 patient years on usual care and 391.9 patient years on naloxegol. See the table below.

Table 15. Duration of Exposure to Naloxegol or Usual Care (Study 008)

	Usual Care (N = 270)	NKTR-118 25 mg (N = 534)
Duration (days) [a]		
n	270	534
Mean	296.7	268.1
SD	120.78	136.51
Median	360.0	358.0
Min	1	1
Max	399	394
Total patient years [b]	219.3	391.9
Duration category, n (%)		
≥1 day	270 (100.0)	534 (100.0)
≥1 week	258 (95.6)	517 (96.8)
≥4 weeks	249 (92.2)	477 (89.3)
≥12 weeks	235 (87.0)	430 (80.5)
≥24 weeks	224 (83.0)	393 (73.6)
≥36 weeks	210 (77.8)	365 (68.4)
≥50 weeks	191 (70.7)	330 (61.8)
≥51 weeks	187 (69.3)	317 (59.4)
≥52 weeks	61 (22.6)	85 (15.9)

Source: Page 68 of the Study 008 CSR.

8.3 Safety Findings

Deaths:

There were a total of seven deaths in the naloxegol clinical program. Narratives are provided in the table below (for deaths adjudicated as CV deaths; and for deaths adjudicated as non-CV deaths). (See discussion of CV-event adjudication committee (CV-EAC) in Appendix 5).

Table 16. Narratives of Deaths in the Naloxegol Clinical Program (Adjudicated as CV Deaths; Adjudicated as Non-CV Deaths)

Adjudicated as CV vs. Non-CV Deaths	Narrative
CV Deaths	▪ 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" 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.
	▪ 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; this event is not included in Table 18).*
Non-CV Deaths	▪ Study 04 Patient E4003038 was a 55-year-old female in the naloxegol 12.5 mg group. She had a SAE of pneumonia on Day 102, which led to a diagnosis of non-small cell lung cancer (reported as a SAE with onset on Day 109; follow-up information suggests that this was a pre-existing cancer). The non-small cell lung cancer resulted in the patient's death on Day 113. This event was adjudicated as a non-CV death.
	▪ Patient 43003, a 56-year-old White female with a history of recurrent deep vein thrombosis and inferior vena cava filter placement, received 6 doses of naloxegol 25 mg and died as a result of a pulmonary embolism 3 days after her last dose. A final autopsy report revealed a pulmonary embolus in the right pulmonary artery which caused a 100% occlusion, a thromboembolus in the right lower lobe, and thrombus material was present in the left lower extremity. There was mild pulmonary congestion and hepatic, renal, and splenic congestion. Cerebral edema with cerebellar tonsillar notching was also present.

CV: Cardiovascular
Narratives of the CV deaths are taken from the FDA Briefing Document and Errata Sheet for the June 11-12, 2014 Advisory Committee.
Narratives of the Non-CV deaths are taken from the Clinical Review.

Serious Adverse Events:

12-week pool (Studies 004 and 005): SAE's were reported in the 12-week pool (Studies 004 and 005) at rates of 5.2%, 5.7%, and 3.4% in the placebo, naloxegol 12.5 mg, and naloxegol 25 mg groups, respectively. See table below.

12-week extension (Study 007): SAE's were reported in the 12-week extension (Study 007) at rates of 5.0%, 6.4%, and 6.2% in the placebo, naloxegol 12.5 mg, and naloxegol 25 mg groups, respectively. See table below.

52-week safety study (Study 008): SAE's were reported in the 52-week safety study (Study 008) at rates of 11.1% and 9.6% in the usual care and naloxegol 25 mg groups, respectively.

Table 17. Number (%) of patients who had an SAE that was reported for ≥2 patients in any treatment group during the treatment period or post-treatment follow-up (Studies 04/05, 07, and 08)

	12-week pool (Studies 04 and 05)			12-week extension of Study 04 (Study 07)			52-week safety study (Study 08)	
	Placebo (N=444)	NGL 12.5 mg (N=441)	NGL 25 mg (N=446)	Placebo (N=100)	NGL 12.5 mg (N=94)	NGL 25 mg (N=97)	Usual care (N=270)	NGL 25 mg (N=534)
Any SAE	**23 (5.2)**	**25 (5.7)**	**15 (3.4)**	**5 (5.0)**	**6 (6.4)**	**6 (6.2)**	**30 (11.1)**	**51 (9.6)**
Non-cardiac chest pain	1 (0.2)	1 (0.2)	2 (0.4)	0	1 (1.1)	0	1 (0.4)	0
Abdominal pain	0	0	2 (0.4)	0	0	0	0	1 (0.2)
Pneumonia	1 (0.2)	3 (0.7)	1 (0.2)	0	0	1 (1.0)	1 (0.4)	5 (0.9)
Syncope	0	2 (0.5)	0	0	0	0	0	1 (0.2)
Accidental overdose	0	2 (0.5)	0	0	0	0	0	0
Renal failure acute	1 (0.2)	1 (0.2)	0	0	1 (1.1)	1 (1.0)	3 (1.1)	0
COPD	0	1 (0.2)	0	0	0	0	1 (0.4)	3 (0.6)
Back pain	0	0	0	0	0	0	1 (0.4)	2 (0.4)
Atrial fibrillation	0	0	0	0	0	0	1 (0.4)	2 (0.4)
Fibula fracture	0	0	0	0	0	0	0	2 (0.4)
Thoracic vertebral fracture	0	0	0	0	0	0	0	2 (0.4)
Tibia fracture	0	0	0	0	0	0	0	2 (0.4)
Suicide attempt	0	0	0	0	0	0	0	2 (0.4)
Asthma	0	0	0	0	0	0	2 (0.7)	1 (0.2)

Note: SAEs are sorted by preferred term by highest incidence on naloxegol 25 mg, then naloxegol 12.5 mg, then placebo in the 12-week pool; followed by naloxegol 25 mg in Study 08; then by naloxegol 25 mg, then naloxegol 12.5 mg, then placebo in Study 07.
COPD; Chronic obstructive pulmonary disease; N Total number of patients in the treatment group; NGL Naloxegol; SAE Serious adverse event.
Table above is modified from the Clinical Review. Source: Page 54 of the Summary of Clinical Safety.

Cardiovascular Events:

Cardiovascular events were identified as a topic of special interest program for two main reasons:

- There were findings in a phase 1 dog telemetry study of decreased blood pressure and heart contractility associated with the use of naloxegol (see Pharmacology/Toxicology Review).

- 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.[1]

The Applicant used a prospective adjudication process and convened a CV-event adjudication committee (CV-EAC) (see discussion of CV-EAC in Appendix 5 of this CDTL Review).

Overall Cardiovascular Events: The number (%) of patients with ≥1 CV outcome event during the treatment period or post-treatment follow-up as determined by the independent CV-EAC (Placebo-controlled Pool and Study 08) is shown in the table below.

- Placebo-Controlled Pool (Studies 004, 005, and 007): In the placebo-controlled pool (Studies 004, 005, and 007), the incidence rate of MACE was 0.5% (2/444), 0.5% (2/441), and 0.2% (1/446) in the placebo, naloxegol 12.5 mg, and naloxegol 25 mg groups, respectively. See table below.
- 52 week Safety Study (Study 008): In the 52 week safety study (Study 008), the incidence of MACE events was 0.7% and 0.4% in the usual care arm and naloxegol 25 mg arm, respectively. See table below.

[1] Meeting Materials for Gastrointestinal Drugs Advisory Committee for Entereg (alvimopan) dated January 23, 2008 available at the following link: http://www.fda.gov/ohrms/dockets/ac/cder08 html#gdac

Table 18. Number (%) of Patients with ≥1 CV Outcome Event During the Treatment Period Or Post-Treatment Follow-up as Determined by the Independent CV-EAC (Placebo-Controlled Pool and Study 008)

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[a]	7 (1.6)	12 (2.7)	13 (2.9)	11 (4.1)	11 (2.1)
Number of AEs submitted[a]	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)[b]	0	1 (0.2)
Stroke	0	0	0	1 (0.4)	0
Other CV events of interest per CV-EAC					
Hospitalization for unstable angina	0	0	0	0	0
Hospitalization for heart failure	0	0	1 (0.2)	1 (0.4)	0

[a] 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.

[b] 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.

The adjudicated events in the table 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 (see "Deaths" subsection above). All other events in the table represent unique patients.

Table above modified from the Clinical Review. Source: Summary of Clinical Safety, p 63

Acute MI: Narratives of patients with acute MI are provided in the table below.

Table 19. Narratives of patients with acute MI

Study/ Patient ID	Narrative
Study 04 Patient E4068050	▪ subject had both an MI and CV death (refer to narrative in CV death Section)
Study 04 Patient E4010003	▪ 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 Note that this patient died approximately 16 months after the MI; this death is not captured in the clinical database and is therefore not included in either Study 04 or pooled data presentations (and is therefore only the MI and not death is included in Table 9).
Study 05 Patient E5237018	▪ 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	▪ 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.
Study 08 Patient E8921021	▪ 55 year old woman in the naloxegol 25mg group. Past history included obesity and hyperlipidemia. On study Day 156 patient was admitted to the hospital with an altered level of consciousness and "twitching" and in the emergency room (ER) was noted to be confused. The patient was hospitalized the same day due to acute renal injury, rhabdomyolysis, elevated troponins, transaminitis and hyperkalemia. Troponin values were monitored as well as serial electrocardiograms (ECG). An ECG revealed junctional rhythm. Peak troponin I 1.74ng/mL (ref. range 0.00 to 0.10 ng/mL) and peak CKMB 199.1ng/mL (ref. range 0.0 to 5.0 ng/mL). The patient had a suspected preliminary diagnosis of non-ST elevated myocardial infarction but final diagnosis was elevated troponin. The event was eventually adjudicated as an acute myocardial infraction.

Narratives of the Acute MI's above are taken from the FDA Briefing Document and Errata Sheet for the June 11-12, 2014 Advisory Committee.

Stroke: The narrative of the patient with stroke is provided in the table below.

Table 20. Narrative of patient with stroke

Study/ Patient ID	Narrative
Study 08 Patient E8873013 (usual care group)	▪ 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 narrative of the stroke above is taken from the FDA Briefing Document and Errata Sheet for the June 11-12, 2014 Advisory Committee.

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

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. See discussion of the methods for assessment of blood pressure-related AE's in Appendix 6 of this CDTL Review.

Decreased BP: The incidence of decreased BP in the placebo-controlled pool and the 52-week safety study is shown below (see table below also).

- Placebo-Controlled Pool: In the placebo-controlled 12 week pool, the incidence of decreased BP was 0.7%, 0.5%, and 1.3% in the placebo, naloxegol 12.5 mg, and naloxegol 25 mg groups, respectively.
- 52-Week Safety Study: During the 52 week safety study, the incidence of decreased BP was 1.9% and 0.9% in the usual care and naloxegol groups, respectively.

Syncope: The incidence of syncope in the placebo-controlled pool and the 52-week safety study is shown below (see table below also).

- Placebo-Controlled Pool: In the placebo-controlled 12 week pool, the incidence of syncope was 0, 0.5%, and 0.4% in the placebo, naloxegol 12.5 mg, and naloxegol 25 mg groups, respectively.
- 52-Week Safety Study: During the 52 week safety study, the incidence of syncope was 0 and 0.6% in the usual care and naloxegol groups, respectively.

The clinical reviewer noted that 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: The incidence of syncope in the placebo-controlled pool and the 52-week safety study is shown below (see table below also).

- Placebo-Controlled Pool: In the placebo-controlled 12 week pool, the incidence of increased BP was 1.1%, 2.3%, and 2.9% in the placebo, naloxegol 12.5 mg, and naloxegol 25 mg groups, respectively.
- 52-Week Safety Study: During the 52 week safety study, the incidence of increased BP was 4.4% and 3.9% in the usual care and naloxegol groups, respectively.

The Clinical Reviewer noted the following regarding the results in the Placebo-Controlled Pool:

- 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.
- 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 (described below):
  - 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.

Table 21. Number (%) of patients with ≥1 AE related to BP changes during the treatment period (placebo-controlled pool and Study 08)

Topic/ Preferred term	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)
Decreased BP	**3 (0.7)**	**2 (0.5)**	**6 (1.3)**	**5 (1.9)**	**5 (0.9)**
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)
Syncope	**0**	**2 (0.5)**	**2 (0.4)**	**0**	**3 (0.6)**
Syncope	0	2 (0.5)	1 (0.2)	0	3 (0.6)
Presyncope	0	0	1 (0.2)	0	0
Increased BP	**5 (1.1)**	**10 (2.3)**	**13 (2.9)**	**12 (4.4)**	**21 (3.9)**
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: Summary of Clinical Safety, p 64/109

The Clinical Reviewer concluded that there was a small numerical imbalance, in the incidence of high blood pressure, low blood pressure, and syncope in the phase 3 trials.

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 DAAAP Consult Review.

DAAAP reviewed the key phase 3 trials 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, there were the following number (%) of patients by treatment arm experiencing possible DWS:
    - 12-week, placebo- controlled studies (04 and 05)
        - Placebo: 1 (0.2%)
        - Naloxegol 12.5 mg: 2 (0.5%)
        - Naloxegol 25 mg: 5 (1.1%)

- Using broader criteria (based upon Agency advice) for determining potential opioid withdrawal syndrome, defined by the presence of ≥3 preferred terms (PTs) potentially related to opioid withdrawal, the following incidences of potential opioid withdrawal were observed:
    - Study 04:
        - Placebo: 5(2%)
        - Naloxegol 12.5 mg: 4 (2%)
        - Naloxegol 25 mg: 10 (5%)
    - Study 05:
        - Placebo: 3 (1%)
        - Naloxegol 12.5 mg: 7 (3%)
        - Naloxegol 25 mg: 20 (9%)

  The above criterion is sensitive but not specific for identifying possible clinical DWS, in that many patients experienced ≥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 ≥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 were as follows:
    - Pooled 12-week, controlled studies:
        - Placebo: 1 (<1%)
        - Naloxegol 12.5 mg: 5 (1%)
        - Naloxegol 25 mg: 14 (3%)
    - Study 07:
        - Placebo: 0
        - Naloxegol 12.5 mg: 1 (1%)
        - Naloxegol 25 mg: 1 (1%)
    - Study 08:
        - Usual Care Group: 3/270 (<1%)
        - naloxegol 25 mg group: 10/534 (2%)

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 clinical trials had at least one PT potentially related to possible opioid withdrawal syndrome and at least one CV PT. However, only one patient who met the

criteria for possible opioid withdrawal syndrome was submitted to the CV-EAC for adjudication. The event was adjudicated as "other chest pain."

Common Adverse Events:

During the 12-week treatment period (Studies 04 and 05), any AE was reported by: 51.1% of placebo patients, 52.4% of naloxegol 12.5 mg patients, and 63.5% of naloxegol 25 mg patients. Abdominal pain was the most common AE reported in all treatment groups (5.6% of placebo patients, 9.8% of naloxegol 12.5 mg patients, and 15.9% of naloxegol 25 mg patients).

During the 52-week study, the incidence of any AE in the usual care arm was 71.9% compared with 80.1% in the naloxegol 25 mg treatment group. Abdominal pain was the most commonly reported AE in the naloxegol 25 mg treatment group (17.8%); abdominal pain was reported by 3.3% of the usual care group.

The Clinical Reviewer noted that severe abdominal pain was reported in 0.7% of placebo patients, 1.4% of naloxegol 12.5 mg patients, and 4.9% of naloxegol 25 mg patients (placebo-controlled pool). A smaller percentage of patients discontinued either study due to the AE of abdominal pain—0.7%, 0.9%, and 2.9% in placebo, 12.5 mg naloxegol, and 25 mg naloxegol patients, respectively.

The Clinical Reviewer commented that while common, abdominal pain did not result in a large percentage of discontinuations and only a small percentage reported an event as severe. Therefore, the Clinical Reviewer recommended only the approval of the 25 mg naloxegol dose (except for special populations) to avoid exposing patients to the 12.5 mg dose given that its efficacy could not be confirmed in both studies. However, the Clinical Reviewer noted that the 12.5 mg dose will be available on the market for special populations; thus, providing instructions on how and when to use the 12.5 mg dose may be appropriate (see Section 7.4 of this CDTL Review).

8.4 Recommendation

An Approval Action is the final recommendation from a Safety standpoint.

A PMR is recommended for a post-marketing, observational epidemiologic study comparing MOVANTIK (naloxegol) to other treatments of opioid induced constipation in patients with chronic non-cancer pain. The study's primary outcome is a composite of major adverse cardiovascular events (MACE): cardiovascular (CV) death, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcomes include, but are not limited to, CV death, nonfatal myocardial infarction, and nonfatal stroke separately. (See PMR wording in Section 13.5 of this CDTL Review.)

The DRISK Reviewer concluded that risk mitigation measures beyond professional labeling are not warranted for naloxegol at this time. The DRISK Reviewer noted that while there are serious risks of concern with the PAMORA class of drugs, there was no signal of an increased risk of these events with naloxegol in the premarketing safety database. Thus, the

benefit-risk profile for naloxegol is acceptable and the risks can be mitigated through professional labeling. (See DRISK Review.)

9 Advisory Committee Meeting

There was not a specific matters Advisory Committee meeting for this application.

However, a general matters meeting of the Anesthetic and Analgesic Drug Products Advisory Committee was convened on June 11-12, 2014 to 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 questions posed to the committee, the results of voting, and a summary of the discussion that took place are provided below:

1. **DISCUSSION:** 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)

    Committee Discussion: *There was a split in the committee members' view of whether the totality of the data suggests a cardiovascular safety signal associated with the use of peripherally active mu opioid receptor antagonists (PAMORAs). Among the committee members that did believe there was a signal, the consensus was that it was a weak signal but not ignorable; their concerns were primarily driven by the Entereg 12-month controlled trial. They advised that whatever studies are requested should be commensurate with the weakness of the signal. Others did not believe there was a cardiovascular safety signal with any member of the class. There was a general consensus that the available data were insufficient to implicate specific biologic mechanisms for the signal. Please see the transcript for details of the committee discussion.*

2. **DISCUSSION:** 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 to the peripherally active mu opioid receptor antagonist or

placebo, as add-on to background therapy. As part of this discussion, consider what would be an acceptable degree of risk that would need to be excluded in such a trial.

Committee Discussion: *The consensus of the committee was that while conducting a cardiovascular outcomes trial is feasible, there are a variety of challenges including, but not limited to, anticipated high dropout rates, and the large sample sizes that would be required to study a population that is not enriched with patients at higher cardiovascular risk. Additionally, the committee recommended that a compressed time frame may eliminate some of the challenges. A few panel members considered a 2-fold increase in risk as an acceptable degree of risk that would need to be excluded in such a trial. Please see the transcript for details of the committee discussion.*

3. **VOTE:** Should FDA require cardiovascular outcomes trials for peripherally active mu opioid receptor antagonists being developed for the treatment of opioid-induced constipation in patients with chronic, non-cancer pain?

   A. Yes, for all peripherally active mu opioid receptor antagonists
   B. Yes, but only for specific peripherally active mu opioid antagonists.
   C. No.

   Discuss your answer. If you choose option "B", please specify which specific mu opioid antagonists should be required to conduct a cardiovascular outcome trial and what concerns form the basis for such a requirement.

   A= 7 B= 5 C= 12 Abstain= 0

   Committee Discussion: *A number of panel members stated they felt the question implied all alternative trial design, such as observational studies, rather than randomized controlled clinical trials. Thus five members verbally changed their answer to "C" which occurred during the committee discussion and is not reflected in the voting results above. The majority of the panel members stated that they wanted to see an observational study conducted, not a randomized controlled clinical trial. However, of the seven panel members who stated that they did in fact intend to choose "A" or "B", the majority stated that they would like to see some kind of controlled clinical trials for Entereg. Two stated that the controlled clinical trial for Entereg would not necessarily have to be a dedicated cardiovascular outcome trial, i.e., limited to repeating the trial in which the signal was observed.*

4. **DISCUSSION:** 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 chronic, non-cancer pain, discuss whether the trial should be required in the pre-approval setting, required in the post-marketing setting, or in a combination of pre-approval and post-marketing settings.

   Committee Discussion: *Question 4 and 5 were discussed together and are summarized below under Question 5.*

5. **DISCUSSION:** 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. Describe specific outcomes that should be assessed in such a trial and the appropriate duration of the trial.

   Committee Discussion: *The consensus of the committee was that for products in development, pre-approval general safety trials should be of sufficient duration to assess long term outcomes (e.g., 12 months). In addition, the committee stated that post-marketing observational studies may also be conducted (post-approval) and that appropriate measures should be taken to enrich them with high cardiovascular risk patients. One member stated that post-marketing observational studies using the Mini-sentinel and Medicare databases may be used. Some members stated that a self-controlled study design may be an option. Please see the transcript for details of the committee discussion.*

10 Pediatrics

10.1 PREA Requirements

The Applicant requested (b) (4) DGIEP and PMHS (b) (4) recommended a full waiver of pediatric studies for OIC because studies would be impossible or highly impractical. The following justification for waiver was presented to PeRC on July 16, 2014:

- Based on the limited available literature, few pediatric patients in all age groups receive round the clock opioids for > 4 wks. There is a lack of consensus on the use of opioids for treatment of chronic non-cancer pain in pediatric patients. There is limited literature and data available in the use of opioid therapies in the pediatric population for conditions associated with chronic non-malignant pain (e.g., sickle cell disease). Multiple articles have noted that the feasibility of conducting safety and efficacy trials in pediatric patients remains a challenge in treatment of chronic pain in non-life limiting diseases.
- Pediatric patients would need to be on opioid therapies for a minimum of 1 month to meet enrollment criteria for a trial designed to evaluate treatment of opioid induced constipation in patients with chronic non-cancer pain. In addition, to adequately assess safety and efficacy in opioid induced constipation (OIC) trials, an adequate number of pediatric patients would need to be followed for 12 weeks for efficacy assessment followed by an additional 3 months for safety assessment for a total treatment duration of 6 months.

The PeRC agreed with the Division to grant a full waiver because studies are impossible or highly impractical.

See Section 13.4 of this CDTL Review.

(b) (4)

11 Other Relevant Regulatory Issues

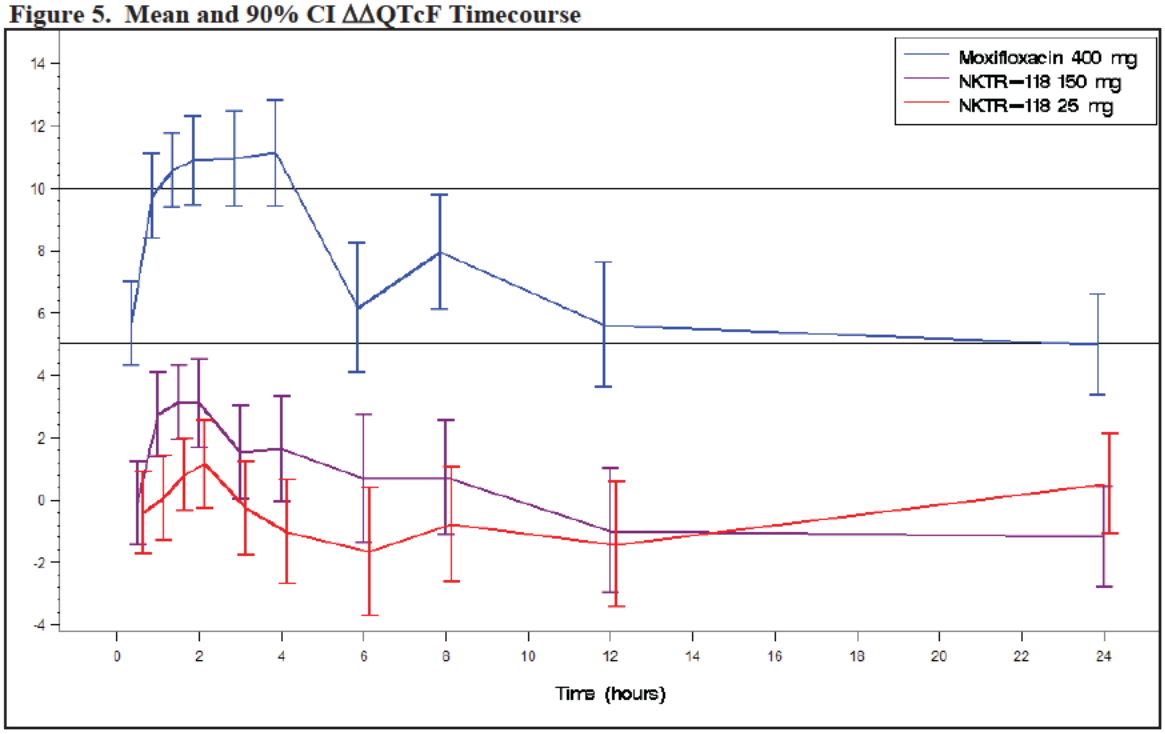
11.1 QT Evaluation

The reader is referred to the QT-IRT Consult Review by Janice Brodsky for complete information.

The QT-IRT Reviewer concluded the following (based on a randomized, blinded, four-period crossover study, of 51 healthy subjects who received NKTR-118, placebo, and a single oral dose of moxifloxacin 400 mg):

- No significant QTc prolongation effect of NKTR-118 was detected in this TQT study.
- The largest upper bound of the 2-sided 90% CI's for the mean differences between NKTR-118 and placebo is below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines.
- The largest lower bound of the two-sided 90% CI's for the ΔΔQTcF effect for moxifloxacin is greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in the figure below, indicating that assay sensitivity was established.

Figure 5. Mean and 90% CI ΔΔQTcF Timecourse



All CI's are unadjusted, including moxifloxacin.
Figure above is taken from Page 13 of the QT-IRT Review.

- The overall summary of findings is presented in the table below.

Table 22. The Point Estimates and the 90% CI's Corresponding to the Largest Upper Bounds for NKTR-118 and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
NKTR-118 25 mg	2	1.2	(-0.3, 2.6)
NKTR-118 150 mg	2	3.1	(1.7, 4.5)
Moxifloxacin 400 mg*	1.5 (2, 3, 4)	10.6	(9.4, 11.8)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 9.0 ms. The largest unadjusted lower bound was the same at all four time points.
Table above is taken from Page 2 of the QT-IRT Review.

- The supratherapeutic dose (150 mg) produces mean C_{max} values 7.7-fold the mean C_{max} for the therapeutic dose (25 mg). These concentrations are not above those for the predicted worst case scenario (drug interaction with ketoconazole). It is expected from drug interaction studies that co-administration of NKTR-118 with ketoconazole can elevate naloxegol's mean C_{max} as much as 9.6-fold.
- The Sponsor states that they plan to contraindicate co-administration of strong CYP3A4 and Pgp inhibitors.
- The maximum tolerated dose is 1000 mg, so the Sponsor could have given a higher dose in this study to cover this scenario.
- A significant relationship between naloxegol concentration and ΔΔQTcF was detected, although the predicted effect at the concentrations observed in this study is small (~ 2 ms).

11.2 Office of Scientific Investigations (OSI) Audits

11.2.1 OSI Site/Sponsor Inspections

The reader is referred to the OSI Clinical Inspection Summary (CIS) by Susan Leibenhaut for complete information.

Overview of Inspections and Final Classifications:

An overview of the four sites inspected and final classifications are presented in the table below. These four clinical sites were chosen because of high enrollment for the clinical trial and because of ranking on the risk-based site selection model. A focused sponsor inspection was also conducted because the product is a new molecular entity.

Table 23. Overview of Sites Inspected and Final Classifications

Investigator / Location / Site No.	Study	No. Pts*	Final Classification
Corey Jacobs Foley, AL / 5235	005	30	VAI
Mahendra Sanapati Evansville, IN / 4056	004	30	VAI
Egilius Spierings Watertown, MA / 5267	005	26	NAI
Rafaelito Victoria Anaheim, CA / 4068	004	44	NAI
Sponsor (Astra Zeneca) Wilmington, DE	004 and 005	N/A	NAI*

*Based on 7/17/14 NAI Letter to AstraZeneca by Lakisha Williams

Inspector's Key Findings:

The Inspector's key findings are summarized below for each of the four site inspections (by Clinical Investigator (CI)) and for the sponsor inspection.

Corey Jacobs:
A Form FDA 483 was issued for the following violations and Dr. Jacobs adequately responded:

- The investigation was not conducted in accordance with the investigational plan with specific instances as follows: (1) The protocol provided that patients on medications that may prolong the QT interval be excluded from the study, but one patient was enrolled who was taking a medication on this list (metoclopramide). (2) The protocol excluded patients who had ECG QTcF > 450 msec at screening, but one patient with an ECG QTcF of 454 at screening was enrolled. (3) The protocol required that subjects have colon cancer screening appropriate to risk, but seven subjects were enrolled without documentation of the screening (the reviewer noted that although this was cited as a protocol violation on the Form FDA 483, it is considered an instance of inadequate record keeping, because subjects had actually had previous colonoscopies). (4) The site

randomized one subject that had failed to meet the inclusion criterion of stable maintenance opioid regimen.

- The clinical investigator did not maintain adequate and accurate records for some start and stop dates for medications (on the Opioid Concomitant Medication Worksheet) with specific instances as follows: (1) One subject's maintenance medication was documented on the Worksheet as Opana ER 20 mg BID from 2010 to 08/01/11 and Opana ER 30 mg from 08/01/11 to ongoing, whereas the eCRF only documented Opana ER 30 mg BID from 2010 to ongoing. (2) One subject's maintenance medication was documented on the Worksheet as Morphine 15 mg TID from 2011 to 06/11/11, Morphine 30 mg TID 2009 to ongoing, and Lortab 10 mg TID 07/07/11 to ongoing whereas the eCRF only documented Morphine 30 mg TID from 2009 to ongoing and Lortab 10mg TID from 2011 to ongoing. (3) One subject's maintenance medication was documented on the Worksheet as Percocet 10/325 mg 1-2 tabs/every 6 hours from 06/25/11 to ongoing whereas the eCRF documented Percocet 10/325 mg 1-2 tabs/every 6 hours from 07/25/11 to ongoing.

The OSI Reviewer concluded that the violations noted above are not considered significant, and that the data generated by this site appear acceptable in supportive of the respective indication.

Mahendra Sanapati:

A Form FDA 483 was issued for the following violation and Dr. Sanapati adequately responded:

- The investigation was not conducted in accordance with the investigational plan. Specifically, the protocol provided that patients on medications that may prolong the QT interval be excluded from the study, but two patients were enrolled who were taking a medication on this list (one patient was taking amitryptiline; another patient was taking nortriptyline).

The OSI Reviewer concluded that the violations are isolated, and the data generated by this site appear acceptable in support of the respective indication.

Other Sites (Egilius Spierings; and Rafaelito Victoria):

No significant regulatory violations were noted. No Form FDA 483 was issued. There was no evidence of underreporting of AE's. The OSI Reviewer concluded that the data generated by each of these sites appear acceptable in support of the respective indication.

Sponsor Inspection:

Records from the four sites noted above and from one additional site (Site 4061 of Study 004) (Dr. James Shoemaker) (enrolling 18 subjects) were inspected. The OSI Reviewer concluded the following:

- Monitoring and other sponsor responsibilities were conducted adequately by the sponsor,
- The sponsor performed numerous vendor audits and clinical site audits prior to launch of the clinical studies.
- Study records were very well organized.
- There were two clinical investigator sites in Florida that were discontinued and these site terminations were reported to FDA.
- Primary efficacy endpoint data were able to verified by comparing the spontaneous bowel movement data located in the e-diary records with the line

listing data for 12 randomly selected subjects and no discrepancies were found.
- No regulatory violations were noted and no Form FDA 483 was issued.

The OSI Reviewer concluded that the studies appear to have been conducted adequately, and the data generated by the sponsor appear acceptable in support of the respective indication.

Final Conclusion:
OSI concluded that the studies appear to have been conducted adequately, and the data generated by each of the four sites and by the sponsor may be used in support of the respective indication.

11.2.2 For-Cause Site Inspection

In addition to the site investigations described above, there was a for-cause inspection of another site (Site 8703 of Study 008) (Dr. Ana Fandino) (randomizing (b) (4) subjects); the sponsor discovered issues with this site in a site audit in June 2012, and alerted the FDA. After the for cause inspection, OSI recommended that data from two patients in Study 008 (patients 014 and 030) not be used in support of this application because the patients were not eligible to enter the study (see OSI Warning Letter dated December 31, 2013 filed under IND 78781; and Clinical Review by Aisha Peterson Johnson).

Prior to data lock, the Applicant excluded patients from this site (Site 8703 of Study 008). In addition, the Applicant excluded patients from an associated site (Site 8939 of Study 008) (randomizing 5 subjects) because there was enrollment at Site 8703 of subjects previously or concurrently enrolled in the same study (Study 008) at Site 8939 (see OSI Warning Letter dated December 31, 2013 filed under IND 78781; and Clinical Review by Aisha Peterson Johnson). It should be noted that additional letters were sent on March 5, 2014 and April 30, 2014 that were the same as the December 31, 2013 letter except for different addresses of Dr. Fandino; both the December 31, 2013 and March 5, 2014 letters were returned because the US Postal Service was unable to forward to Dr. Fandino's current address.

11.3 Controlled Substance Staff (CSS) Review

The reader is referred to the Controlled Substance Staff (CSS) Review by Katherine Bonson for complete information.

The CSS Reviewer noted that naloxegol is currently a Schedule II drug under the Controlled Substances Act (CSA), based on a provision in the CSA that places all derivatives of opium and opioids, including thebaine, into Schedule II.

The CSS Reviewer concluded based on review of the nonclinical and clinical abuse-related data submitted in this NDA that naloxegol is primarily a full opioid antagonist with limited CNS activity; as such, naloxegol does not have abuse potential that is similar to controlled substances in the CSA. The CSS Reviewer provided the following as the basis for these conclusions:
- Naloxegol has limited central nervous system activity, but its primary activity is interaction with peripheral mu-opioid receptors. The peripheral activity of naloxegol is due to its derivation through the attachment of a seven unit ethylene oxide side chain

(also known as a polyethylene oxide or polyethylene glycol (PEG) side chain) to the alpha-naloxol (α-naloxol) molecule (which is synthesized from naloxone by reduction of the ketone group). The PEG side chain restricts penetration of naloxegol across the blood brain barrier, limiting its action on the central nervous system.

- Distribution studies show that naloxegol has little brain and spinal cord penetration. Low central activity suggests that a drug has little possibility for abuse potential.
- Naloxegol acts primarily as a full mu opioid antagonist. In receptor binding studies with 327 sites, naloxegol showed high affinity for mu opioid (7-34 nM), kappa opioid (9-187 nM) and delta opioid (54-203 nM) receptors, but no other sites. Second messenger studies that evaluated [^{35}S]GTPγS binding at opioid receptors showed that naloxegol is a full mu and delta opioid antagonist, but has no mu opioid agonist activity and limited partial kappa opioid agonist activity.
- Naloxegol does not produce opioid-like behaviors. In toxicological studies, naloxegol did not produce general behavioral changes that were different from those induced by vehicle in a 28-day rat study and in 14-day and 28-day beagle studies. Similarly, in the Irwin test (a dedicated general behavioral test), naloxegol did not produce alterations in behavior compared to vehicle.
- Naloxegol does not produce opioid-like analgesic responses. In two tests of analgesia (grid stimulation test and a hotplate test), naloxegol did not produce any behavioral changes different from those produced by vehicle. In contrast, morphine produced expected opioid-like analgesia in these tests.
- Naloxegol does not produce an opioid-like interoceptive cue. In a drug discrimination test with animals trained to discriminate morphine from saline, naloxegol by itself generalized to saline. When naloxegol was given as a pretreatment prior to morphine administration, naloxegol blocked the ability of morphine to induce a response on the morphine-associated lever, demonstrating its ability to act centrally as an opioid antagonist.
- Naloxegol does not produce opioid-like rewarding properties. In animals trained to self-administer cocaine, exposure to naloxegol produced the same level of self-administration as that of saline. In contrast, exposure to morphine produced the expected high level of self-administration compared to saline, showing that it has rewarding properties.
- Chronic administration of naloxegol does not produce physical dependence. In animals treated with naloxegol for 14-30 days, there were no behavioral changes upon drug discontinuation compared to saline. In contrast, morphine produced a classic opioid withdrawal syndrome following chronic administration and subsequent discontinuation of the drug.
- Human pharmacokinetic studies show that naloxegol is rapidly absorbed (Tmax = 1.5-2.0 hours), with a half-life of 7-9 hours. The majority of naloxegol (81%) is eliminated intact in urine. There are no active metabolites.
- Naloxegol does not produce abuse-related adverse events in healthy individuals. In 14 Phase 1 pharmacokinetic, safety and tolerability studies in which healthy individuals received naloxegol at doses ranging from 8 to 1000 mg, no adverse events representative of any euphoria-related signs or symptoms were reported. Few individuals in these studies experienced any nervous system or psychiatric disorders, which were generally limited to dizziness (0-25%), headache (0-25%), and paresthesia (0-13%).

- It is not possible to determine if naloxegol produces abuse-related Aes from efficacy studies conducted in patients. All patients in the Phase 2/3 efficacy and safety studies received opioids for pain management and then received naloxegol to determine if naloxegol could prevent opioid-induced constipation. Since opioids produce abuse-related Aes, it is not possible to attribute abuse-related Aes to naloxegol administration.
- Naloxegol does penetrate the human brain sufficiently to produce withdrawal symptoms in patients taking opioids for analgesia. In Phase 2/3 studies, the overall incidence of naloxegol-induced withdrawal was low, but slightly higher than that of placebo (2% vs. 1%, respectively). There was a greater incidence of opioid withdrawal in patients receiving the higher 25 mg dose of naloxegol (14/446=3%) compared to those receiving the lower 12.5 mg dose of naloxegol (5/441=1%). It is unclear from the data whether the withdrawal signs in humans are mediated through central or peripheral mechanisms, but the animal drug discrimination data show that naloxegol can antagonize a centrally-mediated behavioral response.

The CSS Reviewer recommended that:
- The Sponsor-proposed text for Section 9.0 (Drug Abuse and Dependence) be accepted.
- Naloxegol be recommended for decontrol under the Controlled Substances Act.

11.4 Qualitative Study Report/Protocol for Investigator-Administered Questionnaire to Assess Baseline Laxative Response Status

The applicant provided a qualitative study report/protocol for the investigator-administered questionnaire used to identify a subgroup of patients ("laxative inadequate responders") for assessment of the first secondary endpoint (see Section 7.3 of this CDTL Review). This qualitative study report/protocol was requested in a pre-submission meeting on January 24, 2012 (see Section 2.3 of this CDTL Review). (See Appendix 1 Baseline Laxative Response Status Questionnaire; and Appendix 2 Definitions of LIR, LAR, and LUR.)

A consult was requested for the review of this qualitative study report/protocol. The consult reviewer (Shelly Harris) concluded and recommended the following:

1. The qualitative research study report focused on the Stool Symptom Screener (four constipation symptom questions that are a part of the BLSRQ) and not the entire BLSRQ. The reviewer is not able to assess if the BLSRQ is appropriate for defining the laxative inadequate responder (LIR) population since only the content validity of the four questions was assessed in the qualitative exploratory study report. The entire instrument for the BLSRQ was not assessed with this qualitative research study.

2. The reviewer is unable to determine if the sub-population is appropriately categorized as LIRs (laxative inadequate responders) from the qualitative research report. The criteria used to determine classification into the LIR group was taking laxatives at least four times in a two week period and rating one of four constipation symptoms as moderate, severe, or very severe. There is no additional data that suggests that this is an inadequate response to laxatives.

In addition, patients in the non-LIR group (patients who did not take laxatives in the past two weeks or patients that took laxatives less than four times in the past two weeks) could be considered inadequate responders to laxatives. The majority of patients in the non-LIR group were classified as laxative unknown responders (LUR). In additional clinical studies (Studies 4 and 5-Intent to treat analysis set), patients in the LUR group that did not currently take laxatives were asked why they did not use them. Despite low response rates, 31% (Study 4) and 30% (Study 5) of participants stated it was because of inadequate relief of constipation when using laxatives.

In the initial protocol, participants were classified as laxative inadequate responders (LIR) or laxative adequate responders (LAR), based on the response to the question:

a. Were you satisfied with the amount of symptom relief provided from the laxative(s)?
b. □ Yes (classify as laxative adequate responder)
c. □ No (classify as laxative inadequate responder)

In the revised protocol, the criteria were changed to LIR and non-LIR based on the definitions above. Participants were still asked if they were satisfied with the amount of symptom relief they received from the laxative. Therefore, participants classified as LIR could still report satisfaction with the symptom relief received from the laxative.

3. Overall, participants stated that they would be able to remember the specific constipation symptoms included in the Stool Symptom Screener, over a two-week time period. Participants stated that the two-week time period was reasonable to assess number of bowel movements and number of laxatives used. In the interview guide, participants were also asked what time frame would be best for them to remember constipation symptoms, number of bowel movements, and number of laxatives used. In a response to Information Request, the Sponsor reported that the majority of participants (85% or more) stated that two weeks was a reasonable time frame to remember these items.

4. We are concerned that the two-week recall period may be too long in terms of the entire BLSRQ. The Stool Symptom Screener is adapted from the Patient Assessment of Constipation Symptoms (PAC-SYM), a 12-item questionnaire developed to measure patient's experience of symptoms and symptom severity in constipation over time. The PAC-SYM uses a two-week recall period but this instrument only focuses on symptoms and severity of symptoms. Patients are not required to report items such as number of times symptoms occurred, number of bowel movements, or number of times laxatives are used. Other instruments that have been validated in OIC populations use shorter recall periods ranging from daily to the prior week[2345]. One study reported significant

[2] Constipation Assessment Scales (CAS) (prior week); Bowel Function Index (1 week); Bowel Function Diary (daily recording of the number and type of bowel movements)

[3] Coffin B. and Causse C. Constipation assessment scales in adults: a literature review including the new Bowel Function Index (2011) Expert Reviews. Gastroenterology. Hepatology. 5(5), 601-613.

[4] Camilleri et al. (2010) Validation of a Bowel Function Diary for Assessing Opioid-Induced Constipation. The American Journal of Gastroenterology. 106; 497-506.

[5] Ducrott, P. and Causse, C. (2012) The Bowel Function Index: A new validated scale for assessing opioid-induced constipation. Current Medical Research and Opinion. 28 (3); 457-466.

differences between data collected from questionnaires and data collected from a daily diary about bowel habits based on the patient's recall even after only a few days[6]. Another study reported that symptoms for IBS-C (constipation-predominant IBS) would best be assessed in a 7-day time period[7].

5. DRISK is not the appropriate group to determine if it is acceptable to report results in the labeling.

12 Labeling

12.1 Proprietary Name

For complete information, see the DMEPA Proprietary Name Review by Lisa Khosla, dated October 31, 2013.

DMEPA concluded that the proprietary name of "Movantik" was acceptable. This was communicated to the Applicant in the Proprietary Name Request Conditionally Acceptable Letter dated November 1, 2013, along with a statement that the proposed proprietary name of "Movantik" will be re-reviewed 90 days prior to the approval of the NDA.

12.2 Office of Prescription Drug Promotion (OPDP) Comments

The Office of Prescription Drug Promotion (OPDP) determined that the proposed name (Movantik) is acceptable from a promotional perspective. This is documented in the Proprietary Name Review by Lisa Khosla, dated October 31, 2013.

12.3 Physician Labeling / Medication Guide / Carton and Container Labeling

The main revisions to the Applicant's proposed Physician Labeling are summarized below:

- Dosage and Administration (Section 2 of Label): The Applicant's proposed 25 mg once daily dose appeared to be an adequate starting dose for the overall population. A recommendation for dose reduction to a 12.5 mg once daily dose was added for patients unable to tolerate the 25 mg once daily starting dose. In addition, a recommendation for a 12.5 mg once daily dose was added for patients with renal impairment, and for patients receiving concomitant moderate CYP3A4 inhibitors.. An explanation was added that sustained exposure to opioids prior to starting naloxegol may increase the patient's sensitivity to the effects of naloxegol; also, a statement was added that efficacy was demonstrated in patients that had taken opioids for at least 4 weeks. A statement was included that laxatives can be used as needed if there is a suboptimal response to

[6] Bellini et al. (2010) The daily diary and the questionnaire are not equivalent for the evaluation of bowel habits. Digestive and Liver Disease 42; 99-102

[7] Norquist et al. (2012). Choice of recall period for patient-reported outcome (PRO) measures: criteria for consideration. Quality of Life Research. 21 (6); 1013-1020.

naloxegol after three days. A statement was added that alteration in analgesic dosing regimen prior to initiating naloxegol is not needed.

- Warnings and Precautions (Section 5 of Label): The applicant had originally proposed the statement [redacted] Based on these recommendations, the statement was revised to "Patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal or reduced analgesia."

- Drug Interactions (Section 7 of Label): A table was added summarizing the clinically significant drug interactions (strong CYP3A4 inhibitors, moderate CYP3A4 inhibitors, grapefruit or grapefruit juice, strong CYP3A4 inducers, and other opioid antagonists) along with clinical recommendations and the reference to the section of the label with additional information.

- Mechanism of Action (Section 12.1 of Label): The revised wording for this section is below:

  "Naloxegol is an antagonist of opioid binding at the mu-opioid receptor. When administered at the recommended dose levels, naloxegol functions as a peripherally-acting mu-opioid receptor antagonist in tissues such as the gastrointestinal tract, thereby decreasing the constipating effects of opioids.

  Naloxegol is a PEGylated derivative of naloxone, and is a substrate for the P-glycoprotein transporter (P-gp). Also, the presence of the PEG moiety in naloxegol reduces its passive permeability as compared with naloxone. Due to the reduced permeability and increased efflux of naloxegol across the blood-brain barrier, related to P-gp substrate properties, the CNS penetration of naloxegol is expected to be negligible at the recommended dose levels limiting the potential for interference with centrally mediated opioid analgesia."

  It should be noted that the wording proposed by the applicant [redacted]

- Mechanism of Action (Section 12.1 of Label) and Pharmacodynamics (Section 12.2 of Label): The use of the term "mu-opioid receptor" was limited to these sections in the

context of the description of the mechanism of action. The other sections of the label use the term "opioid receptor" which is the established pharmacological class.

- Clinical Studies (Section 14 of Label): Key revisions to this section included the following:
  - A statement was added that patients suspected of having clinically important disruptions to the blood-brain barrier were not enrolled in the two studies.
  - The first secondary endpoint was assessed in a subgroup of patients that reported using PRN laxatives for at least 4 out of 14 days without resolution of OIC symptoms (see Appendices 1 and 2 of this CDTL Review). (b) (4) the patients were described as follows: "These patients (identified using an investigator-administered questionnaire), prior to enrollment, had reported using laxative(s) at least 4 out of the past 14 days with at least one of the following OIC symptoms of moderate, severe or very severe intensity: incomplete bowel movements, hard stool, straining, or sensation of needing to pass a bowel movement but unable to do so." In addition, to better describe this subgroup, the following information was added: (1) the percentages of patients in this subgroup in each study that reported using laxatives on a daily basis; (2) the most frequently reported laxative classes used on a daily basis and the associated percentages of patients in this subgroup in each study for each laxative class; (3) the percentages of patients in this subgroup in each study that reported use of two laxative classes anytime during the 14 days prior to enrollment; and (4) the most commonly reported combination of laxative classes and associated percentages of patients in this subgroup in each study.

In addition to these revisions, additional revisions are currently being negotiated with the Applicant. Many of these revisions are based on recommendations from the DMPP Patient Labeling Review and the OPDP Labeling Review.

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the carton and container labels. They made a number of recommendations that were communicated to the Applicant on July 25, 2014 (see DMEPA Label and Labeling Review); it should be noted that the letter sent also incorporated recommendations from the Quality Review (see Section 3.4 of this CDTL Review).

13 Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

All of the review disciplines recommended an Approval action. This Reviewer concurs with the recommendations from each of the disciplines.

13.2 Risk Benefit Assessment

The benefit of naloxegol for OIC in adult patients with chronic non-cancer pain has been established in the clinical trials. The safety profile was acceptable based on what was found in the clinical trials. While there are serious risks of concern with the PAMORA class of drugs, there was no signal of an increased risk of these events with naloxegol in the premarketing safety database.[8] The benefit-risk profile for naloxegol is favorable and the risks can be mitigated through professional labeling (see Section 12.3 of this CDTL Review) and a required postmarketing observational study (see Section 13.5 of this CDTL Review).

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategy Requirements (REMS)

No special postmarketing risk management activities are recommended for this Application.

13.4 Recommendation for Postmarketing Required Pediatric Studies

Postmarketing required pediatric studies under PREA are not recommended for the current application, with the following language for the Approval Letter.

> **REQUIRED PEDIATRIC ASSESSMENTS**
>
> Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.
>
> We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. Based on the limited available literature, few pediatric patients in all age groups receive round-the-clock opioids for greater than 4 weeks. There is also a lack of consensus on the use of opioids for the treatment of chronic non-cancer pain in pediatric patients.

[8] DRISK Review by Nyedra Booker dated June 10, 2014.

13.5 Recommendation for other Postmarketing Study Requirements (PMRs)

The following other postmarketing required study is recommended for the current application, with the following language for the Approval Letter.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of major adverse cardiovascular events: cardiovascular (CV) death, nonfatal myocardial infarction, and nonfatal stroke.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2779-1 A post-marketing, observational epidemiologic study comparing MOVANTIK (naloxegol) to other treatments of opioid induced constipation in patients with chronic non-cancer pain. The study's primary outcome is a composite of major adverse cardiovascular events (MACE): cardiovascular (CV) death, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcomes include, but are not limited to, CV death, nonfatal myocardial infarction, and nonfatal stroke separately. Specify concise case definitions and validation algorithms for the primary and secondary outcomes. Justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to MOVANTIK (naloxegol)-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, MACE risk among MOVANTIK (naloxegol) users relative to comparator(s) considering important potential confounders including lifestyle risk factors and over the counter (OTC) medications with potential for cardiovascular effects, with a pre-specified statistical analysis method. For the MOVANTIK (naloxegol)-exposed and comparator(s), clearly define the new user clean period, including any exclusion and inclusion criteria. Ensure an adequate number of patients with at least 12 months of MOVANTIK (naloxegol) exposure at the end of the study.

The timetable you submitted on September 12, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	May 2015
Interim Report Submission:	June 2018
Study Completion:	December 2021
Final Report Submission:	December 2023

Submit the protocol to your IND 078781, with a cross-reference letter to this NDA. Submit the interim and final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: "**Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o).**"

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

13.6 Recommendation for Postmarketing Study Commitments (PMCs)

The following clinical pharmacology postmarketing commitment is recommended for the current application, with the following language for the Approval Letter.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

2779-2 An *in vitro* study to evaluate the time-dependent/mechanism-based inhibition potential of naloxegol on the hepatic CYP2C8 enzyme.

The timetable you submitted on September 12, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	December 2014

Study Completion:	March 2015
Final Report Submission:	April 2015

13.7 Recommended Comments to Applicant

None.

APPENDIX 1: Baseline Laxative Response Status Questionnaire (BLRSQ)

The Baseline Laxative Response Status Questionnaire (BLRSQ) is shown in the figures below. Note that items 11-14 (Severity of Symptoms) are also referred to as the "Stool Symptom Screener". Note also that Item 15 (Laxative Side Effects) was removed from the determination of LIR, LAR, and LUR status (see Appendix 2).

Figure 6. Baseline Laxative Response Status Questionnaire (Items 1-10)

Baseline Laxative Response Assessment [LAXRESP1SC]		
1.* ✔	Has the patient taken a laxative over the past two weeks to relieve constipation while being prescribed an opioid pain reliever? [Any Laxative Taken]	**[LXTKN]** [A:0] ◯ No [A:1] ◯ Yes, specify below
Laxative Class Usage [LAXRESP2SC]		
Ask the patient to describe the use of each of the following laxatives over the past two weeks. Please ask the patient to select a number between 0 (no use) and 14 days (daily use) in the past two weeks.		
2. ✔	Stimulants such as ExLax, Correctol, Dulcolax, Senokot, or natural products known to contain senna, cascara or known stimulant laxative [Stimulants]	**[LXCLDAYS1]** N2
3. ✔	Lubricants such as mineral oil, glycerol and Fleet [Lubricants]	**[LXCLDAYS2]** N2
4. ✔	Osmotics such as Cephulac, Sorbitol and Miralax [Osmotics]	**[LXCLDAYS3]** N2
5. ✔	Saline laxatives such as Milk of Magnesia and Magnesium Citrate [Saline Laxatives]	**[LXCLDAYS4]** N2
6. ✔	Stool softeners, such as Docusate and Colace [Stool Softeners]	**[LXCLDAYS5]** N2
7. ✔	Polyethylene Glycol (PEG), such as Miralax [Polyethylene Glycol]	**[LXCLDAYS6]** N2
8. ✔	Bulk laxatives, such as psyllium or methylcellulose [Bulk Laxatives]	**[LXCLDAYS7]** N2
9. ✔	Prescription constipation products such as Amitiza, Resolor, or Zelnorm [Prescribed]	**[LXCLDAYS8]** N2
10. ✔	Prescription opioid induced constipation products such as Relistor or Entereg [Prescribed OIC]	**[LXCLDAYS9]** N2

Source: Response to Information Request received August 13, 2014.

Figure 7. Baseline Laxative Response Status Questionnaire (Items 11-16)

Severity of Symptoms [LAXRESP3SC]		
Ask the patient to rate the severity of the following symptoms been over the past 2 weeks?		
11. ✔	Feeling like you experience incomplete bowel movements (i.e., like you didn't finish)? [Feel Like Bowel Movements are Incomplete]	**[INCOMPBM]** [A:0] ◯ Absent [A:1] ◯ Mild [A:2] ◯ Moderate [A:3] ◯ Severe [A:4] ◯ Very Severe
12. ✔	Feeling like your bowel movements were too hard? [Feel Like Bowel Movements are Too Hard]	**[HARDBM]** [A:0] ◯ Absent [A:1] ◯ Mild [A:2] ◯ Moderate [A:3] ◯ Severe [A:4] ◯ Very Severe
13. ✔	Feeling like you had to strain or squeeze to try to pass bowel movements? [Feel Like Had to Strain or Squeeze BM]	**[STRSQZBM]** [A:0] ◯ Absent [A:1] ◯ Mild [A:2] ◯ Moderate [A:3] ◯ Severe [A:4] ◯ Very Severe
14. ✔	Feeling like you had to pass a bowel movement but you couldn't, like a false alarm? [Feel Like a BM But Was False Alarm]	**[FALSEBM]** [A:0] ◯ Absent [A:1] ◯ Mild [A:2] ◯ Moderate [A:3] ◯ Severe [A:4] ◯ Very Severe
Laxative Side-Effects [LAXRESP4SC]		
15. ✔	Assess if the patient has experienced any side-effects from a laxative which decreased the patient's willingness to take that laxative? Common side effects include gas, bloating, cramping, diarrhea, and abdominal pain. [Side Effect Decrease Willing to Take Lax]	**[LXSIDEFF]** [A:0] ◯ No [A:1] ◯ Yes
Laxative Response [LAXRESP5SC]		
16. ✔	Patient's Laxative Response *[read-only]* [Patient's Laxative Response]	**[LXPTRESP]** [A:1] ◯ Laxative Adequate Response [A:2] ◯ Laxative Inadequate Response [A:3] ◯ Laxative Unknown Response
Key: [*] = Item is required [✔] = Source verification required		

Items 11-14 (Severity of Symptoms) are also referred to as the "Stool Symptom Screener".
Item 15 (Laxative Side Effects) was removed from the determination of LIR, LAR, and LUR status (see Appendix 2).
Source: Response to Information Request received August 13, 2014.

APPENDIX 2: Definitions of LIR, LAR, and LUR

Definitions

Use of laxatives and the severity of these symptoms during the 2 weeks prior to screening were used to classify patients as LIR, LAR, or LUR according to the following definitions:

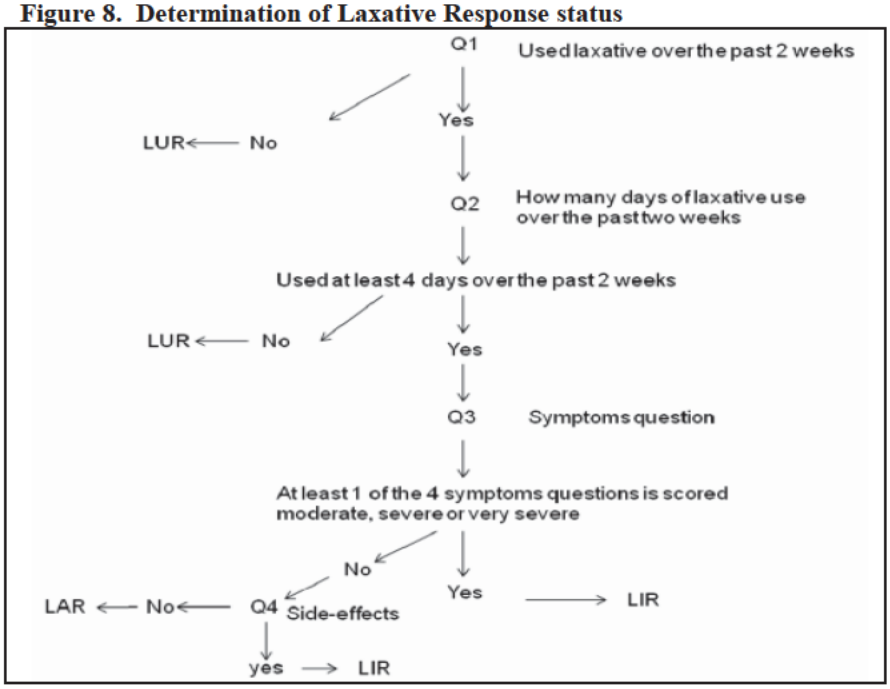
Status	Definition
LIR:	If a patient reported both having used laxative(s) on a minimum of 4 days and continued moderate, severe, or very severe stool symptoms (in response to at least 1 of the Stool Symptom domain questions*), he/she was classified as LIR.
LAR:	If the patient reported both having used laxative(s) on a minimum of 4 days and absent or mild stool symptoms (in response to all Stool Symptoms domain questions*), he/she was classified as LAR.
LUR:	If the patient reported no use of laxatives over the previous 2 weeks, or reported infrequent use, as defined by having used laxatives less than a minimum of 4 days over the previous 2 weeks, he/she was classified as LUR.

*See Stool Symptom Screener in Appendix 1.
The table above is summarized from Page 24 of the Summary of Clinical Efficacy.

Flowchart for Determination of Laxative Response Status:

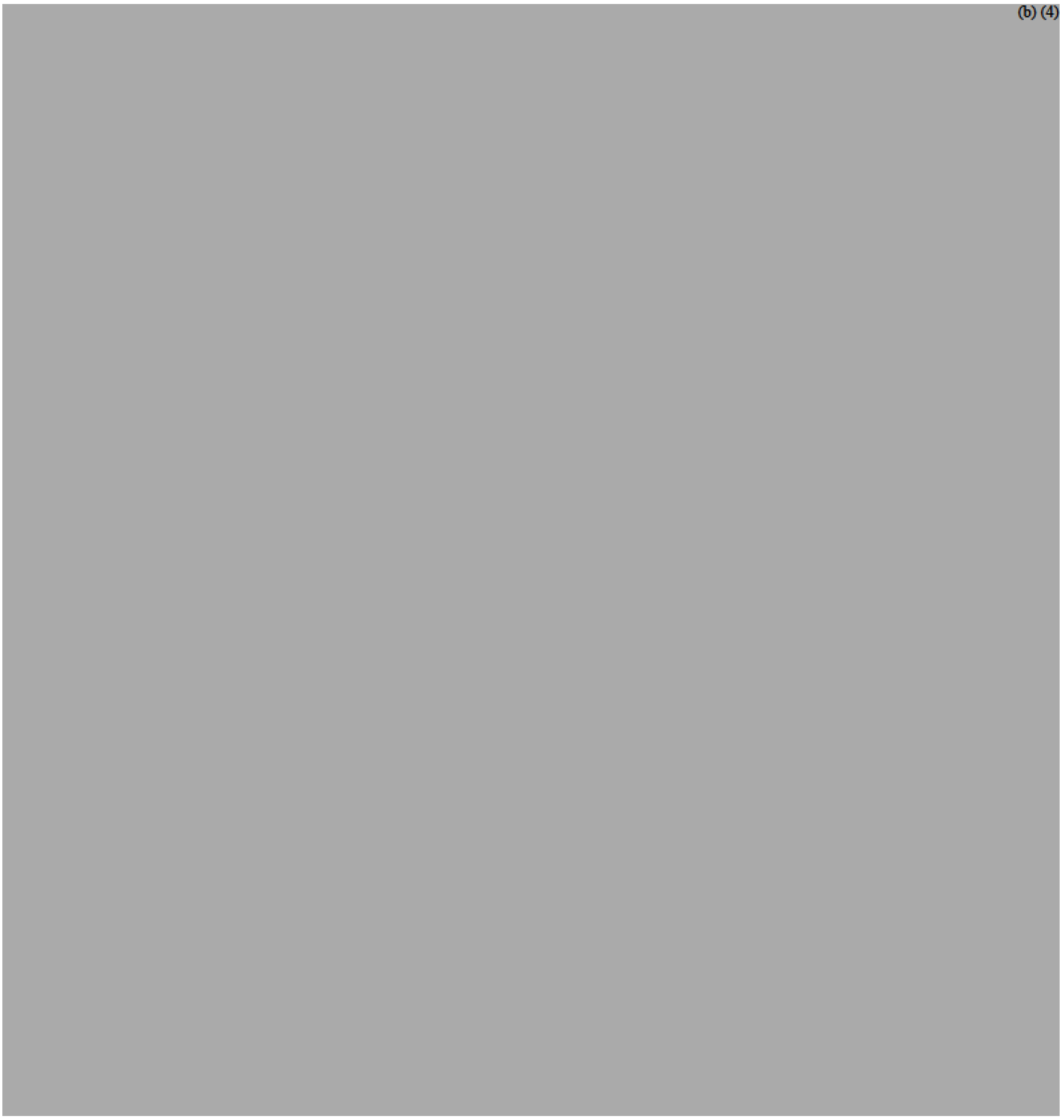
Note that Q4 (regarding side effects) in the figure below was removed from the assessment of LIR vs. LAR status (see discussion in Section 2.3 of this CDTL Review.).

Figure 8. Determination of Laxative Response status



The figure above is taken from Page 382 of the Study 004 Protocol.

APPENDIX 3: Bristol Stool Scale



APPENDIX 4: Prior Laxative Class Usage Reported in the LIR Subgroup

Table 24. Prior Laxative Class Usage Reported (based on Baseline Laxative Response Assessment*) (Prior 2 Weeks) in the LIR Subgroup

	Number (%) of patients[a]							
	Study 04				Study 05			
Baseline laxative class	Placebo (N=118)	NGL 12.5 mg (N=115)	NGL 25 mg (N=117)	Total (N=350)	Placebo (N=121)	NGL 12.5 mg (N=125)	NGL 25 mg (N=124)	Total (N=370)
Stimulants	79 (66.9)	71 (61.7)	67 (57.3)	217 (62.0)	60 (49.6)	68 (54.4)	62 (50.0)	190 (51.4)
Lubricants	16 (13.6)	10 (8.7)	8 (6.8)	34 (9.7)	11 (9.1)	8 (6.4)	11 (8.9)	30 (8.1)
Osmotics	0	3 (2.6)	3 (2.6)	6 (1.7)	6 (5.0)	8 (6.4)	9 (7.3)	23 (6.2)
Saline laxatives	15 (12.7)	18 (15.7)	14 (12.0)	47 (13.4)	15 (12.4)	17 (13.6)	15 (12.1)	47 (12.7)
Stool softeners	32 (27.1)	40 (34.8)	42 (35.9)	114 (32.6)	52 (43.0)	39 (31.2)	43 (34.7)	134 (36.2)
Polyethylene glycol (PEG)	15 (12.7)	18 (15.7)	29 (24.8)	62 (17.7)	17 (14.0)	23 (18.4)	23 (18.5)	63 (17.0)
Bulk laxatives	10 (8.5)	9 (7.8)	9 (7.7)	28 (8.0)	14 (11.6)	12 (9.6)	11 (8.9)	37 (10.0)
Prescription constipation products	1 (0.8)	0	5 (4.3)	6 (1.7)	2 (1.7)	5 (4.0)	1 (0.8)	8 (2.2)
Prescription OIC products	1 (0.8)	1 (0.9)	2 (1.7)	4 (1.1)	2 (1.7)	0	0	2 (0.5)

[a] The percentages are based on the number of intent-to-treat patients in each treatment group and baseline laxative response group.
Note: Response to the question side-effects from laxatives is not used in the determination of response to laxatives at baseline.
Note: The 'Total' column summarizes across all treatment groups.
ITT Intent-to-treat; LIR Laxative inadequate response; NGL Naloxegol; OIC Opioid-induced constipation.

*See Appendix 1

Table above is taken from Response to IR August 13, 2014.

APPENDIX 5: CV-event adjudication committee

The Applicant used a prospective adjudication process and convened a 4-member CV-event adjudication committee (CV-EAC).

The following is taken from the FDA Briefing Document for the June 11-12, 2014 Advisory Committee:

> 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.

APPENDIX 6: Methods for Assessment of Blood Pressure-Related AE's

The following is taken from the FDA Briefing Document for the June 11-12, 2014 Advisory Committee:

> 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 ≥160 mm Hg and ≥20 mm Hg increase or systolic ≥ 180 mm Hg; diastolic ≥95 mm Hg and ≥10 mm Hg increase or diastolic ≥120 mm Hg.
>
> Decreased BP was analyzed as the following: systolic ≤100 mm Hg and ≥20 mm Hg or systolic ≤80 mm Hg; diastolic ≤50 mm Hg and ≥10 mm Hg decrease or diastolic ≤ 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.

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/s/

ANIL K RAJPAL
09/16/2014