CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204760Orig1s000

MEDICAL REVIEW(S)

Clinical Investigator Financial Disclosure
Review Template

Application Number: 204,760

Submission Date(s): 16 September 2013

Applicant: Astra Zeneca

Product: naloxegol

Reviewer: Aisha Peterson Johnson, MD, MPH, MBA

Date of Review: 08 September 2014

Covered Clinical Study (Name and/or Number): D3820C00004, D3820C00005, D3820C00007, D3820C00008

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: Across the four primary clinical trials, there were 604 centers each with an investigator.		
Number of investigators who are sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): one investigator had disclosable financial interests/arrangements (Study D3820C00008)		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 10 (across the four studies listed above)		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation

		from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

The financial interests/arrangements and lack of disclosure despite due diligence does not affect the approvability of this application. The single investigator who had a financial interest disclose enrolled (b) (4) in the long term safety study, but none of those patients was eventually randomized for treatment in the study. Given this fact, no steps were needed to address the financial interest/arrangement. In addition, it appears that the sponsor acted with due diligence in attempting to get financial disclosure from all investigators.

[1] See http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AISHA P JOHNSON
09/09/2014

ANIL K RAJPAL
09/09/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Neurology
Office of Drug Evaluation I

Memorandum

Date: June 25, 2014
From: Heather Fitter, M.D., Medical Officer, DNP

Through: John Marler, M.D., Team Leader, DNP
B Dunn, M.D., Division Director, DNP

To: Maureen Dewey, M.D., Medical Officer, DGIEP

CC: Anil Rajpal, M.D., Team Leader, DGIEP

Re: DNP consult

Materials Evaluated:

Submission: \\CDSESUB1\evsprod\NDA204760\0000

Consult Question:

1. Comment on the characterization of patients with these conditions (active multiple sclerosis, recent brain injury, advanced Alzheimer's disease) as having "clinically important disruptions to the blood-brain barrier" and the appropriateness of this language for the labeling. If you agree with the characterization of patients with these conditions as having "clinically important disruptions to the blood-brain barrier", comment on whether other conditions should also be included.
2. Given the limitation that patients with these conditions were not included in the clinical trials, comment on whether the risk to these patients is a known hazard or a theoretical possibility. Please comment on any specific treatment or management strategies for these patients.
3. Please provide any additional comments you may have.

Background:

The sponsor has submitted a new NDA for an opioid antagonist, naloxegol, with the proposed indication: "…for the treatment of opioid induced constipation (OIC) in adult patients with chronic non-cancer pain." This product is a PEGylated derivative of naloxone. The DGIEP

review team believes that when administered at the recommended dose levels, naloxegol functions as a peripherally acting mu-opioid receptor antagonist in the gastrointestinal tract which decreases the constipating effects of opioids. The sponsor excluded patients from the phase 3 clinical trials with "any condition that may have affected the permeability of the blood brain barrier, e.g., multiple sclerosis, recent brain injury, Alzheimer's disease and uncontrolled epilepsy." Therefore the review team is requesting input from DNP about how to address this exclusion from the trials in labeling. (b) (4) (b) (4) (b) (4) However, in general, a contraindication should be a known hazard, not a theoretical possibility. The review team is considering one of the following three options concerning the statement about "patients with clinically important disruptions of the blood brain barrier":

- Include in Contraindications (if we determine the risk is a known hazard)
- Include in Warnings and Precautions (with revised wording; i.e., including specific treatment or management strategies)
- Include in neither Contraindications nor Warnings and Precautions

Review:

The blood brain barrier (BBB) is a unique system that limits passive diffusion of certain blood borne solutes while actively transporting others. This limitation of passive diffusion is related to the endothelial tight junctions contributing to this blood brain barrier. Evidence exists to suggest that in certain cases these endothelial tight junctions become "leaky", thereby allowing otherwise non-permissible agents to penetrate into the CNS. Although predictability of whether a product will cross the BBB is limited and often theoretical, permeability is thought to be related to the following factors: molecular weight and lipophilic characteristics, whether the product is actively transported into the CNS and whether the product is actively transported out of the CNS. Literature describes neurologic conditions in which BBB disruptions have been suspected. In general, a large class of neurologic diseases has been identified as being associated with BBB disruption in categories such as inflammatory, infectious, ischemic, neoplastic and neurodegenerative. In fact, it may be difficult to identify a disease of the central nervous system that has not been associated some degree of BBB disruption.

Naloxegol functions as a peripherally-acting mu-opioid receptor antagonist (PAMORA) in the gastrointestinal tract, thereby decreasing the constipating effects of opioids without impacting opioid-mediated analgesic effects on the central nervous system. Naloxegol is PEG naloxol, also known as a PEGylated derivative of naloxone. It is a substrate of the P-glycoprotein (P-gp) transporter, which substantially limits its ability to cross the blood-brain barrier (BBB), according to the sponsor.

Clinical exposure of this product has included approximately 438 normal volunteers for the phase 1 trials, 1500 patients for the phase II and III trials, and with approximately 1100 patients

enrolled in long term safety trials. The phase III clinical trials excluded patients with possible disruptions of the blood brain barrier. The sponsor estimated the extent of CNS effects using the following:

- Patients' pain levels, changes from baseline in mean daily opioid dose, and pain-related AEs
- The modified Himmelsbach scale (mHS) for signs of opioid withdrawal
- AEs of opioid withdrawal
- Analysis of abuse potential

The sponsor concludes that CNS effects of naloxegol were minimal even at high exposure levels.

In summary, the pivotal trials of naloxegol did not include patients with neurological diseases that may be associated with disruption of blood brain barrier permeability.

Response to consult questions:

1. *Comment on the characterization of patients with these conditions (active multiple sclerosis, recent brain injury, advanced Alzheimer's disease) as having "clinically important disruptions to the blood-brain barrier" and the appropriateness of this language for the labeling. If you agree with the characterization of patients with these conditions as having "clinically important disruptions to the blood-brain barrier", comment on whether other conditions should also be included.*

DNP response: The list of diseases that alter the permeability of the blood brain barrier is extensive. Some conditions that many would not consider neurological diseases (viz, acute liver failure) can alter blood-brain barrier permeability. We recommend that you characterize the potentially vulnerable patients as those "with conditions that significantly alter blood-brain barrier permeability."

2. *Given the limitation that patients with these conditions were not included in the clinical trials, comment on whether the risk to these patients is a known hazard or a theoretical possibility. Please comment on any specific treatment or management strategies for these patients.*

DNP response: The material available for review suggests that the risk is theoretical rather than a known hazard. We recommend a warning. A contraindication would likely exclude patients who would have no adverse effects and could potentially benefit. The actual mechanism of peripheral selectivity is not known, nor is the mechanism that may restrict the blood-brain barrier permeability for naloxegol clearly defined. Stopping naloxegol when symptoms develop is our only recommendation for treatment. Treating narcotic withdrawal symptoms or increased pain with additional narcotics that have a longer half-life than naloxegol could be risky.

3. *Please provide any additional comments you may have.*

DNP response: None.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HEATHER D FITTER
07/03/2014

JOHN R MARLER
07/08/2014

WILLIAM H Dunn
09/09/2014

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	204,760
Priority or Standard	Standard
Submit Date(s)	September 16, 2013
PDUFA Goal Date	September 16, 2014 (Program NDA)
Division / Office	Division of Gastroenterology and Inborn Errors Products/ Office of Drug Evaluation III
Reviewer Name(s)	Aisha Peterson Johnson, MD, MPH, MBA
Review Completion date	09 May 2014
Established Name	Naloxegol
(Proposed) Trade Name	Movantik
Therapeutic Class	Peripheral μu-opioid receptor antagonist
Applicant	Astra Zeneca
Formulation(s)	Tablet
Dosing Regimen	25 mg once daily
Indication(s)	Opioid-induced constipation
Intended Population(s)	Adults

Reference ID: 3504437

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Reference ID: 3504437

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

In the opinion of this reviewer, naloxegol oxalate should be approved for marketing in the United States for the treatment of opioid-induced constipation (OIC) in adult patients. The recommended dose of 25 mg once daily is supported by the submitted confirmatory studies. The recommendations for a decreased dose for patients with renal impairment (See Pharmacology Review) should also be accepted. The Pharmacometric team recommendation for a labeled dose reduction to 12.5 mg for patients who do not tolerate the 25 mg dose should also be considered. This additional labeling would provide assistance to providers given that off-label use is highly likely given that the 12.5 mg dose will be on the market.

1.2 Risk Benefit Assessment

Opioid induced constipation is a serious medical condition which affects many persons in the United States and around the world. It is the most common adverse reaction associate with the use of opioids. The opioid class of medications is the most prescribed class of medications in the United States. In 2011, hydrocodone was prescribed more often than any other medication (136.7 million prescriptions), with all narcotic analgesics exceeding 238 million prescriptions in that year.[1]

Unlike many of the adverse reactions associated with the use of opioids, constipation generally does not improve with time.[2] Therefore, chronic opioid use results in chronic opioid-induced constipation (OIC) in many patients. Understanding the disease burden of OIC is important. According to one source, the frequency of OIC varies widely, ranging from 15% to as high as 90% of all patients taking opioids.[3]

The European Association of Palliative Care (EAPC) Research Network working group has identified four general approaches to dealing with adverse reactions (including constipation) associated with opioids: dose reduction of systemic opioid, symptomatic management of the adverse effect, opioid rotation, and switching the route of systemic administration.[4] Dose reduction is an option exercised by many physicians, but can result in suboptimal pain control for patients. Symptomatic management of constipation can include dietary modifications (fiber, fluids, etc.), medication use exercise, and bowel

[1] Manchikanti L Helm S, Fellows B, Janata JW, Pampati V, Grider JS, Boswell MV, Opioid epidemic in the United States. Pain Physician. 2012 Jul;15(3 Suppl):ES9-38.
[2] Warner EA. Opioids for the Treatment of Chronic Noncancer Pain, *Am J of Med* (2012) 125, 1155-1161.
[3] Panchal SJ, Muller-Schwefe P, Wurzelmann JI. Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. *Int J Clin Pract*, July 2007, 61, 7, 1181–1187.
[4] Swegle J, Logemann C. Management of Common Opioid-Induced Adverse Effects

training. Opioid rotation refers to the use of an alternative opioid based on which class of opioid receptor is known to be the primary target of that drug or use of a different route of administration of the same opioid (e.g. change from oral subcutaneous). However, a systematic review found insufficient evidence on the effectiveness or safety of opioid rotation in patients with chronic, non-cancer pain.[5]

Laxatives are the primary medication currently used for the treatment of OIC. In 2009 the results of a multinational survey of 322 patients with OIC taking laxatives revealed that 45% of patients continued to have <3 bowel movements per week. Most patients reported that constipation symptoms had at least a moderate negative impact on their quality of life. And a third of patients reported missing, decreasing, or stopping opioids in order to improve symptoms of constipation.[6] These data support the call to address the "pressing need for new therapies that act upon the underlying mechanisms of OBD [opioid bowel dysfunction]."[3]

Currently, there are two medications specifically indicated for the treatment of OIC—lubiprostone (Amitiza) and methylnaltrexone bromide (Relistor). Relistor is approved for use only in patients undergoing palliative care while Amitiza is indicated for all adult OIC patients with OIC or chronic idiopathic constipation (CIC). Naloxegol is also seeking an indication specifically for the treatment of OIC.

The Phase 3 naloxegol clinical program is the primary subject of the current review. Two confirmatory studies support the efficacy of naloxegol 25 mg once daily for the treatment of OIC in adults. The efficacy of the 12.5 mg naloxegol dose was seen only in a single study, but was not reproduced in an identical second study. The response endpoint used in both studies was adequate to measure improvement in the number of bowel movements and other OIC symptoms.

Cardiovascular events were identified as a safety topic of special interest in the naloxegol Phase 3 program for two main reasons. First, a potential CV safety signal (myocardial ischemia) was observed in a long-term safety study of alvimopan, a drug in the same class as naloxegol. Second, there were findings in a Phase 1 dog telemetry study of decreased blood pressure and heart contractility. To evaluate a possible CV safety signal, the Applicant used a prospective adjudication process and convened a 4-member CV-event adjudication committee (CV-EAC) to review all deaths and non-fatal cardiovascular events.

In the 12-week pool, the incidence rate of MACE events was 0.5% in both the placebo and naloxegol12.5 mg treatment groups (2 patients in each group). The incidence of MACE events was 0.2% (one patient). In the 52 week safety study, the incidence of MACE events was 0.7 in the usual care arm compared with 0.4 in the naloxegol 25 mg

[5] http://www.americanpainsociety.org/uploads/pdfs/Opioid_Final_Evidence_Report.pdf. Site accessed March 20, 2014
[6] Bell TJ, Panchal, SJ, Miaskowski C, Bolge SC, Milanova, T. and Williamson, R. (2009), The Prevalence, Severity, and Impact of Opioid-Induced Bowel Dysfunction: Results of a US and European Patient Survey (PROBE 1). Pain Medicine, 10: 35–42

arm. The total number of events in the naloxegol program was low; therefore, it was difficult to make specific conclusions regarding the association of naloxegol with MACE events. An advisory committee meeting is planned in June 2014 to discuss whether a pre-market cardiovascular safety study should be required for all drugs in the mu opioid receptor class.

A second important safety concern related to the mu opioid antagonist class is the occurrence of withdrawal. While the overall incidence was generally low, possible opioid withdrawal symptoms occurred with a higher frequency in patients taking naloxegol (2%) compared to patient taking placebo (<1%) and occurred with a greater incidence in the naloxegol 25mg group (14/446=3%) than in the naloxegol 12.5mg group (5/441=1%). Dr. Elizabeth Kilogore, DAAAP, concluded that based upon all analyses there is evidence of possible opioid-withdrawal related AEs seen in the Phase 3 naloxegol studies. Dr. Kilgore also concluded that naloxegol does not appear to have a negative effect on analgesia based upon the NRS (Numeric Rating Scale) scores and mean opioid use.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

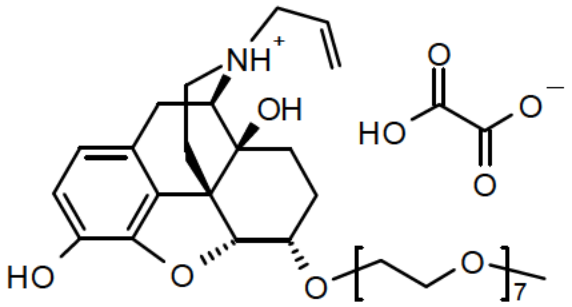
The Sponsor has submitted plans for a pediatric program. However, I recommend that the pediatric program receive a full waiver. See Section 7.6.3 for the reasons for the pediatric waiver recommendation.

2 Introduction and Regulatory Background

2.1 Product Information

Trade Name:	Movantik
Generic Name:	naloxegol oxalate
Chemical Name:	5-amino-2-hydroxybenzoic acid

Structural formula:



Therapeutic Class:	Mu-opioid receptor antagonist
Formulation:	12.5 mg or 25 mg tablets containing naloxegol oxalate.
Proposed indication:	Treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain
Mechanism of Action:	Naloxegol is a PEGylated derivative of the mu-opioid receptor antagonist naloxone. In vitro studies demonstrate that naloxegol is a neutral antagonist of μ-opioid receptors, a neutral antagonist of δ-opioid receptors and a weak partial agonist at the κ-opioid receptors, with the highest binding affinity at μ-opioid receptors. Naloxegol functions as a peripherally-acting mu-opioid receptor antagonist in the gastrointestinal tract, thereby decreasing the constipating effects of opioids without impacting opioid-mediated analgesic effects on the central nervous system.

2.2 Tables of Currently Available Treatments for Proposed Indications

Name of Drug	Indication
Relistor (methylnaltrexone bromide)	treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient
Amitiza (lubiprostone)	treatment of opioid-induced constipation in patients with non-cancer pain

2.3 Availability of Proposed Active Ingredient in the United States

Naloxegol oxalate is a new molecular entity (NME). There are currently no approved drugs containing this active moiety.

2.4 Important Safety Issues With Consideration to Related Drugs

Important safety issues involving the peripheral mu opioid receptor class include association with risk of major cardiovascular adverse reactions, bowel perforation, and opioid withdrawal. These safety issues are discussed in detail in Section 7.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 1. Pre-submission Regulatory History, NDA 204,760

Date	Selected Regulatory Action(s)
16 September 2013	NDA 204,760 submitted
09 August 2013	Advice/Information Request letter sent to AstraZeneca (AZ) regarding opioid withdrawal syndrome and cardiovascular (CV) risk assessments.
23 April 2013	Type C pre-New Drug Application (NDA) meeting. FDA requested additional *post-hoc* analyses of the naloxegol data pertaining to opioid withdrawal and CV effect
29 October 2012	AZ submitted (b) (4)
October 2012	FDA requested narratives of all Phase 3 patients with an AE of chest pain
14 March 2012	TQT Study Submitted
24 January 2012	Type C meeting. Key Clinical Agreement: FDA recommended a sensitivity analysis assessing the treatment effect within the laxative inadequate responder (LIR) and non-LIR subgroups of the Phase 3 studies
18 October 2011	Controlled Substance Staff Meeting: ▪ Human abuse liability study is not needed. ▪ FDA agreed with approach to submit the petition to decontrol NKTR-118 to the DEA.
23 June 2011	Type C meeting: Key Clinical Agreements: ▪ FDA did not agree (b) (4) . ▪ A single cancer-related pain trial would be sufficient to include demographic and efficacy data in the label given that the trial is provides substantial evidence of efficacy. ▪ To demonstrate durability of effect, the key secondary endpoint (12-week responder analysis) should be modified to 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 person to be considered a responder
26 January 2010	EOP2 meeting. Key Clinical Agreements: ▪ Primary endpoint will be based on responder analysis rather than change in bowel frequency. ▪ Definition of responder must require an increase of ≥ 1 SBM/week (a 2-week run-in could allow patients to qualify with 2.5 SBM/week). 3 out of 4 weeks is an acceptable timeframe for which the criteria should be met in order to be a responder.
22 October 2007	Investigational New Drug Application (IND 78,781) for naloxegol submitted

2.6 Other Relevant Background Information

None known, except as discussed in other parts of the review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of reasonable quality. The electronic application was well-organized and easily navigable.

The Office of Scientific Investigations (OSI) performed two site investigations.

The site of Dr. Rafaelito S. Victoria in Anaheim, California was inspected. He was an investigator for Protocol D3820C00004. At this site, a total of 80 subjects were screened, 36 subjects were screen failures, and 44 subjects were randomized. Ten subjects discontinued the study prior to completion and 34 subjects completed the study. An audit of all 39 patients' records was conducted. It was determined that the data generated by this site appeared acceptable.

Mahendra Sanapati, MD in Evansville, Indiana was also inspected. At this site, for Protocol D3820C00004, a total of 54 subjects were screened, 30 subjects were randomized and 18 subjects completed the study. An audit of all 54 subjects' records was conducted. The inspector found that Subject E4056007 on amitriptyline and Subject E4056009 on nortriptyline were enrolled in violation of the exclusion criterion which did not permit patients to be on medications known to increase the Qt interval. Dr. Sanapati responded adequately in a letter dated February 19, 2014 and stated that he had instituted corrective action. OSI did not feel that these violations significantly impacted data integrity. And it was concluded that the data generated by this site may be used in support of the application.

In addition to the routine site investigations described above, there was a for-cause inspection of Dr. Fandino's study site. Below is an excerpt from the OSI Warning Letter (31 December 2013, DARRTS) sent to investigator Anna Fandino, MD:

> *i. Subject 030: Subject 030's opioid regimen at enrollment was 120 mg of codeine daily, taken in the form of a combination product (300 mg acetaminophen and 30 mg codeine) every 6 hours. However, the subject needed to be taking 300 mg codeine daily to meet the protocol-required minimum equivalent of 30 mg oral morphine daily. Subject 030 was*

randomized into the study on September 15, 2011, and remained in the study until August 10, 2012.

On October 6, 2011, your site notified your Institutional Review Board (IRB) of this protocol violation and explained that it happened because the morphine equivalent conversion dose for this subject was miscalculated. Yet, after finding the error, you continued Subject 030 in this study until August 10, 2012, 11 months after the subject was randomized and 10 months after reporting the violation to the IRB.

ii. *Subject 014: Subject 014's opioid regimen at enrollment was 100 mg of Tramadol daily. However, the subject needed to be taking 135 mg of Tramadol daily to meet the protocol-required minimum equivalent of 30 mg oral morphine daily. Subject 014 was randomized into the study on August 12, 2011, and remained in the study until June 22, 2012.*
On August 17, 2012, approximately one year after Subject 014 was randomized into Protocol D3820C00008, you prepared a Memo to File regarding the subject's Tramadol dosing. In this memo, you indicated that a previous study coordinator falsified the Tramadol dosing frequency from once daily to 4 times daily to make the subject appear eligible for the study. On August 29, 2012, you amended Subject 014's Eligibility Checklist to reflect that the subject did not meet the study requirement regarding opioid regimen.

Your study records show that Subject 014 remained enrolled for nearly a year in Protocol D3820C00008 even though the subject did not meet eligibility requirements for the study.

The Applicant discovered issues with site 8703 (Dr. Ana Fandino, Study 08) 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 08 (patients 014 and 030) not be used in support of this application because the patients were not eligible to enter the study. A total of 42 patients were enrolled into Study 08 from Dr. Fandino's site (19 patients were randomized).

However, prior to data lock the Applicant excluded patients from Dr. Fandino's site (8703) and an associated site (8939) from the safety analysis set (08 Jan 2013 SAP amendment). OSI sent a letter to the investigator in June 2013 and the investigator responded. Her responses were found by OSI to be inadequate and an additional letter was sent in December 2013. An additional letter was sent in March 2014 which was a re-send of the December 2013 letter due to a change in address for the investigator. The objectionable conditions outlined in the letter from OSI were as follows:

1. You failed to personally conduct or supervise the clinical investigations [21 CFR 312.60].

2. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].
    a. Enrollment of subjects with inadequate opioid usage
    b. Enrollment of subjects previously or concurrently enrolled in the same study at another center (8939)
3. You failed to take adequate precautions to prevent theft or diversion of an investigational drug that is subject to the Controlled Substances Act [21 CFR 312.69].
    a. Failure to store NKTR-118 in a securely locked enclosure. Rather, you stored the investigational drug in an unlocked and unsecured room. A police report from the City of Miami Police Department indicates that approximately 900 NKTR-118 tablets were stolen from your site on November 3, 2011.

In addition to what is noted above, the Applicant reports that an envelope of investigational product marked as "narcotics for sale" was found at Site 8703 and the DEA was notified.

3.2 Compliance with Good Clinical Practices

According to the Applicant, the Phase 3 clinical studies were performed by AstraZeneca with Quintiles as the main partnering contract research organization (CRO). The Phase 2b study was performed by Nektar Therapeutics. The Applicant reports that standard operating procedures, quality control measures, and audit programs were followed to provide reassurance that the clinical studies presented in this summary were carried out in accordance with the Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines, as documented by the International Conference on Harmonization (ICH) and the FDA.

3.3 Financial Disclosures

See the separate financial disclosure worksheet.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See the complete CMC review in DARRTS.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Nonclinical toxicity studies were conducted. Single- and repeat-dose oral toxicity studies were conducted in mice, rats, and dogs. I*n vitro* and *in vivo* genetic toxicology studies and 2-year carcinogenicity studies in mice and rats were conducted to determine the genotoxic and carcinogenic potential of naloxegol. Additional genetic toxicology studies and a fertility study in rats, embryo-fetal development studies in rats and rabbits, and pre- and postnatal development studies in rats were conducted to determine the potential naloxegol-related effects on reproductive function, embryo-fetal development, gestation, parturition, lactation, and offspring viability and development.

The results of these studies support the conclusion that the naloxegol compound is not genotoxic and does not represent a carcinogenic risk to man. For a complete discussion of these studies and their results, please see the pharmacology/toxicology review by Dr. Yuk-Chow Ng.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Naloxegol is a PEGylated derivative of the mu-opioid receptor antagonist naloxone metabolized primarily by the CYP3A4 enzyme system.

4.4.2 Pharmacodynamics

No significant efficacy or safety issues related to pharmacodynamics were identified.

4.4.3 Pharmacokinetics

See the reviews by Drs. Dilara Jappar (pharmacokinetics) and Dr. Justin Earp (pharmacometrics). Pharmacokinetic study results led the team to recommend that doses for patients with renal impairment should start at 12.5 mg once daily. In addition, the pharmacometrics team recommends that adult patients who are unable to tolerate the 25 mg naloxegol dose (due to adverse events) should try the 12.5 mg dose. This recommendation is based on Pharmacometric assessments which showed the following:

- There is an exposure-response relationship for abdominal pain AEs.
- The majority of abdominal pain AEs occurred early in treatment and at the 25 mg dose
- It appears those with abdominal pain AEs may have a numerically better response (primary endpoint) than those without AEs.

Based on these results, the pharmacometrics team recommends the following:

- Starting dose of 25 mg for everyone (except the renal impairment population)
- dose reduction to 12.5 mg in patients not able to tolerate abdominal pain at the 25 mg dose
- labeling to discourage dose reduction for anyone other group of patients

MO Comment:
The pharmacometrics recommendation to label a dose reduction for patients not able to tolerate the 25 mg dose due to abdominal pain appears reasonable given the pharmacometric analysis results listed above. However, from a clinical standpoint, I have concerns about labeling the 12.5 mg dose given that efficacy for this dose was not reproduced in a second confirmatory study. While the trend was seen in Study 05, the difference between the 12.5 mg dose and placebo was not statistically significant. Exposing patients to a dose whose efficacy is not established is generally not the best course of action. However, given that the 12.5 mg dose will be on the market and will likely be used off-label, it might be reasonable to provide some guidance on how to use this 12.5 mg dose in patients who cannot tolerate the 25 mg dose

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2. Primary Evidence of Efficacy, Naloxegol Clinical Development Program

Study Identifier	Phase	Treatment groups, planned duration and sample size	Countries
D3820C00004 (Study 04)	A Phase III, randomized, doubleblind, placebo-controlled study	Once daily dosing of naloxegol 12.5 mg, 25 mg or placebo tablets for 12 weeks - 652 patients were randomized 1:1:1, of which 641 were in the ITT analysis set (placebo: 214, naloxegol 12.5 mg: 213, and naloxegol 25 mg: 214); 350 (54.6%) patients in the ITT analysis set were LIR.	US, Germany, Slovakia, and Australia
D3820C00005 (Study 05)	A Phase III, randomised, doubleblind, placebo-controlled study	Once daily dosing of naloxegol 12.5 mg, 25 mg or placebo tablets for 12 weeks - 700 patients were randomised 1:1:1, of which 696 were in the ITT analysis set (placebo: 232, naloxegol 12.5 mg: 232, and naloxegol 25 mg: 232); 370 (53.2%) patients in the ITT analysis set were LIR.	US, Belgium, Croatia, Czech Republic, Hungary, Spain, Sweden, United Kingdom

Reviewer's Table.

Table 3. Supportive Evidence of Efficacy, Naloxegol Clinical Development Program

Study Identifier	Phase, Brief Description	Treatment groups, planned duration, and sample size	Countries
D3820C00007 (Study 07)	Safety extension of Phase 3 doubleblind, randomized, placebo-controlled, parallel study (D3820C00004)	Once daily dosing of naloxegol 12.5 mg, 25 mg or placebo tablets for 12 weeks. Patients remained on the same randomised treatment/dose as in Study 04). Before study D3820C00007 was closed for enrolment, a total of 302 patients from the ITT set had continued to the double-blind extension from study D3820C00004. However, only 297 received study treatment in the extension study (placebo: 103, naloxegol 12.5 mg: 96, and naloxegol 25 mg: 98).	US
D3820C00008 (Study 08)	A Phase 3, randomized, open-label parallel group 52 week long-term safety study	Once daily dosing of naloxegol 25 mg or OIC Usual Care (as determined by the physician) for 52 weeks. Patients were randomized in 2:1 ratio to received either naloxegol 25 mg once daily or Usual Care. 844 patients were randomized (naloxegol 25 mg: 563 and Usual Care: 281), 760 of which were new patients and 84 of which were rollover patients from study D382C00005 (78) and study D382C00007 (6).	US

Reviewer's Table.

Table 4. Additional Studies in the Naloxegol Clinical Development Program

07-IN-NX003a	A Phase 2b, randomized, doubleblind, placebo-controlled, multiple dose, dose escalation study	Once daily dosing of naloxegol 5 mg, 25 mg or 50 mg or placebo for 4 weeks. Naloxegol doses were evaluated in separate cohorts of patients; within each cohort patients were randomized to either placebo or naloxegol in 1:1 ratio. A total of 208 patients were randomized across the 3 cohorts, 207 of which received at least one dose of study drug in the placebo run-in period (71 patients in the 5 mg cohort [35 naloxegol and 36 placebo], 60 patients in the 25 mg cohort [31 naloxegol and 29 placebo] and 76 patients in the 50 mg cohort [37 naloxegol and 39 placebo]).	US, Germany, Romania, and Canada
D3820C00006 (Study 06)	A Phase 3 study in 2 parts. Part A: double-blind, randomized, placebo-controlled, parallel group study in patients with cancer pain Part B: active treatment extension.	*Randomization was stopped early* Part A: Once daily dosing of naloxegol 12.5 mg, 25 mg or placebo tablets for 4 weeks, Only 14 out of the planned 336 patients were zin a 1:1:1 ratio (placebo: 4, naloxegol 12.5 mg: 5, and naloxegol 25 mg; 5) Part B: Eligible patients from Part A who had received active treatment were allocated to the same naloxegol treatment/dose as to what they had received in Part A. Patients who had received placebo in Part A were allocated to receive naloxegol 25 mg. The patients were blinded to the dose of naloxegol.	US, Poland, and the Czech Republic

5.2 Review Strategy

For this NDA submission, Phase 3 Studies 04 and 05 were reviewed in detail. Details of the study design and conduct are contained in Section 5. Study results are discussed in Sections 6 (efficacy) and 7 (safety). Safety extension Study 07 and long-term safety Study 08 are included in Section 7 (safety).

5.3 Discussion of Individual Studies/Clinical Trials

General Information Regarding Controlled Efficacy Studies
The placebo-controlled efficacy studies (04 and 05) were identical studies designed to enroll adult patients with a confirmed diagnosis of OIC who were receiving a stable maintenance opioid regimen of 30 mg to 1000 mg per day of oral morphine or equianalgesic amount(s) of 1 or more opioid therapies for a minimum of 4 weeks prior to screening for non-cancer-related pain and who reported a history of fewer than 3 spontaneous bowel movements/week and at least 1 OIC-associated symptom at screening.

5.3.1 Protocol Summary

Title
Study 04
A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of NKTR-118 in Patients with Non-Cancer-Related Pain and Opioid-Induced Constipation (OIC)

Study 05
A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of NKTR-118 in Patients with Non-Cancer-Related Pain and Opioid-Induced Constipation (OIC)

Study Centers
Study 04
This study was conducted in 98 centers in 4 countries. Participating countries included Australia (1 center), Germany (5 centers), Slovakia (4 centers), and the United States (88 centers).

Study 05
This study was conducted in 116 centers in 8 countries. Participating countries included Belgium (1 center), Croatia (4 centers), Czech Republic (4 centers), Hungary (7

centers), Spain (7 centers), Sweden (2 centers), United Kingdom (3 centers), and the United States (88 centers).

Study Period

Study 04
First subject enrolled: 14 March 2011
Last subject last visit: 16 August 2012

Study 05
First subject enrolled: 28 March 2011
Last subject last visit: 20 September 2012

Study Objective

Study 04 and Study 05
The primary objective of both studies was to compare the efficacy of naloxegol 12.5 mg and 25 mg with placebo in the treatment of patients who have OIC.

Study Design

Study 04 and Study 05
This study was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study of two doses (12.5 mg and 25 mg) of naloxegol for the treatment of OIC.

The study duration was up to 18 weeks consisting of the following periods:

- initial screening period (lasting up to 2 weeks)
- 2-week OIC confirmation period to confirm the diagnosis of OIC and stability of the opioid regimen
- 12-week treatment period
- follow-up visit 2 weeks after the last dose of study drug

Patients who successfully completed the 12-week treatment period (for Study 04 only) were eligible to participate in a separate safety extension study (Study 07). During Study 07, patients continued using their same randomized treatment from Study 04. However, while the study was still ongoing, the safety extension study was closed for enrollment because a sufficient number of patients had been enrolled. Patients in Study 05 were permitted to roll-over into Study 08. For Study 08, patients were re-randomized.

During Studies 04 and 05, patients were seen for a study visit at screening, for OIC confirmation, and Study Days 1, 8, 15, 29, 57, and 85. Primary endpoint assessment occurred at Week 12. Patients could be seen for unscheduled study visits at any time

during the study if they experienced worsening of UC symptoms. Patients also had a follow-up visit 14 days after the last dose of study drug.

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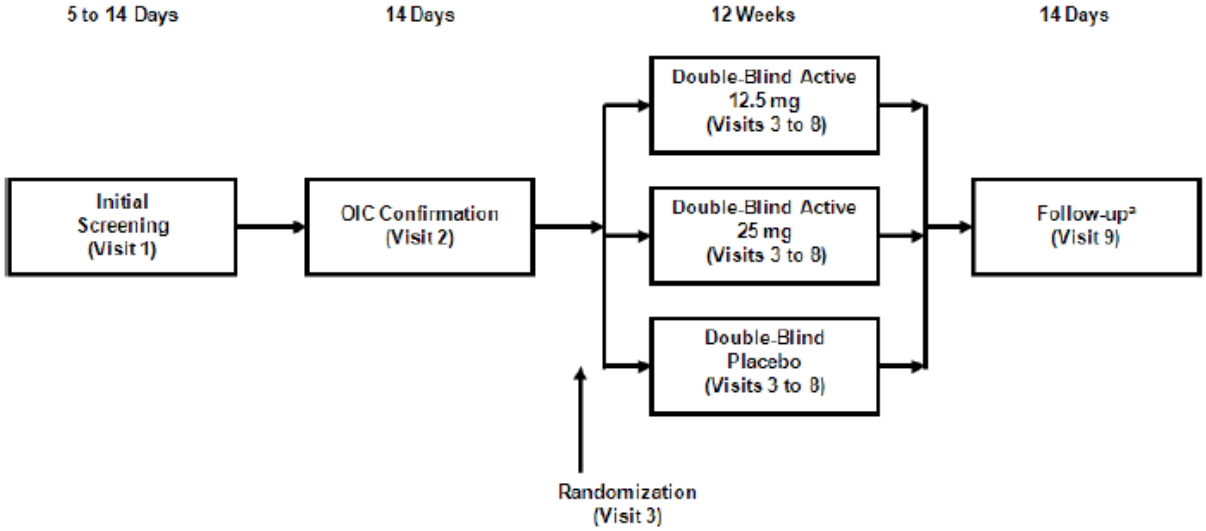
Figure 1. Study Design, Studies 04 and 05



[a] Patients who participated in the long-term safety study were not required to complete the Follow-up visit
OIC Opioid induced constipation

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5.3.2 Key Inclusion Criteria

Studies 04 and 05

For inclusion, patients had to meet all of the following criteria at screening :

1. Provision of written informed consent prior to any study-specific procedures
2. Men and women who were between the ages of ≥18 and <85 years
3. Self-reported active symptoms of OIC at screening (<3 SBMs/week and experiencing ≥1 reported symptom of hard/lumpy stools, straining, or sensation of incomplete evacuation/anorectal obstruction in at least 25% of BMs over the previous 4 weeks); and Documented confirmed OIC (<3 SBMs/week on average over the 2-week OIC confirmation period. Patients with uneven distribution of SBMs across the 2-week OIC confirmation period [0 SBMs in 1 week with ≥4 SBMs in the other week] were excluded. In addition to the SBM frequency criterion, patients must have reported ≥1 of the following symptoms in at least 25% of the BMs recorded in the eDiary during the OIC confirmation period: BSS stool type 1 or 2; moderate, severe, or very severe straining; incomplete BM). Patients who had 0 BMs over the 2-week OIC confirmation period were not randomized.

4. Receiving a stable maintenance opioid regimen consisting of a total daily dose of 30 mg to 1000 mg of oral morphine, or equianalgesic amount(s) of 1 or more other opioid therapies (see Appendix H of the CSP in CSR Appendix 12.1.1) for a minimum of 4 weeks prior to screening for non-cancer-related pain with no anticipated change in opioid dose requirement over the proposed study period as a result of disease progression. The opioid regimen should have been confirmed by a prescription or clearly labeled medication bottle. Regimen stability was confirmed during the 2-week OIC confirmation period. Patients were disqualified from randomization if they consumed >4 additional breakthrough pain medication doses per day for more than 3 days during the 2-week OIC confirmation period, or if their long-acting maintenance opioid dose was modified during this same period. The use of additional doses of opioids for breakthrough pain was captured in the eDiary during the 2-week OIC confirmation period. Patients who were receiving only short-acting opioids were allowed in the study if they were receiving doses according to a fixed schedule. Patients who were receiving only a short-acting opioid on an as-needed basis, that did not follow a fixed schedule, were not eligible for this study. Intrathecal dosing was permitted as long as the patient was taking another orally dosed opioid that met the dosing and duration criteria defined above.
5. Willingness to stop all laxatives and other bowel regimens including prune juice and herbal products throughout the 2-week OIC confirmation period and the 12-week treatment period, and to use only bisacodyl as rescue medication if a BM had not occurred within at least 72 hours of the last recorded BM
6. Patients were required to comply with CRC (colorectal cancer) screening criteria as specified in Appendix E of the CSP in CSR Appendix 12.1.1.
7. Male patients who were sexually active must have used a double-barrier method of contraception (condom with spermicide) from the first dose of investigational product (IP) until 12 weeks after their last dose. Women of childbearing potential must have had a negative pregnancy test and confirmed (by the investigator) use of a highly effective form of birth control for 12 weeks before enrollment and until 12 weeks after their last dose. Highly effective forms of birth control are listed in Appendix I of the CSP in CSR Appendix 12.1.1. Women of non-childbearing potential could participate in this study without adherence to the pregnancy precautions. Women of non-childbearing potential were defined as women who were either permanently sterilized (hysterectomy or bilateral oophorectomy or bilateral salpingectomy) or were postmenopausal. Any woman who was older than 57 years of age was considered postmenopausal. In addition, women who were older than 50 years of age and amenorrheic with at least 12 months having passed since the last menses (after cessation of all exogenous hormone treatments), were also considered postmenopausal.
8. Able to understand and comply with the requirements of the study, as judged by the investigator (includes ability to read and write and use the eDiary device)
9. Outpatient status at enrollment and randomization.

10. In addition, for inclusion in the genetic research, patients must have fulfilled the inclusion criterion outlined in Appendix D of the CSP in CSR Appendix 12.1.1.

If a patient declined to participate in the genetic research, there was no penalty or loss of benefit to the patient. The patient was not excluded from other aspects of the study described in the CSP, so long as they consented.

5.3.3 Key Exclusion Criteria

Patients were excluded, if they met any of the following criteria:

1. Receiving opioid regimen for treatment of pain related to cancer
2. History of cancer within 5 years from the screening visit with the exception of basal cell cancer and squamous cell skin cancer
3. Medical conditions and treatments associated with diarrhea, intermittent loose stools, or constipation, which could confound the interpretation of the results, eg, 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:
    a. Absence of a structural or biochemical explanation for the abdominal pain symptom
    b. At least 12 weeks during a period of 12 months, of abdominal discomfort or pain with at least 2 of the following 3 features:
        i. Relieved with defecation, and/or
        ii. Onset associated with a change in frequency of stool, and/or
        iii. Onset associated with a change in form of stool.
4. Other issues related to the GI tract that could impose risk to the patient (with a special, but not exclusive, emphasis on conditions that might impair the local or global structural integrity of the GI tract) including (but not limited to): inflammatory bowel disease (such as Crohn's disease or ulcerative colitis), 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 (as determined by the investigator), history of rectal prolapse, history of GI hemorrhage related to ongoing GI pathology (eg, ulcer), clinically important or severe peptic ulcer disease (per investigator judgment), 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. In addition, patients having surgery of the colon or abdomen within 60 days of the screening period or expected surgical procedure of the abdomen during the study participation period were excluded.
5. Acute GI conditions that could impose risk to the patient, eg, acute fecal impaction or complete obstipation, acute surgical abdomen, or otherwise

suspicious abdominal/rectal examination. In addition, patients who failed to have an adequate BM after completing the laxative rescue regimen (bisacodyl, enema) during the OIC confirmation period were to be excluded from participation and referred for further medical evaluation.

6. Any other significant and/or progressive medical condition (eg, neurological, psychiatric, or metabolic) or a clinical symptom that could unduly risk the patient or affect the interpretation of study data (eg, uncontrolled hypothyroidism, inadequately controlled clinical depression, poorly controlled seizure disorder)
7. Any of the following findings and/or conditions:
    a. Serum alanine aminotransferase (ALT) or aspartate aminotransferase(AST) >2.5 x upper limit of normal (ULN) and/or serum bilirubin >1.2 x ULN (unless elevation is due to Gilbert's syndrome
    b. Diagnosis of liver cirrhosis as defined by Child-Pugh classes of B (moderate) or C (severe), or acute liver disease
    c. Creatinine clearance (CrCl) <30 mL/min (calculated by the central laboratory using the Cockcroft-Gault formula)
    d. Absolute neutrophil count (ANC) <1500 cells/mm3; platelets <60,000 mm3; or hemoglobin (Hg) <9 g/dL
8. Signs and symptoms at the time of randomization that the investigator believed may be related to opioid withdrawal
9. Ongoing use of manual maneuvers to induce a BM (eg, digital evacuation or pelvic floor support)
10. Any condition that may have affected the permeability of the blood-brain barrier, e.g., multiple sclerosis, recent brain injury, Alzheimer's disease, and uncontrolled epilepsy
11. Severe background pain (eg, typical average daily pain intensity rating of 8 to 10 on an 11-point NRS) refractory to opioid therapy
12. Patients who had a QTcF >500 msec at screening, had a recent history of myocardial infarction within 6 months before randomization, had symptomatic congestive heart failure, or had any other overt CV disease.
13. Active substance or alcohol use that, in the opinion of the investigator, could compromise patient's ability to comply with the study instructions. Patients with a positive urine drug screen at the screening visit for cocaine or amphetamines (unless verified by prescription that the patient was receiving amphetamine for treatment of Attention-Deficit Hyperactivity Disorder or other neuropsychiatric condition) were excluded. Patients who were receiving methadone for maintenance treatment of opioid addiction were excluded from the study (Note: patients who were receiving methadone for pain management were eligible for participation). The disposition of patients with suspected opiate abuse during the study was handled on a case by case basis.
14. Use of prohibited medications (see section 5.3.4 below for a list of prohibited concomitant medications).
15. Pregnancy or lactation

16. Known history of intolerance or hypersensitivity to alvimopan, methylnaltrexone, or other peripherally acting opioid antagonists, or to any other component in the tablets
17. Involvement in the planning and/or conduct of the study (applies to AstraZeneca staff, Nektar staff, staff at the study site, and third-party vendors)
18. Previous randomization in the present study or any study with NKTR-118
19. Was currently participating in or had participated in another clinical study within 30 days prior to screening for this study
20. Any receipt of an investigational medication within 30 days of screening.

5.3.4 Study Medication, Laxative Rescue Treatment, and Prohibited Concomitant Medications

Once eligible for the study, patients were randomized to receive Naloxegol 12.5 mg, Naloxegol 25 mg, or placebo. Patients received study drug during the 12-week treatment period of the study (Days 1 to 85) administered once daily as two tablets. Patients were instructed to take the tablets one hour before eating each morning. See Table 5 below.

Table 5. Administration of Study Drug

	NKTR-118		
Treatment day	**12.5 mg/day**	**25 mg/day**	**Placebo**
Days 1 to 85[a]	1 x 12.5 mg NKTR-118 tablet 1 x 25 mg placebo tablet	1 x 12.5 mg placebo tablet 1 x 25 mg NKTR-118 tablet	1 x 12.5 mg placebo tablet 1 x 25 mg placebo tablet

[a] Patients enrolling in the extension study were instructed not to take study medication at home on the day of their V8 (Day 85) visit.

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At visits 2, 3, 4, 5, 6, and 7, patients received bisacodyl 5 mg tablets for use as laxative rescue medication. Patients were permitted to take laxatives during the screening period of the study, but were to discontinue use of laxatives at least 24 hours prior to the start of the OIC confirmation period.

During the OIC confirmation period and the treatment period, a patient were permitted to take bisacodyl as a laxative rescue medication only if a BM had not occurred within at least 72 hours. If after a minimum of 72 hours, the patient had not experienced a BM,

he/she was permitted to take bisacodyl rescue therapy (10 to 15 mg dose, i.e., 2 to 3 bisacodyl tablets at a time). If the patient remained constipated, bisacodyl rescue therapy could be repeated up to two additional times, as necessary, each 10 to 15 mg dose separated by 12 hour intervals. If after 3 doses of bisacodyl rescue therapy, the patient still had not experienced a BM, the investigator could have prescribe one-time use of an enema. The timing of administration of this therapy will be noted and recorded in the eDiary. In addition, the site was to record any enema prescription on the enema eCRF. If these secondary interventions failed, patients were to be discontinued from the study (or excluded from the study if the patient failed the rescue regimen prior to randomization) and referred for additional medical evaluation.

Investigators were encouraged to maintain each patient's baseline pain control regimen, with dose adjustments made as needed in accordance with the patient's clinical needs. Patients who had their pain regimens managed by a physician not connected with the study were asked to notify their personal physicians of their participation in the study, and to ask their physicians to notify the study investigator should a change in their pain control regimen be made.

Prohibited Concomitant Medications:

- Opioid antagonists and mixed antagonists were prohibited during the study, including:
  - Pentazocine
  - Buprenorphine
  - Nalbuphine
  - Naloxone,
  - other naloxone containing products (eg, Targin®)
  - naltrexone and other naltrexone containing products (eg, Embeda®),
  - methylnaltrexone (Relistor®), and alvimopan (Entereg®)
- Strong inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) were prohibited (due to *in vitro* data available at the time of study initiation suggesting that strong CYP3A4 and P-gp inhibitors might increase NKTR-118 plasma concentrations)

5.3.5 Study Visits and Procedures

All study visits occurred in an outpatient setting. The study visits and related safety assessments are summarized in Table 6 below.

Table 6. Study Procedures, Studies 04 and 05

	Screening	OIC Confirmation	Treatment Period					Final	
Week	**-4 to -2[a]**	**-2 to -1**	**0**	**1**	**2**	**4**	**8**	**12**	**14**
Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8/ET**	**9**
Study Day	**-28 to -14**	**-14 to -1**	**D1[b]**	**D8**	**D15**	**D29**	**D57**	**D85[c]**	**D99[d]**
Visit Window (Days)			**-1 to +3**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**
Informed consent & genetic informed consent[e]	√								
Randomization			√						
Demographic information	√								
Inclusion/exclusion criteria	√		√						
CRC risk factor evaluation (including FIT as necessary)	√								
Medical and surgical history (including OIC history)	√								
Complete physical examination (including height, weight, temperature, respiratory rate)[f]	√		(√)[f]					√	
Sitting blood pressure, pulse	√		√	√	√	√	√	√	√
LIR, LAR, LUR status[g]	√								
Pregnancy test for WOCBP[h]	√		√			√	√	√	√
12-lead ECG[i]	√		√	√	√	√	√	√	√
Clinical chemistry and hematology[j]	√		√	√	√	√	√	√	√
Total cholesterol			√					√	
Urinalysis[k]	√							√	
Urine drug screen[l]	√							√	
Genetic sampling[g]			√						
PK sampling[m]			√	√	√	√	√	√	
C-SSRS	√	√	√	√	√	√	√	√	√
Maintenance opioid regimen recorded	√	√	√	√	√	√	√	√	√
Modified Himmelsbach scale[n]	√		√	√		√		√	
PAC-SYM[o]			√		√	√	√	√	
PAC-QOL[o]			√			√		√	
EQ-5D[o]			√			√		√	
OIC Healthcare Resource Utilization Assessment[o]				√	√	√	√	√	√
Prior/concomitant medication (other than laxative rescue medication and opioid medication)[p]	√	√	√	√	√	√	√	√	√
eDiary device dispensed	√								
eDiary ([daily]: BM, straining, complete/incomplete evacuation, stool consistency (BSS), pain level [NRS], laxative rescue medication [bisacodyl, enema], opioid medication for breakthrough pain)[q]	√	◄----------	----------	----------	----------	----------	----------	---------►√	
eDiary (including proper documentation of bisacodyl and enema use) review		√	√	√	√	√	√	√	
eDiary device returned		√[r]	√[r]					√	
AEs		√[s]	√[s]	√	√	√	√	√	√
Return unused study drug[t]				√	√	√	√	√	
Dispense study drug			√			√	√		
Dispense bisacodyl		√	√	√	√	√	√		
Return unused bisacodyl			√	√	√	√	√	√	
Willingness to Take Drug Again questionnaire[o]								√	
Make appointment for next visit	√	√	√	√	√	√	√	√	

[a] The screening period lasted at least 5 days, and up to 14 days.
[b] A minimum of 11 days of eDiary data collection must have occurred since the start of the OIC confirmation period before the patient could be randomized. Day 1 visit required 4-hour post-dose in-office stay.
[c] Day 85 assessments were to be performed at the time of early termination for patients who discontinued early, with the exception that patients who discontinued prior to Visit 3 (randomization) were not required to have Day 85 assessments.
[d] Patients who entered the safety extension study did not need to participate in Visit 9.

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Reference ID: 3504437

5.3.6 Control Procedures

Randomization

Study 04 and Study 05
Randomization occurred at the onset of the 12-week, double-blind treatment period at Visit 3. Patients were stratified based on their response to laxative use (LIR, LAR, LUR), and were randomly assigned in a 1:1:1 ratio (approximately 210 patients per treatment group) to receive placebo, or Naloxegol at a dose of 12.5 or 25 mg once daily with a minimum of 50% of patients randomized in the LIR category.

Placebo Control

Study 04 and Study 05
Patients randomized to placebo received tablets that matched the naloxegol tablets. Study drug tablets were round, biconvex, and white film coated. Tablets were supplied in high-density polyethylene (HDPE) bottles, dispensed every 30 days. Each 30-day supply consisted of 2 bottles of study drug, each containing 35 tablets

5.3.7 Primary Efficacy Endpoint

Studies 04 and 05 used the same primary and secondary endpoint definitions.

The primary efficacy variable was the response (responder/non-responder) to study drug during Weeks 1 to 12. A responder to study drug during Weeks 1 to 12 was defined as a patient with at least 3 spontaneous bowel movements (SBMs) per week and at least a 1 SBM/week increase over baseline for at least 9 out of the 12 treatment weeks and 3 out of the last 4 treatment weeks during the double-blind treatment period demonstrated by the primary analysis in the ITT analysis set. A SBM was defined as a BM without the use of rescue laxatives (bisacodyl or enema) administered in the previous 24 hours.

The efficacy analysis set was predetermined be the Intent-to-Treat (ITT) population, defined as all randomized patients who received at least 1 dose of study drug and had at least 1 post-baseline efficacy assessment.

5.3.8 Secondary Efficacy Endpoint(s)

To control the overall type I error rate to be ≤ 0.05 for the multiple comparisons in the primary and the key secondary endpoints, a Multiple Testing Procedure (MTP) with

Bonferroni-Holm over Groups, and Fixed-Sequence within groups was applied. Specifically, the 2 dose groups were defined by the doses of 12.5 and 25 mg, and within each group there was a pre-defined fixed-sequence MTP of comparisons of the key secondary endpoints (i.e., responder analysis in LIR subgroup, responder analysis for the 12-week treatment period, and regularity analysis) at level of α/2. If the null hypotheses for 1 dose group could be rejected entirely (i.e., significant difference between active vs. placebo for all 4 endpoints at α=0.025), the level to α (i.e., 0.05) was increased for the other group. This amounted to using Bonferroni-Holm over groups, and fix-sequence within groups.

The following were categorized as key secondary endpoints:

- Comparison of the response rate of Weeks 1 to 12 of naloxegol 12.5 mg vs placebo and naloxegol 25 mg vs placebo in the LIR subgroup. The response rate for each treatment group will be calculated as the number of responders in a particular treatment group divided by the number of ITT patients in that treatment group. Difference between treatment groups in response rate will be analyzed using Chi-Square tests.
- Comparison of the response rate of Weeks 1 to 12 of naloxegol 12.5 mg vs placebo and NKTR-118 25 mg vs placebo. The response rate for each treatment group was calculated as the number of responders in a particular treatment group divided by the number of ITT patients in that treatment group. The difference between treatment groups in response rate was analyzed using CMH tests stratified by response to laxatives at baseline (LIR, LAR, LUR).
- Comparison of the regularity during the first 4 weeks of treatment of naloxegol 12.5 mg vs placebo and NKTR-118 25 mg vs placebo. Differences between treatment groups in the mean number of days per week with at least 1 SBM will be analyzed using analysis of covariance (ANCOVA), with treatment group and response to laxatives at baseline as fixed effects, and the mean number of days per week with at least 1 SBM during the baseline period as a covariate.

Additional secondary efficacy variables included:

- Response (responder/non-responder) to study drug during Weeks 1 to 4, where a responder is defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline, for at least 3 out of the first 4 weeks.
- Response (responder/non-responder) to study drug in the LIR subgroup during Weeks 1 to 4, where a responder is defined as having at least 3 SBMs/week, with at least 1 SBM/week increase over baseline, for at least 3 out of the first 4 weeks.
- Change from baseline in the SBMs/week for Weeks 1 to 4 and 1 to 12.
- Time (in hours) to first post-dose laxation without the use of rescue laxatives within the previous 24 hours in the LIR subgroup.
- Mean number of days per week with at least 1 SBM for Weeks 1 to 4
- Change from baseline in the mean degree of straining for Weeks 1 to 4 and 1 to 12.

- Change from baseline in the mean stool consistency (BSS) for Weeks 1 to 4 and 1 to 12.
- Percentage of days with complete SBM (CSBM) for Weeks 1 to 4 and 1 to 12.
- Mean bisacodyl dose per week for Weeks 1 to 4 and 1 to 12.
- Change from baseline in PAC-SYM total score and each domain score for Weeks 2, 4, 8, and 12.
- Change from baseline in PAC-QOL total score and each domain score for Weeks 4 and 12.

5.3.9 Protocol Amendments

Study 04
The original protocol was amended twice. The study began 14 March 2011.

Amendment 1 was finalized 17 February 2011 (before the study began). The change was introduced for the following primary reason:
To revise inclusion criterion 4 to clarify that patients who are receiving only a short acting opioid on an as needed basis that does not follow a fixed schedule, are not eligible for this study (patients who are receiving a short acting opioid PRN on a fixed basis will still be eligible for inclusion).

Amendment 2 was finalized 02 November 2011 (after the study began). The change was introduced for the following primary reasons:

1. To clarify that patients who are receiving methadone for maintenance treatment of opioid addiction are excluded from the study, but that patients who are receiving methadone for pain management are eligible for participation.
2. To revise the definition of the ITT population to include all randomized patients (no longer limited to randomized patients who received at least 1 dose of study drug and had at least 1 post-baseline efficacy assessment). The primary analysis will be repeated on randomized patients who received at least 1 dose of study drug and had at least 1 post-baseline efficacy assessment (now called the modified ITT population), as a sensitivity analysis.
3. To change the primary efficacy endpoint to response to study drug during Weeks 1 to 12 (instead of Weeks 1 to 4). Response during Weeks 1 to 4 has been moved to an additional secondary efficacy variable.
4. To add time (in hours) to first post-dose laxation without the use of rescue laxatives within the previous 24 hours as a key secondary efficacy variable.
5. To change the rule for missing data for the Modified ITT so that if more than 25% of the 8 signs are missing at a visit the composite score will be set to missing.
6. To define complete evacuation will as the number of days with complete evacuation of an SBM instead of percentage of days with complete evacuation of a BM.

Reference ID: 3504437

6 Review of Efficacy

Efficacy Summary

Statistically significant higher response rates were observed in the naloxegol 25 mg groups compared with the placebo groups in both Studies 04 and 05. However, a statistically significant higher response rate was observed for the 12.5 mg only in Study 04. The results for the 12.5 mg naloxegol group were not statistically significant in Study 05. According to the multiple testing procedure, only the 25 mg dose group could be carried for statistical significance testing into the secondary endpoints.

For an additional discussion of the efficacy summary results, see the Risk Benefit Assessment in Section 1.2 above.

6.1 Indication

Movantik (naloxegol oxalate) is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

6.1.1 Methods

Section 5.3 contains a discussion of the study protocols; Section 6 contains the study results.

6.1.2 Demographics

Baseline demographic characteristics for the ITT population of confirmatory Studies 04 and 05 are presented in

Table **7** below. These populations represent the primary efficacy analysis populations of each of these studies. Both studies randomized a predominance of white patients in the range of 40 to 65 years of age and there were more females than males in both studies. In both studies, randomization produced demographic subgroups which were well-balanced between treatment groups.

Table 7. Demographics, Studies 04 and 05

Demographic Subgroup	Study 04 (ITT Population)			Study 05 (ITT Population)		
	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg
N	214	213	214	232	232	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 range (years) (n,%)						
< 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)

Source: Table 9, p 66 Study 04 CSR and Table 9, p 68 Study 05 CSR

Other important characteristics of the patients enrolled in Studies 04 and 05 include diagnosis necessitating chronic opioid use and daily opioid dose. See

Table **8** and Table 9 below.

The primary reason for the use of opioids in both studies was back pain. Joint pain and arthritis were other prominent reasons. It is likely that there is overlap between many of the diagnoses necessitating opioid use. In both studies, approximately 15-20% of patients in all treatment groups had "other" diagnoses. In both studies, in the category of "other", the majority of patients reported localized musculoskeletal pain as their primary type of pain.

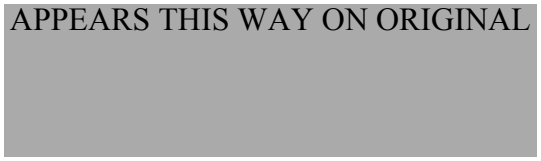

Table 8. Primary Reasons for Opioid Use, Studies 04 and 05

Demographic Subgroup	Study 04 (ITT Population)			Study 05 (ITT Population)		
	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg
N	214	213	214	232	232	232
Primary Reason for Pain, n (%)						
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)

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

The maintenance baseline opioid requirement for enrollment into the study was a total daily dose ranging from 30 mg to 1000 mg oral morphine equivalent units (MEU). The mean baseline dose for patients in Study 04 was 135.6 mg, 139.7mg, and 143.2 mg in the placebo, naloxegol 12.5 mg, and naloxegol 25 mg dose groups, respectively.

Table 9. Baseline Daily Opioid Use (MEU/Day), Studies 04 and 05

Demographic Subgroup	Study 04 (ITT Population)			Study 05 (ITT Population)		
	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg
N	213	211	214	231	230	232
Mean	135.6	139.7	143.2	119.9	151.7	136.4
SD	145.80	167.39	150.07	103.75	153.02	134.31
Q1	45.0	45.0	45.0	45.0	45.0	45.0
Median	75.0	87.6	90.0	77.1	90.0	84.6
Q3	180.0	178.9	191.3	180.0	195.0	180.0
Min	15	1	18	15	11	15
Max	968	1280	1080	607	990	750

Source: Study 04 CSR, Table 44, p 150; Study 05, Table 43, p 150

6.1.3 Subject Disposition

Study 04

In Study 04, a total of 1750 patients were screened and a total of 652 patients completed the 2 week OIC confirmation period and were randomized. A total of 649 patients actually received study treatment, and 524 (80.4%) completed the study (defined as completing the Week 12 Visit for patients who continued into the extension study, or completing the Week 14 visit for patients who did not continue into the

extension study). Overall, 297 patients from the ITT set (45.6% of randomized patients) completed this study and entered the double-blind extension Study 07.

A total of 11 patients who completed the study (4 patients each in the naloxegol 12.5 mg and 25 mg groups and 3 patients in the placebo group) had been previously randomized within the naloxegol program at a different study center. These patients are included in the number of patients who received treatment but were excluded from the ITT and Safety analysis sets and are therefore not included as patients who completed the study. See

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Table 10 below.

Study 05

In Study 05, a total of 1969 patients were screened and a total of 700 patients completed the 2 week OIC confirmation period and were randomized. A total of 697 patients actually received study treatment. And 537 (76.7%) completed the study. Overall, 78 patients from the ITT set (11.1 % of randomized patients) completed this study and entered long-term extension Study 08. See

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Table 10 below.

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Table 10. Patient Disposition, Studies 04 and 05 (ITT population)

	Study 04				Study 05			
	PL	NGL 12.5 mg	NGL 25 mg	Total	PL	NGL 12.5 mg	NGL 25 mg	Total
Randomized	217	217	218	652	233	233	234	700
Received Treatment	216 (99.5)	215 (99.1)	218 (100)	649 (99.5)	232 (99.6)	231 (99.1)	234 (100)	697 (99.6)
Completed Study	177 (81.6)	174 (80.2)	173 (79.4)	524 (80.4)	187 (80.3)	177 (76.0)	173 (73.9)	537 (76.7)
Discontinued Early	36 (16.6)	37 (17.1)	41 (18.8)	114 (17.5)	44 (18.9)	53 (22.7)	59 (25.2)	156 (22.3)
Patient Request	13 (6.0)	17 (7.8)	6 (2.8)	36 (5.5)	13 (5.6)	23 (9.9)	20 (8.5)	56 (8.0)
Did not Meet Eligibility Criteria	1 (0.5)	0	0	1 (0.2)	1 (0.4)	0	0	1 (0.1)
Death	0	1 (0.5)	0	1 (0.2)	0	0	0	0
Adverse Event	11 (5.1)	9 (4.1)	22 (10.1)	42 (6.4)	12 (5.2)	11 (4.7)	24 (10.3)	47 (6.7)
Severe Protocol violation	2 (0.9)	0	5 (2.3)	7 (1.1)	2 (0.9)	2 (0.9)	2 (0.9)	6 (0.9)
Lack of therapeutic response	2 (0.9)	0	0	2 (0.3)	3 (1.3)	3 (1.3)	0	6 (0.9)
Development of study-specific withdrawal criteria	2 (0.9)	3 (1.4)	1 (0.5)	6 (0.9)	3 (1.3)	0	3 (1.3)	6 (0.9)
Lost to follow-up	4 (1.8)	7 (3.2)	6 (2.8)	17 (2.6)	9 (3.9)	11 (4.7)	9 (3.8)	29 (4.1)
Other	1 (0.5)	0	1 (0.5)	2 (0.3)	1 (0.4)	3 (1.3)	1 (0.4)	5 (0.7)
Completed the study and entered into extension study 07	104 (47.9)	95 (43.8)	98 (45.0)	297 (45.6)	n/a			
Completed the study and entered into long-term safety study 08	n/a				30 (12.9)	26 (11.2)	22 (9.4)	78 (11.1)

Source: CSR Study 04, Table 11.1.1.1, p 182; CSR Study 05, Table 11.1.1.1
In both studies, patients who were randomized and did not receive treatment were excluded because they were found not to meet the eligibility criteria

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6.1.4 Analysis of Primary Endpoint(s)

Studies 04 and 05

The primary efficacy variable was the response (responder/non-responder) to study drug during Weeks 1 to 12. A responder to study drug during Weeks 1 to 12 was defined as a patient with at least 3 spontaneous bowel movements (SBMs) per week and at least a 1 SBM/week increase over baseline for at least 9 out of the 12 treatment weeks and 3 out of the last 4 treatment weeks during the double-blind treatment period demonstrated by the primary analysis in the ITT analysis set. A SBM was defined as a BM without the use of rescue laxatives (bisacodyl or enema) administered in the previous 24 hours.

The efficacy analysis set was predetermined to be the Intent-to-Treat (ITT) population, defined as all randomized patients who received at least 1 dose of study drug and had at least 1 post-baseline efficacy assessment.

In Study 04, the differences in response rates between naloxegol 12.5 mg and 25 mg were statistically significantly higher than response rate seen in placebo patients. The response rate was highest in the naloxegol 25 mg group (44.4%, p=0.001) compared with 40.8% (p=0.015) in the naloxegol 12.5 mg group.

In study 05, the difference in response rate between naloxegol 12.5 mg and placebo was not statistically significant (p=0.202). In the naloxegol 25 mg group, the response rate (39.7%, p=0.021) continued to be significantly different from the placebo response rate (29.3%). See Table 11 below.

Table 11. Analysis of response rate for Weeks 1 to 12 – Studies 04 and 05, (ITT)

	Study 04			Study 05		
	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg
n	214	213	214	232	232	232
Number (%) of patients responding	63 (29.4)	87 (40.8)	95 (44.4)	68 (29.3)	81 (34.9)	92 (39.7)
RR (Comparison vs. placebo)[a]	NA	1.380	1.509	NA	1.188	1.348
95% CI	NA	1.062, 1.795	1.168, 1.949	NA	0.911, 1.548	1.045, 1.739
p-value	NA	0.015*	0.001*	NA	0.202	0.021*

[a] Analysis via Cochran Mantel-Haenszel test stratified by response to laxatives at baseline (LIR, LAR, LUR).
* Statistically significant under the MTP.
CI confidence interval; ITT Intent-to-treat; NA Not applicable; RR Relative risk (a RR >1 is indicative of higher response rate on the naloxegol arm).

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MO Comment: The 25 mg efficacy data was reproduced in both Phase 3 confirmatory studies—04 and 05.

However, the 12.5 mg naloxegol dose was only shown to have efficacy statistically significantly different from placebo in Study 05. Therefore, given the lack of serious safety concerns with the 25 mg dose, I recommend approval of only the 25 mg dose for adult patients with OIC. See Section 7 for a more comprehensive review of the safety information of both doses.

The 12.5 mg dose will be available on the market for special populations. And in Study 05, although not statistically significant, there was a numerically higher response rate with the 12.5 mg dose compared with placebo. The risk of potentially exposing patients to an ineffective dose underlies my recommendation to approve only the 25 mg dose. However, because the 12.5 mg dose will be available on the market, providing some instructions for providers on how and when to use the lower dose may be appropriate. The Pharmacometric review team (Dr. Justin Earp and Nitin Mehrotra) currently recommends a dose reduction to 12.5 mg for patients who are not able to tolerate the 25 mg dose due to abdominal pain based on the exposure response that is seen for GI adverse events. For final Pharmacometric recommendations, see the Pharmacometric review in DARRTS.

Sensitivity Analyses

To evaluate the robustness of the primary efficacy results, the Applicant completed several sensitivity analyses using different analysis types and study populations from those pre-specified in the SAP. See

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Reference ID: 3504437

Table **12** below for details. The nominal p-values for these analyses were all less than 0.05 and support the efficacy of naloxegol for the treatment of OIC in adult patients.

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Table 12. Sensitivity Analyses of Primary Efficacy Results

Variable	Analysis type (Estimate)	Placebo	NKTR-118 12.5 mg	NKTR-118 25 mg	Comparison between groups		
		n	n	n	Comparison	Estimate (95% CI)	p-value
Response (PP population)	Cochran Mantel Haenzel (Relative risk) [a]	199	201	201	12.5 mg vs placebo	1.346 (1.028, 1.761)	0.029
					25 mg vs placebo	1.502 (1.157, 1.949)	0.002
Response (mITT population)	Cochran Mantel Haenzel (Relative risk) [a]	211	211	212	12.5 mg vs placebo	1.374 (1.058, 1.786)	0.016
					25 mg vs placebo	1.502 (1.163, 1.938)	0.002
Response (ITT population)	Logistic Regression (Odds ratio) [b]	214	213	214	12.5 mg vs placebo	1.659 (1.110, 2.480)	0.013
					25 mg vs placebo	1.917 (1.286, 2.858)	0.001
Response (ITT population)	Chi-square (Relative risk) [c]	214	213	214	12.5 mg vs placebo	1.387 (1.067, 1.805)	0.014
					25 mg vs placebo	1.508 (1.167, 1.948)	0.001

[a] Analysis via Cochran Mantel-Haenszel test stratified by response to laxatives at baseline (LIR, LAR, LUR).
[b] The logistic regression model included treatment group and response to laxatives at baseline (LIR, non-LIR).
[c] Unadjusted Chi-square test, with the treatment effect characterized as the relative risk (NKTR-118/placebo) with associated 2-sided 95% CIs.
Note: The sensitivity analyses were not part of the multiple testing procedure, which was based on the primary analysis only. For the primary analysis, $p<0.025$ and $p<0.05$ were considered statistically significant for 25 mg and 12.5 mg groups versus placebo, respectively.
CI confidence interval; ITT intent-to-treat; LAR Laxative Adequate Responder/Response; LIR Laxative Inadequate Responder/Response; LUR Laxative Unknown Responder/Response; mITT modified intent-to-treat; PP per-protocol.

MO Comment:
The results of the sensitivity analyses support the conclusion that naloxegol is efficacious for the treatment of OIC in adults.

6.1.5 Analysis of Secondary Endpoints(s)

Given that only the 25 mg dose group had statistically significant primary efficacy in confirmatory Studies 04 and 05, only secondary endpoint results for the 25 mg treatment groups will be further discussed (although many of the tables included will provide the secondary endpoint results for the 12.5 mg group).

The key secondary efficacy variables were analyzed in the order outlined below following the testing of the primary efficacy variable in each group. These secondary endpoints were part of the statistical Multiple Testing Procedure.

1. Response (responder/non-responder) to study drug in the LIR subgroup during Weeks 1 to 12.
2. Time (in hours) to first post-dose laxation without the use of rescue laxatives within the previous 24 hours.
3. Mean number of days per week with at least 1 SBM (and less than 4 SBMs/day) during Weeks 1 to 12.

Response (responder/non-responder) to study drug in the LIR subgroup

The response rate for the LIR subgroup among patients taking naloxegol 25 mg was statistically significantly different than the placebo response rate for LIR patients in both Studies 04 and 05. The response rate among LIR patients was 48.7% (p=0.002) in Study 04 and 46.8% (p=0.014) in Study 05. These rates were higher than the total ITT population response rates seen in Study 04 (44.4%) and 05 (39.7%).

Table 13. Analysis of response rate for Weeks 1 to 12 in the LIR subgroup –Studies 04 and 05 (ITT)

	Study 04			Study 05		
	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg
n	118	115	117	121	125	124
Number (%) of patients responding	34 (28.8)	49 (42.6)	57 (48.7)	38 (31.4)	53 (42.4)	58 (46.8)
RR (Comparison vs. placebo)[a]	NA	1.479	1.691	NA	1.350	1.489
95% CI	NA	1.038, 2.107	1.205, 2.373	NA	0.967, 1.884	1.078, 2.058
p-value	NA	0.028*	0.002*	NA	0.074	0.014*

[a] Analysis via Chi-squared test.
* Statistically significant under the MTP.
RR Relative risk (a RR >1 is indicative of higher response rate on the naloxegol arm); CI Confidence interval; NA Not applicable.
Note: Response in the LIR subgroup is included within the Multiple Testing Procedure.
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MO Comment:
The LIR subpopulation was designed to represent conventional laxative users who continued to have moderate to very severe OIC symptoms at study entry. To define these patients, the Applicant developed the (b) (4) *that was to be administered by the investigator at screening* (b) (4) *There is currently no accepted method of defining patients with an inadequate response to laxatives; therefore, the* (b) (4) *in conjunction with a board of external experts.*

The Applicant has proposed the (b) (4) *Further, during multiple pre-submission discussions, the Division expressed concern about* (b) (4) (b) (4) *At multiple times during pre-submission discussions with*

the Applicant, the Division expressed these concerns. We acknowledge that (b) (4)

[redacted]

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Time (in hours) to first post-dose laxation

The time to first post-dose laxation without the use of rescue laxatives within the previous 24 hours was the second secondary endpoint included in the statistical Multiple Testing Procedure (MTP).

Table 14. Time in hours to first post-dose SBM –Studies 04 and 05 (Intent-to-treat analysis set)

	Study 04			Study 05		
	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 (h) to first SBM [a] (95% CI)	35.8 (27.0,48.1)	20.4 (11.5,22.7)	5.9 (4.8,11.5)	37.2 (30.0,46.9)	19.3 (9.4,22.3)	12.0 (7.0,21.5)
SBM by ≤6 h (%)	33 (15.4)	72 (33.8)	109 (50.9)	40 (17.2)	80 (34.5)	91 (39.2)
SBM by ≤12 h (%)	49 (22.9)	93 (43.7)	122 (57.0)	57 (24.6)	102 (44.0)	115 (49.6)
SBM by ≤24 h (%)	79 (36.9)	125 (58.7)	150 (70.1)	85 (36.6)	136 (58.6)	142 (61.2)
HR (Comparison vs. placebo)[a]	NA	1.610	2.384	NA	1.590	1.576
95% CI	NA	1.320,1.963	1.933,2.940	NA	1.313,1.925	1.303,1.906
p-value	NA	<0.001*	<0.001*	NA	<0.001	<0.001*

[a] Estimates calculated using the Kaplan-Meier technique.
* Statistically significant under the MTP.
Note: The percentages are based on the number of intent-to-treat patients in each treatment group.
CI Confidence interval; SBM spontaneous bowel movement

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Table 15. Time in hours to First Post-dose SBM, Studies 04 and 05 (ITT set)

Study 04	Placebo	Naloxegol 12. 5 mg	Naloxegol 25 mg
n	209	211	213
Mean (SD)	79.7 (125.52)	44.5 (80.50)	28.4 (61.02)

Source: information Request, submitted by sponsor on April 23, 2014, submission 0023

In study 04, the median time to first post-dose SBM was 5.9 hours in the naloxegol 25 mg group, 20.4 hours in the naloxegol 12.5 mg group, and 35.8 hours in the placebo group. This trend of decreasing hours to first post-dose SBM from placebo to high dose naloxegol was replicated in Study 05. Also, the mean time to first post-dose SBM showed a decrease as naloxegol dose increased. There was a lot of variability in the mean times to first post-dose SBM as reflected in the large standard deviations. See Table 14 and

Table 15 above.

MO Comment:
In Study 04, less than half of placebo patients (36.9%) had a SBM within 24 hours post first dose. In contrast, 70.1% of naloxegol 25 mg patients had a SBM after the first dose within 24 hours. In Study 05, the results for the placebo group were similar. However, a smaller proportion of naloxegol 25 mg patients (61.2%) in Study 05 had a SBM within 24 hours after the first dose of study drug.

Mean number of days per week with at least 1 SBM (and less than 4 SBMs/day) during Weeks 1 to 12

The difference between the LS mean change from baseline in number of days per week with at least 1 SBM between placebo and naloxegol patients in the 25 mg dose group was statistically significant in both Studies 04 and 05. See

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Table 16 below.

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Table 16. Repeated measures analysis of mean number of days per week with at least 1 SBM (and less than 4) over Weeks 1 to 12 –Studies 04 and 05 (ITT)

	Study 04			Study 05		
	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg
Baseline[a]						
n	213	213	214	232	232	232
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[b]						
LS mean	NA	0.55	0.82	NA	0.39	0.68
95% CI	NA	0.24, 0.86	0.51, 1.13	NA	0.09, 0.69	0.37, 0.98
p-value	NA	<0.001	<0.001	NA	0.010	<0.001

[a] Baseline based on a patient's mean number of days with SBMs over the OIC confirmation period
[b] Analysis via MMRM with fixed effects for baseline, baseline laxative response, treatment and treatment time interaction. Study pooled center is included as a random effect.
* Statistically significant under the MTP.
Days with > 3 SBMs are /day are not included (Section 1.2.1.7)
CI Confidence interval; NA Not applicable; SBM Spontaneous bowel movement; SD Standard deviation; SE Standard error.
Note: Mean number of days per week with at least 1 SBM is included within the Multiple Testing Procedure.
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MO Comment:

Reference ID: 3504437

The three secondary endpoints included in the statistical Multiple Testing Procedure all showed a statistically significant difference between placebo and the naloxegol 25 mg dose in Studies 04 and 05. The same is true for the three secondary endpoints and the 12.5 mg dose in Study 04. The trend was also there for the 12.5 mg dose in Study 05. However, the results were not statistically significant due to statistical significance failure of the primary endpoint for the 12.5 mg dose in Study 05. In general, the ranked secondary endpoints support the primary endpoint in supporting the conclusion that naloxegol is efficacious for the treatment of OIC in adult patients.

6.1.6 Other Endpoints

In addition to the secondary endpoints included in the multiple testing procedures (MTP), other endpoints were examined by the Applicant and underwent formal statistical analysis. Results are presented with nominal p-values only, with no consideration to the impact of multiplicity. The statistical Mixed Model for Repeated Measures (MMRM) was used for these analyses.

Change from baseline in symptoms associated with OIC
Summaries of mean degree of straining per week, mean stool consistency per week, and percent number of days per week with a complete SBM (CSBM) were measured.

Degree of straining
Degree of straining was measured on the following scale: 1=not at all; 2=a little bit; 3=a moderate amount; 4=a great deal; 5=an extreme amount. At baseline, the mean degree of straining scores were similar across all treatment groups in Studies 04 and 05. Mean baseline scores ranged from 3.1-3.3. The change from baseline scores was negative for all treatment groups in both studies (indicating improvement). And the change in scores showed stepwise improvement with increasing naloxegol doses in both studies.

Table 17. Repeated measures analysis of change from baseline in mean degree of straining per week –Studies 04 and 05 (Intent-to-treat analysis set)

	Study 04			Study 05		
	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg
Baseline[a]						
n	213	213	214	232	232	232
Mean (SD)	3.3 (0.78)	3.1 (0.79)	3.2 (0.84)	3.3 (0.81)	3.1 (0.82)	3.2 0.82)
Change from Baseline[b]						
LS Means (SEM)	-0.54 (0.05)	-0.64 (0.05)	-0.73 (0.05)	-0.48 (0.06)	-0.67 (0.06)	-0.80 (0.06)
Difference versus Placebo[b]						
LS mean	NA	-0.09	-0.18	NA	-0.19	-0.32
95% CI	NA	-0.23, 0.04	-0.32, -0.05	NA	-0.32, -0.06	-0.45, -0.18
p-value	NA	0.176	0.008	NA	0.005	<0.001

[a] Baseline based on a patient's mean degree of straining over the OIC confirmation period
[b] Analysis via MMRM with fixed effects for baseline, baseline laxative response (LIR, non-LIR), treatment and treatment time interaction. Study pooled centre is included as a random effect.
Note: Patient is included in the repeat statement, and an unstructured covariance matrix has been assumed.
Note: Baseline value used to calculate LS Means=3.20 in both studies.
Note: All patients with evaluable data at both baseline and at least 1 post-baseline week are included in the analysis.
CI Confidence Interval; LIR Laxative Inadequate Responder/Response; LS Mean Least-Squares Mean, estimated via the contrast statement in PROC MIXED; MMRM Mixed model for repeated measures; NA Not applicable; SEM Standard error of the mean

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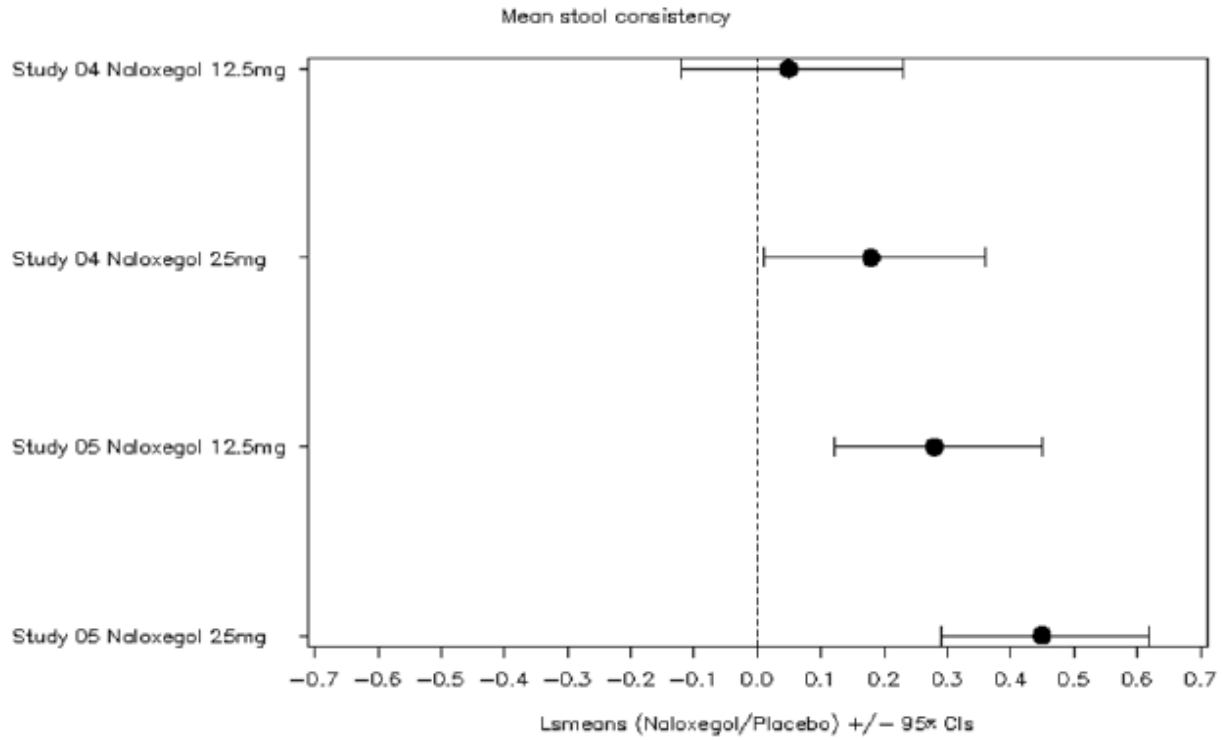
Stool Consistency

Stool consistency was measured using the Bristol Stool Scale (BSS). BSS types 1 and 2 stools are considered to reflect constipation, whereas BSS types 3 and 4 are considered to reflect "ideal stools."

Bristol Stool Chart

At baseline, all treatment groups in both studies had mean BSS stool ratings ranging from 2.8 to 3.0. The LS mean change from baseline in all treatment groups in Studies 04 and 05 was positive (indicative of more normal stool consistency). However, for the 12.5 mg dose group in Study 04, the 95% CI of the MMRM analysis crossed zero. See below.

Figure 2. Analyses of change from baseline in stool consistency (BSS ratings) for Weeks 1 to 12 – Studies 04 and 05 (Intent-to-treat analysis set)



Note: Difference versus placebo in change from baseline in LS mean >0 favours the naloxegol treatment groups.

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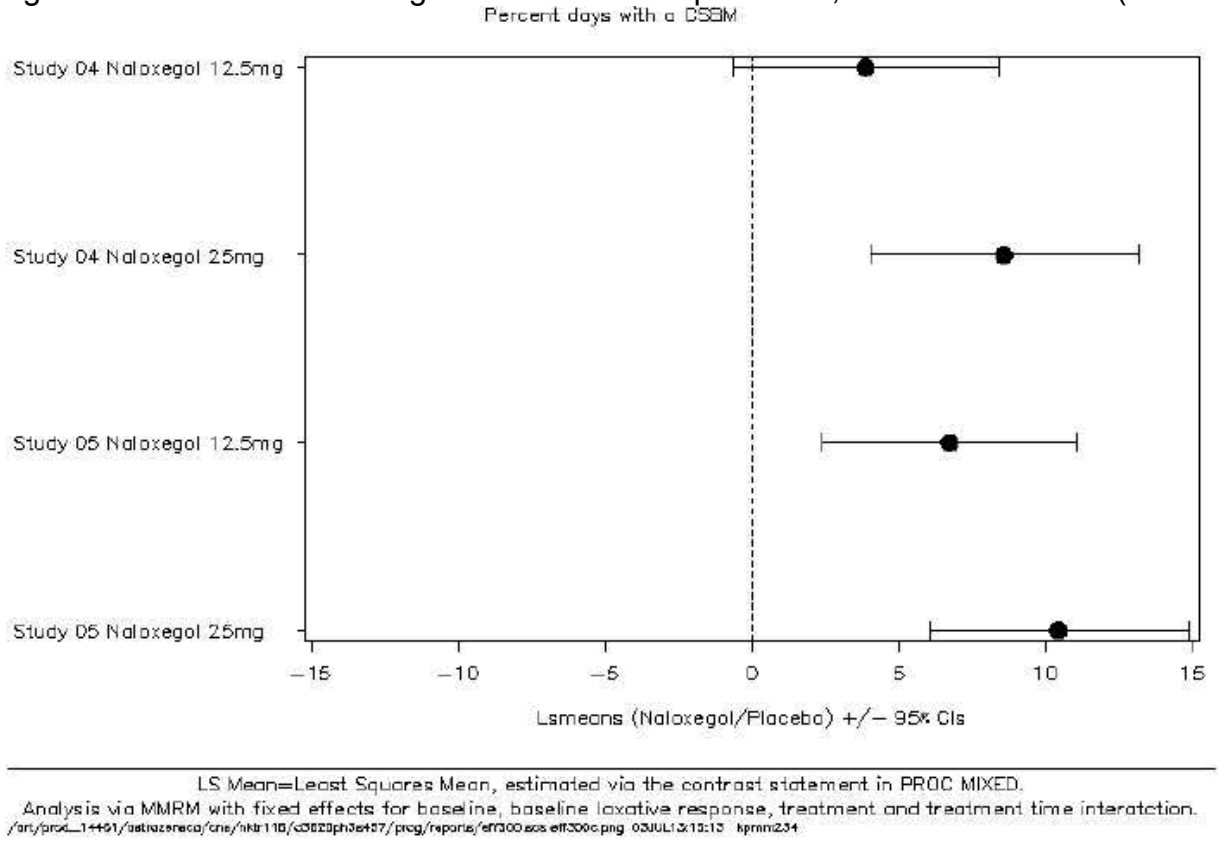
Number of days per week with at least 1 CSBM

The mean number of days during which patients reported having completeness of evacuation at baseline in all treatment groups in Studies 04 and 05 ranged from approximately 0.4 to 0.5 days/week. The mean change from baseline was positive for all treatment groups in both studies. However, the 95% confidence interval for the 12.5 mg naloxegol dose in Study 04 included zero. See Figure 3 below.

Figure 3. Forest Plot of change in Mean CSBMs per Week, Studies 04 and 05 (ITT Set)



LS Mean=Least Squares Mean, estimated via the contrast statement in PROC MIXED.
Analysis via MMRM with fixed effects for baseline, baseline laxative response, treatment and treatment time interaction.
/prd_14491/astrazeneca/cne/nkb110/d3820ph3e457/prog/reports/eff300.sas.eff300c.png 03JUL13:15:13 kprnn234

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Table 18. Repeated measures analysis of change from baseline in number of days per week with at least one CSBM – Studies 04 and 05 (ITT set)

	Study 04			Study 05		
	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg
n	211	211	212	231	228	226
LS Means (SEM)	1.29 (0.12)	1.56 (0.12)	1.89 (0.12)	1.17 (0.13)	1.64 (0.13)	1.90 (0.14)
Difference versus Placebo [b]						
LS mean	NA	0.27	0.60	NA	0.47	0.73
95% CI	NA	-0.05, 0.59	0.28, 0.92	NA	0.17, 0.77	0.42, 1.04
p-value	NA	0.094	<0.001	NA	0.002	<0.001

[a] Analysis via MMRM with fixed effects for baseline, baseline laxative response (LIR, non-LIR), treatment and treatment time interaction. Study pooled centre is included as a random effect.
Note: Patient is included in the repeat statement, and an unstructured covariance matrix has been assumed.
Note: Baseline value used to calculate LS Means=0.42 and 0.43 in Studies 04 and 05, respectively.
Note: All patients with evaluable data at both baseline and at least 1 post-baseline week are included in the analysis.
CI Confidence Interval; CSBM Complete spontaneous bowel movement; LIR Laxative Inadequate Responder/Response; LS Mean Least-Squares Mean, estimated via the contrast statement in PROC MIXED; MMRM Mixed model for repeated measures; NA Not applicable; SEM Standard error of the mean.
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MO Comment:
The feeling of completeness as assessed by a patient is important, but in my opinion not as important as having any bowel movement at all. Because the feeling of complete evacuation is subjective, these results do not provide as much information as the primary endpoint. Also, it seems possible to have an evacuation that is "complete", but still have the sensation of incomplete evacuation as the sensation may not always represent the state of the colon. Conditions such as hemorrhoids could alter a person's ability to determine "completeness".

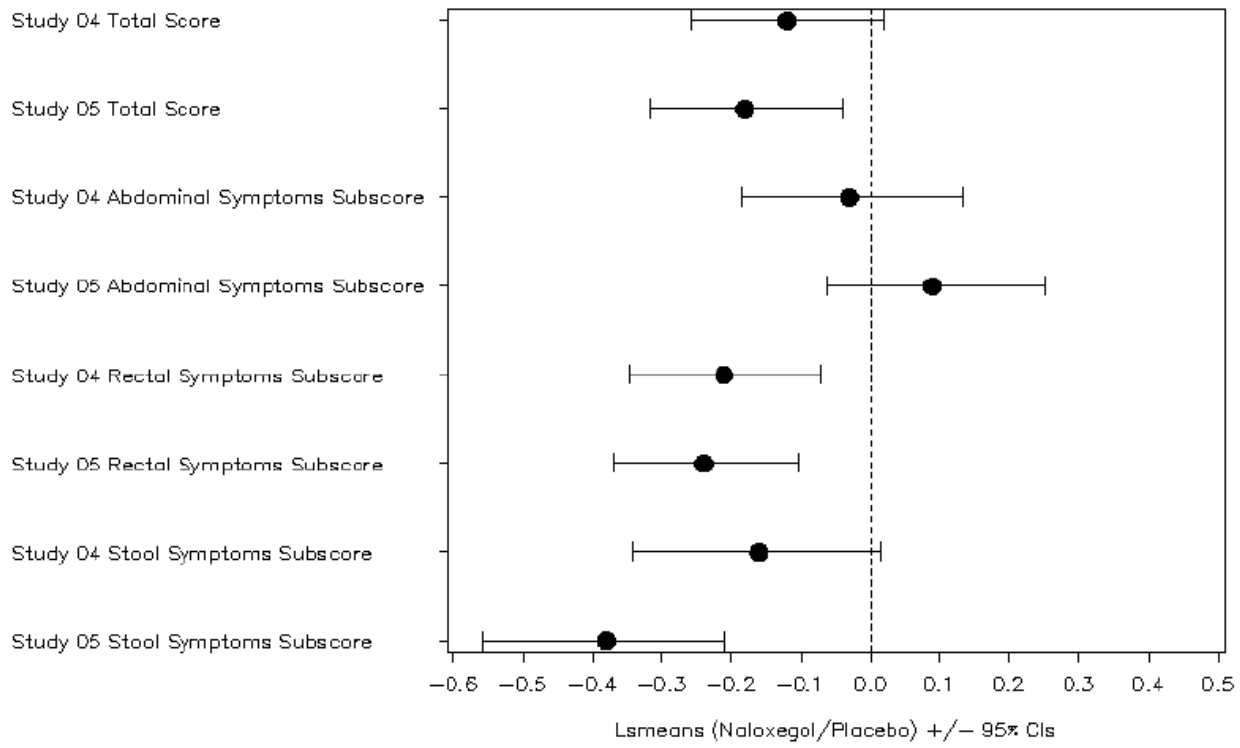
Change in Mean PAC-SYM Score

The Patient Assessment of Constipation – Symptom (PAC-SYM) questionnaire is a tool to assess symptom frequency and severity of chronic constipation. The authors used a definition for constipation based on the Rome II criteria. This 12-item self-report measure is divided into three symptom subscales (i.e., abdominal, rectal, and stool). Scoring on the PAC-SYM ranged from 0 (absence of symptoms) to 4 (very severe) for each domain. A total score for the PAC-SYM can range from 0 to 48. A negative change from baseline using PAC-SYM indicates improvement.

At baseline, the 25 mg treatment groups were similar in PAC-SYM total score and abdominal, rectal, and stool domain scores. At baseline, PAC-SYM scores were highest in the stool domain indicating that patients were mostly impacted by stool symptoms. The change in total PAC-SYM score was negative for both studies indicating overall improvement (it should be noted that the 95% CI for Study 04 included 0). There was no mean change in the abdominal pain domain score in Study 04 and there was worsening of the abdominal pain score in Study 05. Figure 4, below, represents the

results of MMRM analysis of the difference versus placebo in mean change from baseline in PAC-SYM scores at the final visit for the naloxegol 25 mg groups in both studies.

Figure 4. Change from baseline in PAC-SYM scores – Studies 04 and 05 (ITT), 25 mg naloxegol treatment groups



Note: Difference versus placebo in change from baseline in LS mean <0 favours the naloxegol treatment groups.
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Response Incorporating Symptom Data

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency advised the Applicant that improvement of OIC symptoms is important in assessing the success of a treatment for the condition. Therefore, the Applicant conducted an additional supporting secondary analysis using a definition of responder that takes symptoms into account (response incorporating symptom data). In addition to the definition of response for the primary variable, patients were required to demonstrate symptom improvement and no clinically relevant symptom deterioration during Weeks 1 to 12.

Symptom improvement/deterioration was defined as meeting ≥1 of the following criteria (based on the mean change from baseline over the 12-week treatment period):

- Improvement/worsening from baseline in mean BSS by ≥1 point
- Improvement/worsening from baseline in mean straining score by ≥0.5 point
- Improvement/worsening from baseline in mean number of days/week with at least one CSBM by ≥1 day

Table 19. Response rate incorporating symptom data for Weeks 1 to 12 – pooled data, Studies 04 and 05 (Cochran Mantel-Haenszel, ITT)

	Study 04			Study 05		
	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg	Placebo	Naloxegol 12.5 mg	Naloxegol 25 mg
n	214	213	214	232	232	232
Number (%) of patients responding	54 (25.2)	71 (33.3)	83 (38.8)	53 (22.8)	65 (28.0)	80 (34.5)
RR (Comparison vs. placebo)[a]	NA	1.312	1.538	NA	1.221	1.499
95% CI	NA	0.974,1.768	1.156,2.046	NA	0.894,1.669	1.117,2.012
p-value	NA	0.072	0.003	NA	0.209	0.006

[a] Analysis via Cochran Mantel-Haenszel test stratified by response to laxatives at baseline (LIR, LAR, LUR).
RR Relative risk (a relative risk >1 is indicative of higher response rate on the naloxegol arm); CI Confidence interval; NA Not applicable.

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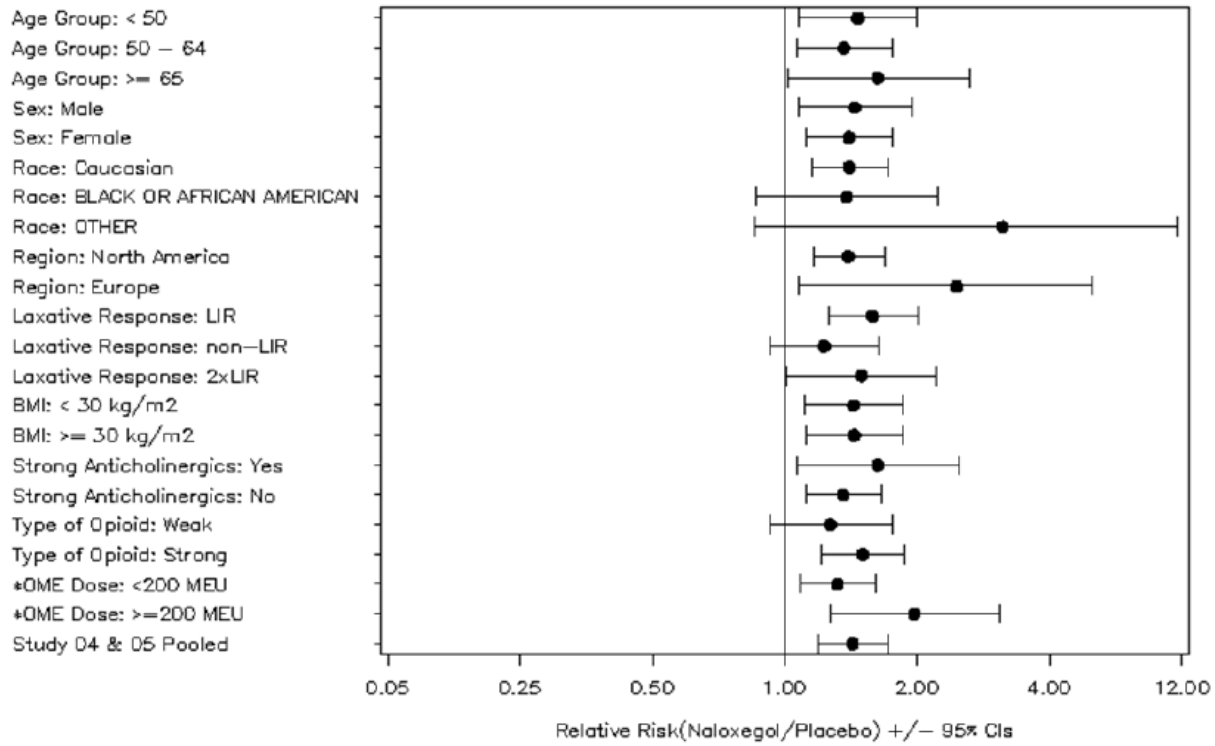
6.1.7 Subpopulations

For the analysis of efficacy within certain subpopulations, data from Studies 04 and 05 were pooled.

Figure 5. Response (naloxegol 25 mg vs placebo) to study drug during Weeks 1 to 12 in subgroups of interest – pooled data, Studies 04 and 05 (ITT)



A RR > 1 favors the naloxegol treatment groups.
OME Total/overall morphine-equivalent unit at baseline; RR Relative risk.
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Table 20. 12-week Response by Selected Subgroups, Naloxegol 25 mg dose group

Variable Subgroup	Studies 04 and 05			
	Placebo	NGL 25 mg	Relative Risk (95% CI)	p-value
Gender				
Male	46/161 (28.6%)	76/181 (42.0%)	1.444 (1.075, 1.941)	0.013
Female	85/285 (29.8%)	111/265 (41.9%)	1.401 (1.117, 1.758)	0.003
Age				
<50 yrs	46/165 (27.9%)	64/157 (40.8%)	1.465 (1.076, 1.995)	0.014
50-64 yrs	69/231 (29.9%)	64/157 (40.8%)	1.363 (1.061, 1.751)	0.014
≥65 yrs	16/50 (32.0%)	27/53 (50.9%)	1.629 (1.014, 2.620)	0.037
Race				
Caucasian	106/343 (30.9%)	157/362 (43.4%)	1.402 (1.151, 1.707)	0.001
Black/African-American	22/88 (25.0%)	27/78 (34.6%)	1.382 (0.859, 2.222)	0.179
Other	3/15 (20.0%)	3/6 (50.0%)	3.125 (0.850, 11.483)	0.106
Region				
North America	124/418 (29.7%)	175/423 (41.4%)	1.395 (1.158, 1.681)	<0.001
Europe	6/27 (22.2%)	12/23 (52.2%)	2.463 (1.070, 5.668)	0.025
Laxative Response				
LIR	72/239 (30.1%)	115/241 (47.7%)	1.584 (1.253, 2.001)	<0.001
Non-LIR	59/207 (28.5%)	72/205 (35.1%)	1.230 (0.926, 1.635)	0.153
2 x LIR	27/90 (30.0%)	44/99 (44.4%)	1.495 (1.010, 2.213)	0.040
BMI				
< 30 kg/m2	67/229 (29.3%)	91/217 (41.9%)	1.433 (1.111, 1.850)	0.005
≥ 30 kg/m2	64/217 (29.5%)	96/226 (42.5%)	1.440 (1.115, 1.860)	0.005
Strong Anticholinergics				
Yes	21/83 (25.3%)	38/86 (44.2%)	1.628 (1.068, 2.483)	0.020
No	110/363 (30.3%)	149/360 (41.4%)	1.358 (1.114, 1.656)	0.002
Type of Opioid				
Weak	47/157 (29.9%)	52/137 (38.0%)	1.270 (0.922, 1.751)	0.144
Strong	84/289 (29.1%)	135/309 (43.7%)	1.504 (1.208, 1.874)	<0.001
Opioid Morphine Equivalent				
<200 MEU	111/356 (31.2%)	143/348 (41.1%)	1.318 (1.080, 1.608)	0.006
≥200 MEU	20/88 (22.7%)	44/98 (44.9%)	1.972 (1.265, 3.076)	0.002

Reviewer's Table. Source: Appendices from ISS and ISE, Table 3.1.1.2.1, ITT Set

A relative risk (RR) greater than 1 is indicative of a higher response rate in the naloxegol arm compared to the placebo arm. In the majority of subgroups, the trend continued to be seen that patients taking naloxegol had a higher response rate than placebo patients. In fact, of the subgroups in Table 20 only the pooled response results of black race patients, other race patients, non-LIR patients, and patients who used weak opioids had a 95% confidence interval that included 1 when compared to placebo. The number of patients in these groups was generally smaller than the other subgroups.

MO Comment:
Most patients in the confirmatory studies used strong opioids. Mechanistically, it is plausible that naloxegol might be less efficacious in patients using weak opioids. Given the fact that naloxegol antagonizes mu-opioid receptors, persons with minimal opioid

agonism with constipation may only benefit minimally from opioid antagonism. In these patients, constipation could be due to other causes.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Applicant is recommending approval of the 25 mg once daily dose for most adult patients. I concur with this recommendation based on the lack of efficacy demonstrated in one of the two confirmatory Phase 3 studies for the 12.5 mg dose.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The primary endpoint for the confirmatory Phase 3 studies was whether or not a patient was a responder to study drug during Weeks 1 to 12. A responder was defined as a patient with at least 3 spontaneous bowel movements (SBMs) per week and at least a 1 SBM/week increase over baseline. To account for persistence of efficacy, the response had to include at least 9 out of the 12 treatment weeks and 3 out of the last 4 treatment weeks.

MO Comment:
Persistence of efficacy is further suggested by the relatively low rate of dropouts seen in the 52-week long-term safety study (08). Among patients taking naloxegol 25 mg once daily, nearly 60% of patients remained at the end of the 52-week study. See Section 7.2.1 below.

6.1.10 Additional Efficacy Issues/Analyses

N/A

7 Review of Safety

Safety Summary

In general, the use of naloxegol for the proposed indication appears to represent an acceptable risk. See the Risk Benefit Assessment Section 1.2.

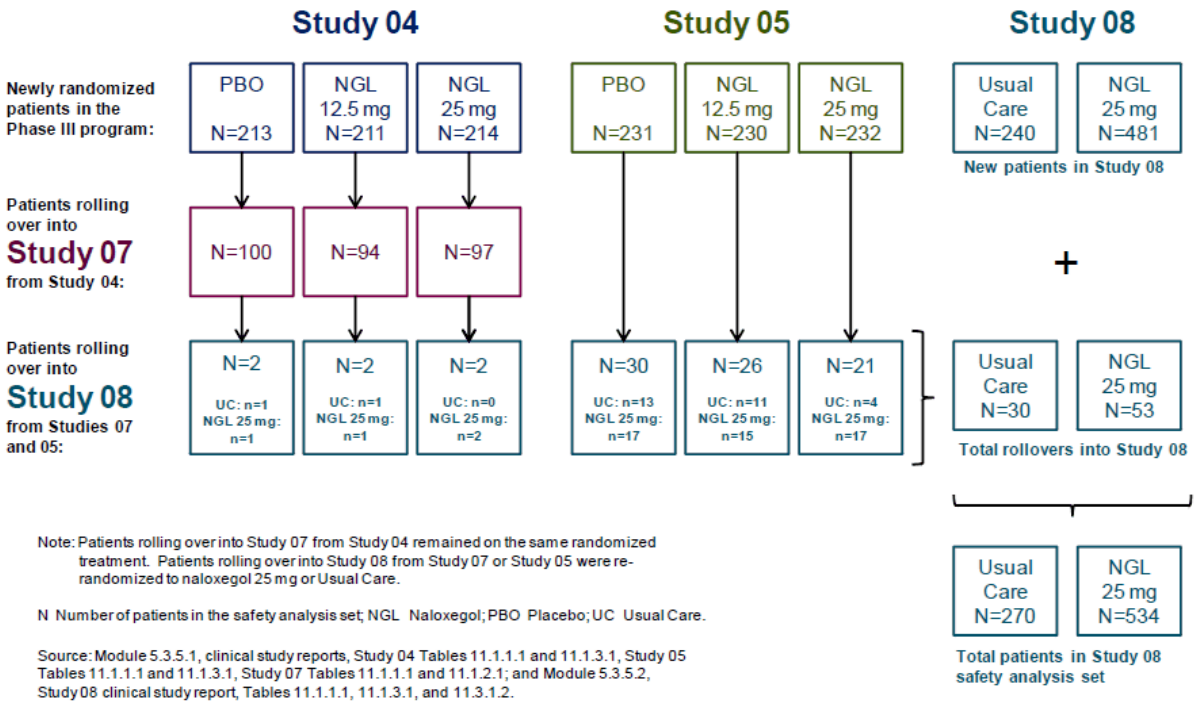
7.1 Methods

The safety analysis set (safety population) was defined as all randomized patients who received at least 1 dose of study drug. Within this larger safety population, three primary analysis sets will be used for the review of safety: the 12-week pool (Studies 04 and 05), the placebo-controlled safety pool (Studies 04, 05, and 07), and the 52-week

pool (Study 08). For each safety analysis in the review, the most appropriate pool will be presented and discussed.

For Studies 04, 05, and 07, all safety analyses were based on the safety analysis set, by treatment first received (i.e., placebo, naloxegol 12.5 mg, or naloxegol 25 mg). All Study 08 analyses were done based on the treatment received in Study 08 (i.e., naloxegol 25 mg or Usual Care) regardless of the treatment received in a prior study. For patients in the Usual Care group in Study 08, no specific rescue laxative protocol was specified. Instead, patients could use whatever laxative regimen was prescribed by their provider. However methylnaltrexone and naloxone-containing products were prohibited.

Figure 6. Disposition of Safety Patients in Studies 04, 05, 07, and 08



Note: Patients rolling over into Study 07 from Study 04 remained on the same randomized treatment. Patients rolling over into Study 08 from Study 07 or Study 05 were re-randomized to naloxegol 25 mg or Usual Care.

N Number of patients in the safety analysis set; NGL Naloxegol; PBO Placebo; UC Usual Care.

Source: Module 5.3.5.1, clinical study reports, Study 04 Tables 11.1.1.1 and 11.1.3.1, Study 05 Tables 11.1.1.1 and 11.1.3.1, Study 07 Tables 11.1.1.1 and 11.1.2.1; and Module 5.3.5.2, Study 08 clinical study report, Tables 11.1.1.1, 11.1.3.1, and 11.3.1.2.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data were reviewed primarily from Studies 04, 05, 07, and 08 (described earlier). The Applicant submitted a 120-day safety update that did not include any new safety data as all studies had been completed with study reports submitted with the original NDA submission on September 16, 2013. The Sponsor also submitted responses to

several clinical information requests. No new study data were submitted in these responses.

7.1.2 Categorization of Adverse Events

Adverse events were classified by the Applicant using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Version 15.0 was used for categorizing adverse events (AEs) in the individual Phase 3 studies. However, the pooled displays and the Study 08 (i.e., 52-week) displays, used version 15.1. A list of AEs reported in the Phase 3 studies for which the MedDRA coding changed from version 15.0 to version 15.1 is provided below.

Table 21. Differences between MedDRA version 15.0 and 15.1 relevant to the Phase 3 naloxegol Program

Verbatim term	MedDRA version	System organ class	Preferred term	Lower-level term
Parodontitis	15	Gastrointestinal disorders	Periodontitis	Periodontitis
	15.1	Infections and infestations	Periodontitis	Periodontitis
Face sunburn rash	15	Injury, poisoning and procedural complications	Sunburn	Sunburn
	15.1	Skin and subcutaneous tissue disorders	Sunburn	Sunburn
Walking pneumonia	15	Infections and infestations	Pneumonia primary atypical	Walking pneumonia
	15.1	Infections and infestations	Atypical pneumonia	Walking pneumonia

MedDRA Medical Dictionary for Regulatory Activities.
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An AE was defined as an undesirable medical condition or the deterioration/exacerbation of a pre-existing medical condition, whether or not considered causally related to the product.

In the Phase 3 program, all patients who were randomized and received at least 1 dose of study drug were to be followed over the course of the treatment period and the post-treatment follow-up period. Patients who rolled-over from 1 study into another study were to have their 2-week post-treatment follow-up period at the end of the final study. Patients who discontinued any study prematurely were asked to return to the study center for an early termination (ET) visit. This ET visit was scheduled as soon as possible after the patient discontinued from the study. Any patient who discontinued and had clinically significant or abnormal results for any safety assessment were to have had an additional follow-up visit 1 week after discontinuation and at appropriate intervals thereafter, as medically indicated and determined by the investigator.

Reference ID: 3504437

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Adverse event incidence data were included from four studies: Study 04, Study 05, Study 07, and Study 08. See Section 7.1 for a description of how pooled data is presented in this review.

7.2 Adequacy of Safety Assessments

The safety assessments performed were adequate. Safety variables included adverse events (AEs), clinical laboratory evaluations (hematology, clinical chemistry, and urinalysis), vital signs, and physical examination parameters. Patients who were given at least one dose of the study medication were included in the safety analysis population.

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

The key Phase 3 placebo-controlled studies were Studies 04 and 05. Following Study 04, patients had the option of rolling over into Study 07 for an additional 12 weeks of randomized study treatment (the same treatment received in Study 04). The mean duration of exposure to naloxegol during the placebo-controlled studies was 93.0 days (12.5 mg) and 90.3 days (25 mg). See

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Table **22** below.

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Table 22. Duration of exposure to double-blind treatment (Placebo-controlled pool [Studies 04, 05, and 07])

	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.
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During Study 08, a 52-week safety study, the mean duration of exposure to Naloxegol 25 mg was 268.1 days compared with a mean of 296.7 days for usual care patients. During the first three months of the study, discontinuation rates were higher in the Naloxegol group than the usual care group which helps explain this difference in mean durations between the two groups. Patients could enter the study as roll-over patients from studies 05 or 07 (n=53 naloxegol patients) or as new patients (n=481 naloxegol patients). More than half of all patients in Study 08 were still enrolled at or after Week 51 (59.4% of Naloxegol patients and 69.3% of usual care patients).

MO Comment:
As a point of clarification, although visits were to be scheduled as "monthly" (according to the protocol), the IVRS was actually programmed using a 30 day visit regardless of the actual number of days in the month. Using a 30 day visit cycle instead of "monthly" combined with the allowed +/-3 days visit window allowed patients to complete all study-related treatments in 50-51 weeks. This explains the sharp decrease in extent of exposure from ≥51 weeks to ≥52 weeks.

7.2.2 Explorations for Dose Response

There were two naloxegol dosing regimens included in the Phase 3 program —12.5 mg and 25 mg once daily. There was a trend of higher incidences of AEs with increasing naloxegol dose seen in the identical placebo-controlled Studies, 04 and 05 (placebo 51.1%, naloxegol 12.5 mg 52.4%, naloxegol 25 mg 63.5%). The trend continued at the individual AE level. For example, the most common AE reported in both dose groups was abdominal pain. This AE was reported in 15.9% of patients in the 25 mg dose group compared with 9.8% of patients in the 12.5 mg dose group. Of the most common AEs (incidence ≥2% in any treatment group), only fall and dizziness had a higher incidence in the 12.5 mg group compared with the 25 mg group. See Table 31 (Common Adverse Events, Section 7.4.1) below.

In the 52-week study (Study 08), the trend continued. In the usual care group, the incidence rate of AEs was 71.9% compared with 80.1% in the naloxegol 25 mg group.

MO Comment:
The trend of higher incidence of AEs in the 25 mg naloxegol patients compared with the naloxegol 12.5 mg patients in the Phase 3 studies was not seen in the subset of SAEs. See section 7.3.2.

7.2.3 Special Animal and/or In Vitro Testing

N/A

7.2.4 Routine Clinical Testing

Routine clinical testing as described in Section 7.2 was included as part of the safety assessments in the three submitted studies. See Section 5.3.5 for detailed information on study visits and procedures.

7.2.5 Metabolic, Clearance, and Interaction Workup

For more information, see the Clinical Pharmacology Review in DARRTS by Elizabeth Shang, PhD.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Drugs in the peripherally acting mu opioid receptor antagonist (PAMORA) class have been associated with bowel perforation, CV adverse events, and opioid withdrawal.

Bowel perforation

Background:
There have been reports of bowel perforation associated with the use of methylnaltrexone (a drug in the same class as Naloxegol). These events occurred in the post-marketing setting and some resulted in death. Currently, bowel perforation is a Warning in Relistor labeling. For the Naloxegol program, all GI SAEs were adjudicated by an independent GI external committee given that bowel perforation was identified as a topic of special interest in the Phase 3 program.

Excerpt from current Relistor labeling:

> ***5.2 Intestinal Perforation***
> *Rare cases of gastrointestinal (GI) perforation have been reported in advanced illness patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the GI tract (i.e., cancer, peptic ulcer, Ogilvie's syndrome). Perforations have involved varying regions of the GI tract: (e.g., stomach, duodenum, colon).*
>
> *Use RELISTOR with caution in patients with known or suspected lesions of the GI tract. Advise patients to discontinue therapy with RELISTOR and promptly notify their physician if they develop severe, persistent, and/or worsening abdominal symptoms.*[7]

Results:
There were no AEs of bowel perforation reported or adjudicated in the Naloxegol clinical development program.

Applicant's plan to address safety issue:
AstraZeneca has proposed to include information regarding the risk of bowel perforation in the Contraindication and Warnings/Precautions sections of the naloxegol label.

MO Comment:
I agree with the Applicant's plan to address the risk of bowel perforation by placing a warning in the label.

Cardiovascular-related Adverse Events

Background:
Cardiovascular events were identified as a topic of special interest in the naloxegol Phase 3 program for two main reasons: First, a potential CV safety signal (myocardial ischemia) was observed in a long-term safety study of alvimopan, a drug in the same class as naloxegol. Second, there were findings in a Phase 1 dog telemetry study using naloxegol of decreased blood pressure and heart contractility. Therefore, the Applicant used a prospective adjudication process and convened a 4-member CV-event adjudication committee (CV-EAC). See Appendix A for the CV-EAC charter.

Results:

[7] http://labeling.pfizer.com/showlabeling.aspx?id=499. Site accessed January 12, 2014.

Major Adverse Cardiovascular Events (MACE) were pre-specified AEs of special interest. The total number of events was low; therefore, it was difficult to make specific conclusions regarding the association of naloxegol with MACE events. In the 12-week pool, the incidence rate of MACE events was 0.5% in both the placebo and naloxegol12.5 mg treatment groups (2 patients in each group). The incidence of MACE events was 0.2% (one patient). In the 52-week safety study, the incidence of MACE events was 0.7 in the usual care arm compared with 0.4 in the naloxegol 25 mg arm.

Table 23. 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)

	Placebo-controlled pool (Studies 04/07 and 05)			52-week safety study (Study 08)	
Category	**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.

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MO Comment:
The adjudicated events in Table 23 do not represent unique patients. However, only one patient experienced two events. There was a 73 y/o male with MI on day 16 and CV death on day 19 in the 12.5 naloxegol group of the placebo-controlled pool. All other events in the table represent unique patients.

Narratives of patients with CV death

- Study 04 Patient E4068050 was a 73-year-old male in the naloxegol 12.5 mg group with multiple CV risk factors. He had a SAE of acute MI on Day 16 that led to surgery for aortic valve replacement and a coronary artery bypass graft with complications of pneumonia, sepsis, and renal failure. The SAE of cardiac valve replacement complication on Day 19 resulted in the patient's death on Day 49. This event was adjudicated as a CV death and acute myocardial infarction.

- Study 07 Patient E4073006 was a 54-year-old male in the naloxegol 12.5 mg group with diabetes. He was in a serious road traffic accident on Day 146 (Day 60 of Study 07), after a "blackout" due 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. An autopsy showed that the patient died of myocardial ischemia, 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 the current study, 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 by the investigator to have a SAE of idiopathic generalized epilepsy on Day 111 that resulted in the patient's death. There was no previous history of epilepsy for this patient and the patient 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 the patient stopped taking study drug on Day 92; the reason for study drug discontinuation could not be determined. This event was adjudicated as a CV death.

- Patient E4010003 (naloxegol 25 mg), a 40-year-old male with a medical history of multiple CV risk factors, had a severe MI on study Day 1, and study drug was discontinued. The MI was reported as resolved on Day 3. The CV-EAC asked for additional information regarding this patient and received the following 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. (*This case is not included in the Table above)

- There was 1 death in the Phase I studies of naloxegol. In Study 09, Subject E0001005 (severe renal impairment group), a 61-year old, White male,

experienced a post-study SAE of MI that led to death. The patient received a single dose of naloxegol 25 mg on Day 1, had the MI on Day 18, and died on Day 35. While hospitalized, the subject's diagnosis revealed multi-vessel coronary artery disease and a 5-vessel coronary bypass was performed on Day 25. Complications during hospitalization included pericarditis, atrial fibrillation, and pneumonia. Hemodialysis was started during hospitalization. The subject was discharged 14 days after being admitted to the hospital and died of sudden cardiac death in his sleep on Day 35. Other AEs during the study included ecchymosis. Notable medical history included congestive heart failure; Grade 1/6 systolic murmur, right base; Type 2 diabetes, kidney impairment, and hypertension. (Phase 1 studies were not adjudicated and this death occurred after completion of the study).

Narratives of patients with Acute MI

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

- Study 04 Patient E4010003 was a 40-year-old white man randomized to the naloxegol 25 mg group. The patient had a past medical history 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 brand of energy drink the patient drank before the event was "Monster" (the size is unknown). The patient had a SAE of myocardial infarction on Day 1 of randomized treatment. The patient subsequently withdrew from the study. The event was adjudicated as a myocardial infarction.

- Study 05 Patient E5237018 was a 60-year-old American Indian or Alaska Native man randomized to the placebo group. The patient had a past medical history 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 has a strong history of cardiovascular disease (CVD). The patient had a SAE of chest pain with shortness of breath and sweating. The event was adjudicated as an acute myocardial infarction.

- Study 05 Patient E5265013 was a 42-year-old white man randomized to the placebo group. The patient's relevant medical history included hypercholesterolemia and depression. The patient had a SAE of non-ST elevated myocardial infarction on Day 34 of randomized treatment. The patient was found lying in bed semi-conscious and unable to be fully aroused. Stool was noted in the area, but there was no report of observed blood. Upon paramedics' arrival, the patient was confused and was taken to the emergency room (ER). The patient was admitted to hospital for non-responsiveness and final diagnosis was non ST elevated myocardial infarction. The event was adjudicated as an acute myocardial infarction

Narrative of patient with Stroke
Study 08 Patient E8873013 (usual care group) was a 48-year-old white woman. The patient had a serious adverse event of frontal lobe infarction (MedDRA: ischaemic cerebral infarction) on Day 74 of randomized treatment. The adverse event required special treatment: atorvastatin and warfarin. The event was continuing at the time of study withdrawal. The patient's relevant medical history included hypertension, smoking half a pack per day and bilateral artery obstruction in the carotid artery. Relevant concomitant medications included aspirin, lisinopril and hydrochlorothiazide. The patient 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-like state. According to the hospital notes, there was some concern of possible factitious disorder but nevertheless she clearly demonstrated significant left-sided weakness and numbness. She was also unresponsive even to noxious stimuli. She did have a significant psychiatric history with bipolar affective disorder.

A computerized tomography and MRI of the brain were performed. The MRI of the head 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. And the neurosurgeon considered the findings on spinal imaging not to be consistent 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, being able to independently ambulate from bed to bathroom and back with assistance of a rolling walker. The event was adjudicated as an ischemic (non-hemorrhagic) stroke.

The CV safety risk associated with the use of naloxegol was evaluated by the Division of Cardiology and Renal Products (DCaRP). The DCaRP reviewer concluded the following (regarding the naloxegol program):

> *There is no definitive CV safety signal from naloxegol's preclinical data, ECG data and TQT study, clinical vital sign data (changes in SBP, DBP, and HR), or*

MACE outcomes (stoke, MI, CV death, hospitalization for unstable angina, hospitalization for CHF)

For a detailed discussion regarding CV AEs associated with the use of naloxegol, see the full DCaRP review by Dr. Preston Dunnmon in DARRTS (10 March 2014).

Applicant's plan to address the safety issue:
Astra Zeneca plans to participate in the upcoming Advisory Committee (AC) meeting regarding cardiovascular risk associated with the mu-opioid receptor class of drugs. The AC is tentatively scheduled for June 11-12, 2014. During this meeting, experts will discuss whether a pre-market CV study should be required for this class of drugs.

MO Comment:
While there does not appear to be a CV safety signal in the naloxegol program, it will be important to hear the opinion of the experts at the AC regarding the entire PAMORA class. Once the entire class has been discussed at the AC, a decision regarding the naloxegol program and the need for a pre-market CV safety study will be made by the review team.

Opioid withdrawal
Background:
Opioid withdrawal symptoms have been reported with the use of Relistor. Given this fact combined with the mechanism of action of the peripherally-acting μ-opioid receptor antagonists (PAMORAs) there are concerns that their use may lead to reversal of opioid effect and other generalized opioid withdrawal symptoms. Further, there are concerns that this withdrawal could have effects on the autonomic nervous system, potentially leading to hemodynamic changes known to increase the risk of CV adverse events.

To understand and quantify the possible risk of opioid antagonism, pain intensity and opioid dose were assessed throughout the Phase 3 studies. In Studies 04 and 05, pain intensity data were collected through daily electronic diary entries. Patients in Studies 07 and 08 completed the NRS question on paper forms indicating their average pain during the 7 days prior to study visits. The NRS is an 11-point point scale (1 [no pain] to 10 [worst pain imaginable]). For the naloxegol Phase 3 program, an increase in the NRS score of ≥2 in NRS score relative to baseline was selected as an appropriate cutoff for identifying individual patients with potentially clinically important (PCI) increases in pain.

To evaluate the risk of other opioid withdrawal associated with the use of naloxegol, the Applicant prospectively planned to evaluate the occurrence of the Standardized MedDRA Query (SMQ) list of PTs related to drug withdrawal.

In response to discussions during a Type C pre-NDA meeting held 23 April 2013 and the FDA's subsequent May 2013 responses to the Applicant's background document

questions, the Applicant expanded the list of PTs potentially related to opioid withdrawal to include the following:

- PTs related to the modified Himmelsbach Scale (mHS) signs
- AEs contained within the Clinical Opiate Withdrawal Scale (COWS), the Short Opiate Withdrawal Scale (SOWS), and/or the Objective Opioid Withdrawal Scale (OOWS)
- AEs discussed in the FDA medical review of another peripherally acting opioid antagonist, alvimopan (Entereg)
- Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV

See Table 24 below for a list of the 45 actual preferred terms from the categories listed above.

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Table 24. Updated comprehensive list of MedDRA preferred terms potentially related to opioid withdrawal syndrome

Source	Symptom or opioid withdrawal scale item	Preferred term
MedDRA SMQ Drug Withdrawal	NA	Drug withdrawal convulsions
	NA	Drug withdrawal headache
	NA	Drug withdrawal syndrome
	NA	Drug withdrawal syndrome neonatal
	NA	Rebound effect
	NA	Steroid withdrawal syndrome
	NA	Withdrawal arrhythmia
	NA	Withdrawal syndrome
	NA	Drug withdrawal maintenance therapy
	NA	Drug rehabilitation
Modified Himmelsbach Scale (mHS)	Yawning	Yawning
	Lacrimation	Lacrimation increased
	Rhinorrhea	Rhinorrhoea, Rhinitis
	Perspiration	Hyperhidrosis; Night sweats, Cold sweat
	Tremor	Tremor; Feeling Jittery
	Mydriasis	Mydriasis
	Piloerection	Piloerection
	Restlessness	Restlessness; Akathisia
Clinical Opiate Withdrawal Scale (COWS)	Resting pulse rate	Heart rate increased; Palpitations; Tachycardia; Sinus tachycardia
	Sweating	Hyperhidrosis, Night sweats, Cold sweat
	Restlessness	Restlessness; Akathisia
	Pupil size	Mydriasis
	Bone or Joint aches	Bone pain; Arthralgia
	GI upset (stomach cramps, nausea, vomiting, diarrhea)	Abdominal pain; Abdominal pain upper; Abdominal pain lower; Nausea; Vomiting; Diarrhoea[a]
	Tremor	Tremor; Feeling jittery
	Yawning	Yawning
	Anxiety or Irritability	Anxiety; Irritability; Agitation; Anxiety disorder
	Gooseflesh skin	Piloerection
	Runny nose or tearing	Rhinorrhoea; Lacrimation increased, Rhinitis

Table 24 cont'd

Source	Symptom or opioid withdrawal scale item	Preferred term
Subjective Opiate Withdrawal Scale (SOWS)	"I feel anxious"	Anxiety; Irritability; Agitation; Anxiety disorder
	"I feel like yawning"	Yawning
	"I am perspiring"	Hyperhidrosis; Night sweats; Cold sweat
	"My eyes are teary"	Lacrimation increased
	"My nose is running"	Rhinorrhoea, Rhinitis
	"I have goosebumps"	Piloerection
	"I am shaking"	Tremor; Feeling jittery
	"I have hot flashes"	Hot flush; Feeling hot; Flushing
	"I have cold flashes"	Chills, Feeling Cold
	"My bones and muscles ache"	Bone pain; Myalgia
	"I feel restless"	Restlessness; Akathisia
	"I feel nauseous"	Nausea[a]
	"I feel like vomiting"	Vomiting[a]
	"My muscles twitch"	Muscle twitching; Muscle spasms; Myoclonus
	"I have stomach cramps"	Abdominal pain; Abdominal pain upper; Abdominal pain lower[a]
	"I feel like using now"	Drug abuse; Drug dependence; Drug effect decreased
Objective Opioid Withdrawal Scale (OOWS)	Yawning	Yawning
	Rhinorrhea	Rhinorrhoea, Rhinitis
	Piloerection (observed arm)	Piloerection
	Perspiration	Hyperhidrosis; Night sweats; Cold sweat
	Lacrimation	Lacrimation increased
	Tremor	Tremor; Feeling jittery
	Mydriasis	Mydriasis
	Hot and cold flushes	Hot flush; Feeling hot; Flushing
	Restlessness	Restlessness; Akathisia
	Vomiting	Vomiting[a]
	Muscle twitches	Muscle twitching; Muscle spasms; Myoclonus
	Abdominal cramps	Abdominal pain; Abdominal pain upper; Abdominal pain lower[a]
	Anxiety	Anxiety; Irritability; Agitation; Anxiety disorder
FDA Clinical Review of alvimopan with respect to the topic of opioid withdrawal[b]	Insomnia	Insomnia, Initial insomnia
	Return of pain	Drug effect decreased
	Sneezing	Sneezing

Table 24. continued

Source	Symptom or opioid withdrawal scale item	Preferred term
DSM-IV[c]	Fever	Pyrexia
	Dysphoric moods	Agitated depression; Depressed mood; Depression; Dysphoria; and Depressive symptom

Note: PTs related to the DSM-IV criteria for opioid withdrawal, other than fever and dysphoric moods, are included in the table under another heading or headings: MedDRA SMQ, mHS, COWS, SOWS, OOWS, or FDA Clinical Review of alvimopan

[a] In the "Additional opioid withdrawal and cardiovascular (CV) risk assessments" document in Module 5.3.5.3, gastrointestinal adverse events were excluded because of the potential to confound the assessment of opioid withdrawal. These events may be associated with the intended action of naloxegol and in the absence of other events potentially related to withdrawal, they do not constitute opioid withdrawal per se. They are included in the assessments presented in this document. Note that abdominal pain and abdominal pain lower were not in the original table but have been added to be as comprehensive as possible.

[b] Terms from the FDA Clinical Review of alvimopan are included here only if they are not already included in the list.

[c] Terms related to the DSM-IV criteria for opioid withdrawal were inadvertently omitted from the comprehensive list used in "Additional opioid withdrawal and cardiovascular (CV) risk assessments" document in Module 5.3.5.3. They are included in the assessments presented in this document. Terms based on the DSM-IV criteria are included here only if they are not already included in the list.

DSM Diagnostic and Statistical Manual of Mental Disorders; MedDRA Medical Dictionary for Regulatory Activities; NA Not applicable; SMQ Standardized MedDRA Query.

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Results:
For assistance with the analysis of the AEs possibly related to opioid withdrawal, DGIEP consulted the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP). Dr. Elizabeth Kilgore completed a formal review and brief excerpts of the review are included below. For a more full discussion of the association between naloxegol and opioid withdrawal, see the complete DAAAP consult review in DARRTS (30 January 2014).

DGIEP Question for DAAAP: For Studies 04 and 05, is there evidence of opioid withdrawal in study drug compared to placebo?

DAAAP Response: Yes, based upon all analyses, there is evidence of possible opioid-withdrawal related AEs which occurred in the controlled 12-week Studies 04 and 05.

- **While the overall incidence was generally low, possible opioid withdrawal symptoms occurred with a higher frequency in patients taking naloxegol (2%) compared to placebo (<1%) and occurred with a greater incidence in the naloxegol 25mg group (14/446=3%) than the naloxegol 12.5mg group (5/441=1%).**
- **Analyzing the data using expanded terms from DSM-IV, COWS, SOWS, OOWS and other relevant terms including GI terms resulted in the identification of a higher number of cases with potential opioid withdrawal**

terms but not all cases met the criteria of clinically meaningful possible OWS.

When the list of PTs was exploded (as described above), a post-hoc analysis of the 12-week pool revealed that the incidence of PTs potentially related to opioid withdrawal remained higher in patients in the naloxegol treatment groups (24.0%, 12.5 mg; 33.6%, 25 mg) compared with 18.9% of patients in the placebo group. Similarly, in the 52 week study, the incidence of PTs potentially related to opioid withdrawal was higher in the naloxegol 25 mg group (47.4%) than in the usual care group (25.9%).

Table 25. Number (%) of patients with pre-specified AEs of opioid withdrawal during the treatment period (placebo-controlled pool and Study 08)

	Placebo-controlled pool (Studies 04/07 and 05)			52-week safety study (Study 08)	
	Placebo (N=444)	NGL 12.5 mg (N=441)	NGL 25 mg (N=446)	Usual care (N=270)	NGL 25 mg (N=534)
Any PT	**1 (0.2)**	**2 (0.5)**	**6 (1.3)**	**0**	**2 (0.4)**
Drug withdrawal syndrome	1 (0.2)	2 (0.5)	**6 (1.3)**	0	2 (0.4)
Any PT and no concurrent interruption of opioid treatment or treatment with a central opioid antagonist	1 (0.2)	1 (0.2)	5 (1.1)[a]	0	0

Note: PTs prospectively identified as AEs of opioid withdrawal were: Drug withdrawal convulsions, Drug withdrawal headache, Drug withdrawal syndrome, Drug withdrawal syndrome neonatal, Rebound effect, Steroid withdrawal syndrome, Withdrawal arrhythmia, Withdrawal syndrome, Drug withdrawal maintenance therapy, Drug rehabilitation.

[a] All 5 of these patients had concurrent gastrointestinal AEs. Four were on methadone.

AE Adverse event; N Number of patients in safety population; NGL Naloxegol; PT Preferred term.

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Table 26. Number (%) of patients with at least 1 PT potentially related to opioid withdrawal syndrome during the treatment period (12-week pool and Study 08)

	12-week pool (Studies 04 and 05)			52-week safety study (Study 08)	
	Placebo (N=444)	NGL 12.5 mg (N=441)	NGL 25 mg (N=446)	Usual care (N=270)	NGL 25 mg (N=534)
Any PT	**84 (18.9)**	**106 (24.0)**	**150 (33.6)**	**70 (25.9)**	**253 (47.4)**
Any non-GI PT	**31 (7.0)**	**35 (7.9)**	**58 (13.0)**	**49 (18.1)**	**131 (24.5)**
Hyperhidrosis	1 (0.2)	2 (0.5)	13 (2.9)	1 (0.4)	17 (3.2)
Anxiety	5 (1.1)	7 (1.6)	7 (1.6)	4 (1.5)	17 (3.2)
Arthralgia	5 (1.1)	4 (0.9)	5 (1.1)	16 (5.9)	33 (6.2)
Pyrexia	2 (0.5)	3 (0.7)	5 (1.1)	6 (2.2)	14 (2.6)
Drug withdrawal syndrome	1 (0.2)	2 (0.5)	5 (1.1)	0	2 (0.4)
Hot flush	2 (0.5)	2 (0.5)	4 (0.9)	3 (1.1)	6 (1.1)
Muscle spasms	3 (0.7)	3 (0.7)	3 (0.7)	8 (3.0)	17 (3.2)
Palpitations	1 (0.2)	3 (0.7)	3 (0.7)	1 (0.4)	2 (0.4)
Tremor	2 (0.5)	1 (0.2)	3 (0.7)	1 (0.4)	2 (0.4)
Rhinorrhea	0	1 (0.2)	3 (0.7)	1 (0.4)	4 (0.7)
Myalgia	0	0	3 (0.7)	1 (0.4)	3 (0.6)
Depression	4 (0.9)	3 (0.7)	2 (0.4)	10 (3.7)	14 (2.6)
Insomnia	3 (0.7)	1 (0.2)	2 (0.4)	5 (1.9)	15 (2.8)
Flushing	1 (0.2)	1 (0.2)	2 (0.4)	0	3 (0.6)
Cold sweat	0	1 (0.2)	2 (0.4)	0	1 (0.2)
Yawning	1 (0.2)	0	2 (0.4)	0	3 (0.6)
Feeling jittery	1 (0.2)	2 (0.5)	1 (0.2)	0	1 (0.2)
Chills	1 (0.2)	1 (0.2)	1 (0.2)	0	11 (2.1)
Irritability	0	1 (0.2)	1 (0.2)	0	2 (0.4)
Tachycardia	1 (0.2)	0	1 (0.2)	0	3 (0.6)
Restlessness	1 (0.2)	0	0	0	4 (0.7)
Sneezing	0	0	0	2 (0.7)	2 (0.4)
Muscle twitching	0	0	0	0	2 (0.4)
Selected GI PT[a]	**62 (14.0)**	**86 (19.5)**	**127 (28.5)**	**39 (14.4)**	**190 (35.6)**
Abdominal pain	25 (5.6)	43 (9.8)	71 (15.9)	9 (3.3)	95 (17.8)
Diarrhea	19 (4.3)	25 (5.7)	41 (9.2)	16 (5.9)	69 (12.9)
Nausea	20 (4.5)	29 (6.6)	36 (8.1)	11 (4.1)	50 (9.4)
Vomiting	13 (2.9)	10 (2.3)	20 (4.5)	15 (5.6)	27 (5.1)
Abdominal pain upper	7 (1.6)	8 (1.8)	17 (3.8)	3 (1.1)	27 (5.1)
Abdominal pain lower	0	1 (0.2)	2 (0.4)	3 (1.1)	9 (1.7)

Note: PTs reported for ≥2 patients in any treatment group are included in the table, sorted by highest incidence on naloxegol 25 mg, then naloxegol 12.5 mg, then placebo in the 12-week pool; followed by naloxegol 25 mg, then Usual Care in Study 08.
Percentages are based on the number of patients in the safety set for each treatment group.
Patients with >1 event in the same category are counted only once in that category. Patients with events in >1 PT are counted once in each of those PTs.
AEs that started on or after the first dose through the last dose of Investigational Product are included.
Medical Dictionary for Regulatory Activities (MedDRA) version 15.1.

a These GI PTs were based on GI AEs contained within any of the following: the Clinical Opiate Withdrawal Scale (COWS), the Short Opiate Withdrawal Scale (SOWS), and/or the Objective Opioid Withdrawal Scale (OOWS); AEs discussed in the FDA medical review of another peripherally acting opioid antagonist, alvimopan (Entereg); and /or the DSM-IV criteria for opioid withdrawal.

DSM Diagnostic and Statistical Manual of Mental Disorders; GI Gastrointestinal; N Number of patients in the safety population; NGL Naloxegol; PT Preferred term.

Copied and reproduced, Sub. 002, 10/9/2013 "Response document: opioid withdrawal and CV risk assessments," p 11-12, Table 1

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

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

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

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

(Table, Elizabeth Kilgore DAAAP reviewer)

Applicant's plan to address the safety issue:
Astra Zeneca addressed opioid withdrawal in labeling by proposing the following:

(b) (4)

(b) (4)

14. Clinical Studies

(b) (4)

The DAAAP reviewer did not agree with the proposed labeling (b) (4) In addition, the DAAAP reviewer did not agree that the Applicant's proposed language is appropriate (b) (4)

DGIEP Proposed labeling (see approved label for final wording):

5.4 Opioid Withdrawal

(b) (4)

DAAAP recommended, and DGIEP agreed, that the statements in Section 14 (b) (4) should be deleted entirely. In the Midcycle Communication Meeting, DAAAP and DGIEP explained that because there was evidence of opioid withdrawal in study patients receiving naloxegol, the proposed statement is not fully supported by the data.

7.3 Major Safety Results

During the 12-week, placebo-controlled studies, 52.4% of naloxegol 12.5 mg patients reported any adverse event compared with 63.5% of naloxegol 25 mg patients. This increase in the proportion of patients experiencing AEs in the 25 mg group was driven primarily by GI-related adverse events. During the 52-week study, the incidence of adverse events was higher in the naloxegol 25 mg group than in the usual care group (difference=8.2%). The incidence of serious adverse events (SAEs) was the same in placebo and Naloxegol 12.5 mg patients in the 12 week pool (4.5% in both groups). The incidence of SAEs was slightly lower in the naloxegol 25mg group of the 12-week

pool—4.1%. The incidence of SAEs was higher in the usual care group than the naloxegol 25 mg treatment group in the 52-week study. See Table 27 below.

Table 27. Summary of Safety Results

	12-week pool (Studies 04 and 05)			52 week Set (Study 08)	
	Placebo N=444	Naloxegol 12.5 mg N=441	Naloxegol 25 mg N=446	Usual Care N=270	Naloxegol 25 mg N=534
Any Adverse Event	227 (51.1)	231 (52.4)	283 (63.5)	194 (71.9)	428 (80.1)
Serious Adverse Event (SAE)	20 (4.5)	20 (4.5)	14 (3.1)	30 (11.1)	46 (8.6)
Discontinuation due to Adverse Event	21 (4.7)	20 (4.5)	46 (10.3)	n/a	50 (9.4)
Death	0	2	0	1 (0.4)	1 (0.2)

Source: Summary of clinical safety, table 8 p 44, table 10 p 52,

7.3.1 Deaths

There were a total of 7 deaths in the naloxegol clinical program: 5 in the Phase 3 studies, 1 in the Phase 2b study, and 1 in the Phase 1 studies. Of these deaths, 4 were adjudicated as CV deaths by the CV-EAC. For details of these deaths see the narratives in Section 7.2.6 above.

Narratives of deaths as non-CV deaths (for deaths adjudicated as CV deaths see Section 7.2.6 above):

- 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.

7.3.2 Nonfatal Serious Adverse Events

The incidence of SAEs in patients in the 12-week pool was the same in the placebo and naloxegol 12.5 mg treatment groups—4.5%. In contrast, the incidence of SAEs was lower in the naloxegol 25 mg dose group—3.1%. A similar trend of lower SAE incidence rate was seen in the 52 week study. During this study 11.1% of usual care patients reported a SAE compared with only 8.6% of naloxegol 25 mg patients. Abdominal pain was not the most commonly reported SAE and there was no apparent preferred term predominance.

Table 28. 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.
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MO Comment:
There was a trend seen of increasing AEs in all Phase 3 studies for patients in the naloxegol 25 mg group (driven mainly by GI AEs). The opposite trend was seen in the subset of SAEs which confirms that the while there were more AEs in the higher naloxegol dose group this was not driven by SAEs.

The SAEs that may be related to CV events and are, therefore, of particular interest include non-cardiac chest pain and syncope. In the confirmatory studies, no clear trend of higher incidence of these events was seen associated with naloxegol use. In Studies 04 and 05, there was one patient in the placebo group and one patient in the naloxegol

12.5 mg group who reported an AE of non-cardiac chest pain. In those same studies, there were two patients who reported an AE of non-cardiac chest pain in the naloxegol 25 mg group. In the 12-week safety extension study (07), a single patient (in the naloxegol 12.5 mg group) reported non-cardiac chest pain. No patients in the placebo or naloxegol 25 mg groups reported non-cardiac chest pain. In the 52-week safety study, one patient in the usual care group and no patients in the naloxegol 25 mg group reported non-cardiac chest pain.

Syncope is discussed in Section 7.3.5 below.

7.3.3 Dropouts and/or Discontinuations

Discontinuations due to adverse events (DAEs) were highest in the naloxegol 25 mg group in the confirmatory Phase 3 studies and in the 12-week and 52-week safety studies. In this dose group, diarrhea was the most common AE leading to discontinuation. Abdominal pain, the most commonly reported AE, was the second most common AE. See Table 29 below.

Table 29. Number (%) of patients who had a DAE that was reported for ≥2 patients in any treatment group (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[a] (N=270)	NGL 25 m (N=534)
Any DAE	**24 (5.4)**	**21 (4.8)**	**46 (10.3)**	**3 (3.0)**	**4 (4.3)**	**4 (4.1)**	**NA**	**56 (10.5)**
Diarrhea	3 (0.7)	4 (0.9)	14 (3.1)	0	1 (1.1)	0	NA	11 (2.1)
Abdominal pain	1 (0.2)	4 (0.9)	13 (2.9)	0	0	0	NA	9 (1.7)
Nausea	1 (0.2)	5 (1.1)	5 (1.1)	1 (1.0)	0	0	NA	3 (0.6)
Abdominal pain upper	0	0	5 (1.1)	0	0	0	NA	2 (0.4)
Vomiting	1 (0.2)	2 (0.5)	4 (0.9)	1 (1.0)	0	0	NA	5 (0.9)
Hyperhidrosis	1 (0.2)	0	4 (0.9)	0	0	0	NA	3 (0.6)
Back pain	1 (0.2)	1 (0.2)	2 (0.4)	0	0	0	NA	1 (0.2)
Myalgia	0	0	2 (0.4)	0	0	0	NA	1 (0.2)
Liver function test abnormal	0	0	2 (0.4)	0	0	0	NA	0
Headache	0	0	2 (0.4)	0	0	0	NA	1 (0.2)
Flatulence	1 (0.2)	1 (0.2)	1 (0.2)	0	0	0	NA	2 (0.4)
Depression	0	1 (0.2)	1 (0.2)	0	0	0	NA	2 (0.4)
Hypotension	0	1 (0.2)	1 (0.2)	0	0	1 (1.0)	NA	0
Fatigue	1 (0.2)	0	1 (0.2)	1 (1.0)	0	0	NA	3 (0.6)
Chills	0	0	1 (0.2)	0	0	0	NA	3 (0.6)
Influenza like illness	0	0	1 (0.2)	0	0	0	NA	2 (0.4)
Dizziness	1 (0.2	2 (0.5)	0	0	0	1 (1.0)	NA	0
Abdominal discomfort	0	1 (0.2)	0	0	0	0	NA	2 (0.4)
Abdominal pain lower	0	0	0	0	0	0	NA	2 (0.4)
Arthralgia	0	0	0	0	0	0	NA	2 (0.4)

a Patients in the Usual Care group in Study 08 were not taking investigational product and therefore could not have DAEs.
Note: DAEs 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.
DAE Adverse event leading to discontinuation of investigational product; N Total number of patients in treatment group; NGL Naloxegol.
Source: Module 5.3.5.3, Appendix 2.7.4.7, Table 4.1.2.42 and Table 4.2.2.29; Module 5.3.5.1, Study 07 clinical study report, Table 11.3.5.1.1; and Module 5.3.5.2, Study 08 clinical study report, Table 11.3.5.1.2.

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Discontinuations for any reason occurred in roughly 20% of patients in the Phase 3 confirmatory studies (04 and 05). The most common reason was adverse events (6.4% of patients) in Study 04 and patient request (8.0% of patients) in Study 05. See Section 6.1.3 above for additional information. In the 52-week safety study, 70 patients (12.4%) in the naloxegol 25 mg group withdrew from the study compared with 38 patients (13.5%) of usual care patients. Patient decision was the most common reason for study discontinuation and was nearly equal in both treatment groups (12.0% usual care, 12.2% naloxegol 25 mg).

7.3.4 Significant Adverse Events

Significant adverse events are discussed throughout the review.

7.3.5 Submission Specific Primary Safety Concerns

In addition to the class-related safety concerns discussed above, there was a submission-specific safety concern related to blood pressure due to the results of Phase 1 animal studies.

Adverse Events Related to Blood Pressure (BP)

Background: Changes in blood pressure were regarded as AEs of special interest given the changes in BP seen in dog telemetry studies. Changes in BP were not adjudicated because, according to the Applicant, there are no established adjudication criteria for changes in BP. The specific AEs related to BP were categorized as decreased BP, syncope, and increased BP.

Results: There was a small numerical imbalance in the incidence of high blood pressure, low blood pressure, and syncope between the placebo and Naloxegol groups in the phase 3 studies (in favor of placebo). See Table 30 below.

Table 30. Number (%) of patients with ≥1 AE related to BP changes during the treatment period (placebo-controlled pool and Study 08)

	Placebo-controlled pool (Studies 04/07 and 05)			52-week safety study (Study 08)	
Topic/ Preferred term	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: Module 5.3.5.3, Appendix 2.7.4.7, Table 4.3.3.4; and Module 5.3.5.2, Study 08 clinical study report, Table 11.3.6.3.1.

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

Syncope was not reported by any placebo patients in the placebo-controlled pool. Similarly, none of the usual care patients in the 52-week study reported syncope. In contrast, four Naloxegol patients reported syncope during placebo controlled studies (one of these was reported as pre-syncope) and 3 patients reported syncope during the 52-week safety study. None of the patients who reported syncope also reported a CV AE or a PCI ECG event near the time of the syncopal event. All patients who reported syncope were on concomitant medication known to be associated with syncope and/or had a relevant medical history. The patient who reported pre-syncope also reported a concurrent AE of "infection".

Increased BP was reported in more patients taking Naloxegol than placebo patients in the placebo-controlled pool. Specifically, 5 patients (1.1%) taking placebo reported increased BP compared with 10 patients (2.3%) taking Naloxegol 12.5 mg and 13 patients (2.9%) taking Naloxegol 25 mg. In the 52 week study, the incidence of increased BP was slightly higher in the usual care group. At total of 12 patients (4.4%) in the usual care group reported increased BP compared with 21 patients (3.9%) taking Naloxegol 25 mg. See
Table 30 above.

The incidence of hypertension was slightly higher in patients taking naloxegol in the placebo-controlled pool. Specifically, hypertension was reported in 3 patients (0.7%) taking placebo in the placebo-controlled pool. In contrast, hypertension was reported in 6 patients (1.4%) taking Naloxegol 12.5 mg and 8 patients (1.8%) taking Naloxegol 25 mg. Additionally, there was one patient in the post-treatment period (randomized to 25 mg Naloxegol) who reported an AE of hypertension. Of the 9 patients randomized to the Naloxegol 25 mg group, 7 had either a document history of hypertension or were taking a blood pressure medication along with having at least 1 recognized CV risk factor. Additionally, 7 of the 9 patients had elevated pressure at baseline. None of the 9 hypertension AEs was associated with any AEs related to opioid withdrawal was adjudicated as a CV event of interest. Two of the 9 events in the Naloxegol 25 mg group were SAEs:

- Patient E5212025- 58 year old black female with AE of malignant hypertension. Baseline BP 169/82, multiple CV risk factors, possible noncompliance with cardiac medications

- Patient E524006- 69 year old white female with AE of accelerated hypertension. Baseline BP 185/96, history of diabetes, noncompliant with BP medication

During the 52-week safety study, the incidence of hypertension was slightly lower (approximately 1%) in the Naloxegol 25 mg group than in the usual care group. Specifically, 9 patients (3.3%) in the usual care group and 13 patients (2.4%) in the naloxegol 25 mg group reported hypertension.

Applicant's plan to address safety issue: Changes in blood pressure will be closely monitored as part of the standard pharmacovigilance activities and will be considered "keep under review" topics in the annual safety report.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

During the 12-week treatment period (Studies 04 and 05), 51.1% of placebo patients, 52.4% of 12.5 mg naloxegol patients, and 63.5% of naloxegol 25 mg patients reported any adverse event. Abdominal pain was the most common AE reported in all treatment groups. The only common AE with a higher incidence in the placebo group than either naloxegol group was upper respiratory tract infection (2.7% placebo, 2.0% naloxegol 12.5 mg, 2.5% naloxegol 25 mg). There was a trend for a higher incidence of AEs in the higher naloxegol dose group than the other treatment groups. See

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Table **31** below.

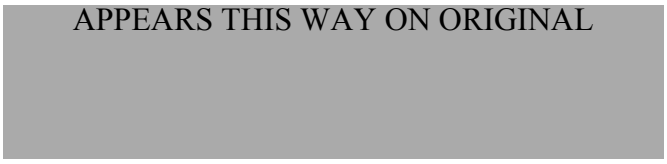

Table 31. Number (%) of patients with the most common (≥2% incidence in any treatment group) AEs during the treatment period (12-week pool, Studies 04 and 05)

Preferred term	Placebo (N=444)	NGL 12.5 mg (N=441)	NGL 25 mg (N=446)
Patients with any AE	227 (51.1)	231 (52.4)	283 (63.5)
Abdominal pain	25 (5.6)	43 (9.8)	71 (15.9)
Diarrhea	19 (4.3)	25 (5.7)	41 (9.2)
Nausea	20 (4.5)	29 (6.6)	36 (8.1)
Flatulence	11 (2.5)	13 (2.9)	26 (5.8)
Headache	12 (2.7)	17 (3.9)	20 (4.5)
Vomiting	13 (2.9)	10 (2.3)	20 (4.5)
Back pain	9 (2.0)	12 (2.7)	19 (4.3)
Abdominal pain upper	7 (1.6)	8 (1.8)	17 (3.8)
Hyperhidrosis	1 (0.2)	2 (0.5)	13 (2.9)
Abdominal distension	9 (2.0)	11 (2.5)	11 (2.5)
Upper respiratory tract infection	12 (2.7)	9 (2.0)	11 (2.5)
Fatigue	6 (1.4)	7 (1.6)	10 (2.2)
Sinusitis	6 (1.4)	6 (1.4)	10 (2.2)
Pain in extremity	3 (0.7)	5 (1.1)	10 (2.2)
Nasopharyngitis	1 (0.2)	5 (1.1)	9 (2.0)
Fall	8 (1.8)	9 (2.0)	4 (0.9)
Dizziness	9 (2.0)	11 (2.5)	3 (0.7)

Note: Patients with events in ≥1 PT are counted once in each of those PTs. AEs that started on or after the first dose of investigational product through end of study are included. AEs are sorted by PT in decreasing order of frequency (by total number on NGL 25 mg, 12.5 mg, then placebo).
AE Adverse event; DAE AE leading to discontinuation of investigational product; N Total number of patients; n Number of patients in category; NGL Naloxegol.
Source: Module 5.3.5.3, Appendix 2.7.4.7, Table 4.1.2.20.
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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. During this study, the incidence of the most common AEs (occurring in ≥5% of patients) was 71.9% in the usual care group compared with 90.1% in the naloxegol 25 mg treatment group. Similar to the AEs reported in the 12-week safety pool, the most common AEs reported were abdominal pain (17.8% naloxegol 25 mg, 3.3% usual care), diarrhea (12.9% naloxegol 25 mg, 5.9% usual care), and nausea (9.4% naloxegol 25 mg, 4.1% usual care). See

Table 32 below.

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Table 32. Number (%) of patients who had at least 1 AE for a preferred term occurring in ≥5% of patients in any treatment group during the treatment period only, by preferred term (Safety analysis set)

Preferred term	Number (%) patients [a]	
	Usual Care (N = 270)	NKTR-118 25 mg (N = 534)
Patients with any AE	194 (71.9)	428 (80.1)
Abdominal pain	9 (3.3)	95 (17.8)
Diarrhoea	16 (5.9)	69 (12.9)
Nausea	11 (4.1)	50 (9.4)
Back pain	24 (8.9)	48 (9.0)
Headache	13 (4.8)	48 (9.0)
Flatulence	3 (1.1)	37 (6.9)
Arthralgia	16 (5.9)	33 (6.2)
Nasopharyngitis	15 (5.6)	33 (6.2)
Upper respiratory tract infection	23 (8.5)	31 (5.8)
Bronchitis	12 (4.4)	30 (5.6)
Vomiting	15 (5.6)	27 (5.1)
Abdominal pain upper	3 (1.1)	27 (5.1)
Sinusitis	19 (7.0)	23 (4.3)
Urinary tract infection	22 (8.1)	22 (4.1)

[a] The percentages are based on the number of patients in the safety analysis set in each treatment group and patient group.
Note: AEs are coded using MedDRA version 15.0.
Note: AEs that started on or after the first dose of study drug (NKTR-118 25 mg or Usual care) through the day of the last dose of study drug are included.
Note: Patients are counted no more than once for incidence of preferred term.
Note: Sorted by preferred term in decreasing order of frequency (by total number on NKTR-118 25 mg).
AE adverse event; MedDRA Medical Dictionary for Regulatory Activities.
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In the confirmatory, placebo-controlled studies, abdominal pain was reported in 5.6% of placebo patients, 9.8% of naloxegol 12.5 mg patients, and 15.9% of naloxegol 25 mg patients. 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. A smaller percentage of patients discontinued either study due to the adverse event of abdominal pain—0.7%, 0.9%, and 2.9% in placebo, 12.5 mg naloxegol, and 25 mg naloxegol patients, respectively.

MO Comment:
Given that abdominal pain was reported in 15.9% of patients in the confirmatory studies taking 25 mg of naloxegol, the review team discussed the possibility of approving the 12.5 mg dose for patients unable to tolerate the 25 mg dose. While common, only 4.9% of naloxegol 25 mg patients reported any abdominal pain event as severe and only

2.9% of patients discontinued a study due to abdominal pain. Overall, it appears 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, I continue to recommend 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. See Table 33 below.

Table 33. Number (%) of patients who had at least 1 AE by PT and max intensity, On-study, S004 and S005 (Safety set)

		Number (%) of patients		
Preferred term	Maximum reported intensity	Placebo (N=444)	NKTR-118 12.5 mg (N=441)	NKTR-118 25 mg (N=446)
Patients with any AE	Mild	92 (20.7)	102 (23.1)	114 (25.6)
	Moderate	98 (22.1)	94 (21.3)	123 (27.6)
	Severe	46 (10.4)	45 (10.2)	54 (12.1)
ABDOMINAL PAIN	Mild	13 (2.9)	17 (3.9)	28 (6.3)
	Moderate	9 (2.0)	23 (5.2)	22 (4.9)
	Severe	3 (0.7)	6 (1.4)	22 (4.9)
DIARRHOEA	Mild	11 (2.5)	18 (4.1)	18 (4.0)
	Moderate	5 (1.1)	6 (1.4)	17 (3.8)
	Severe	4 (0.9)	2 (0.5)	6 (1.3)
NAUSEA	Mild	13 (2.9)	20 (4.5)	21 (4.7)
	Moderate	8 (1.8)	6 (1.4)	13 (2.9)
	Severe	0	6 (1.4)	2 (0.4)
FLATULENCE	Mild	8 (1.8)	8 (1.8)	20 (4.5)
	Moderate	4 (0.9)	4 (0.9)	5 (1.1)
	Severe	0	1 (0.2)	1 (0.2)
VOMITING	Mild	6 (1.4)	3 (0.7)	9 (2.0)
	Moderate	6 (1.4)	5 (1.1)	6 (1.3)
	Severe	4 (0.9)	4 (0.9)	8 (1.8)
HEADACHE	Mild	7 (1.6)	7 (1.6)	10 (2.2)
	Moderate	4 (0.9)	9 (2.0)	8 (1.8)
	Severe	1 (0.2)	1 (0.2)	2 (0.4)
BACK PAIN	Mild	4 (0.9)	2 (0.5)	5 (1.1)
	Moderate	3 (0.7)	7 (1.6)	11 (2.5)

AZVAL:SM.25SEP2012.1.YR.04DEC2012
Patients with multiple events in the same PT are summarized under the highest reported intensity.
AEs that started on or after the first dose of investigational product through end of study are included.
AEs are sorted by PT in decreasing order of frequency (by total number on NKTR-118 25 mg, 12.5 mg, then placebo).
Medical Dictionary for Regulatory Activities (MedDRA) version 15.1.
Electronically copied and reproduced from NDA Submission 0000, Appendix 2.4.7.4, p 491

7.4.2 Laboratory Findings

Clinical laboratory trends, individually clinically significant abnormalities, and changes over time were reviewed for clinical chemistry, hematology, and urinalysis parameters. No clinically important findings were observed.

7.4.3 Vital Signs

Vital sign trends were reviewed. No clinically important findings were seen except those discussed in Section 7.2.6 above related to BP and HR.

Reference ID: 3504437

7.4.4 Electrocardiograms (ECGs)

In the Phase 3 program, serial digitalized ECGs were to be collected at screening, and Weeks 0, 1, 2, 4, 8, 12, and the end of study visit. At Week 0, serial digitalized ECGs were collected (in triplicate) 2 hours after administration of the first dose of IP to correlate with naloxegol T_{max}, and at all subsequent study visits, and were read centrally.

Because of a slight imbalance for QRS, individual cases of potentially clinically important (PCI) QRS values were reviewed. Among patients with QRS ≥140 msec in the 12-week pool, all 7 placebo patients and 16/23 naloxegol-treated patients had values ≥140 msec at baseline. Of the remaining 7 naloxegol-treated patients, 5 had a CV-related medical history and were on CV medications; 1 of these 5 patients (E4068050) had a CV-related AE at the time of the PCI QRS value (this patient had an adjudicated CV death; see Section 2.1.4). In Study 08, for both newly randomized and rollover patients combined, 3 (1.1%) patients in the Usual Care group and 9 (1.7%) in the naloxegol 25 mg group had QRS ≥140 msec during treatment. Among these patients, 1/3 in the Usual Care group and 7/9 in the naloxegol group had values ≥140 msec at baseline. The remaining 2 patients in the naloxegol group had a CV-related medical history and were on CV medications. Overall, the QRS results do not raise a safety concern.

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Table 34. Summary of patients with PCI ECG abnormalities (12-week pool and Study 08)

		12-week pool (Studies 04 and 05)			52-week safety study (Study 08)[a]	
Parameter	**Criterion**	**Placebo**	**NGL 12.5 mg**	**NGL 25 mg**	**Usual care**	**NGL 25 mg**
Number (%) of patients with PCI values 2 hours post-first-dose of study drug						
N[b]		438	437	444	232	478
PR (msec)	≥210 and ↑≥15	8 (1.8)	9 (2.1)	7 (1.6)	4 (1.7)	7 (1.5)
	≥240	4 (0.9)	6 (1.4)	4 (0.9)	3 (1.3)	4 (0.8)
QRS (msec)	≥120 and ↑≥15	0	0	2 (0.5)	0	0
	≥140	7 (1.6)	7 (1.6)	11 (2.5)	1 (0.4)	6 (1.3)
QT (msec)	≥500	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.4)	0
QTcB (msec)	≥450 and ↑≥30	4 (0.9)	3 (0.7)	5 (1.1)	3 (1.3)	4 (0.8)
	≥500	0	0	1 (0.2)	0	0
QTcF (msec)	≥450 and ↑≥30	0	2 (0.5)	2 (0.5)	1 (0.4)	2 (0.4)
HR (bpm)	≤40	0	1 (0.2)	1 (0.2)	0	0
	≥100 and ↑≥20	0	0	2 (0.5)	0	1 (0.2)
RR (msec)	≤600	7 (1.6)	5 (1.1)	10 (2.3)	3 (1.3)	7 (1.5)
	≥1200	14 (3.2)	17 (3.9)	14 (3.2)	10 (4.3)	8 (1.7)
Number (%) of patients with PCI values at any time during the treatment period						
N[b]		444	439	446	234	479
PR (msec)	≤110 and ↓15	2 (0.5)	2 (0.5)	1 (0.2)	0	0
	≥210 and ↑≥15	13 (2.9)	14 (3.2)	10 (2.3)	11 (4.7)	20 (4.2)
	≥240	6 (1.4)	6 (1.4)	7 (1.6)	4 (1.7)	5 (1.0)
QRS (msec)	≥120 and ↑≥15	0	3 (0.7)	2 (0.4)	2 (0.9)	2 (0.4)
	≥140	7 (1.6)	11 (2.5)	12 (2.7)	1 (0.4)	7 (1.5)
QT (msec)	≥500	3 (0.7)	1 (0.2)	2 (0.4)	2 (0.9)	0
QTcB (msec)	≥450 and ↑≥30	22 (5.0)	20 (4.6)	21 (4.7)	15 (6.4)	41 (8.6)
	≥500	2 (0.5)	3 (0.7)	2 (0.4)	2 (0.9)	0
QTcF (msec)	≥450 and ↑≥30	3 (0.7)	7 (1.6)	10 (2.2)	5 (2.1)	14 (2.9)
	≥500	1 (0.2)	1 (0.2)	0	2 (0.9)	0
HR (bpm)	≤50 and ↓≥20	2 (0.5)	0	2 (0.4)	2 (0.9)	1 (0.2)
	≤40	2 (0.5)	1 (0.2)	1 (0.2)	2 (0.9)	0
	≥100 and ↑≥20	10 (2.3)	8 (1.8)	7 (1.6)	4 (1.7)	21 (4.4)
	≥120	1 (0.2)	3 (0.7)	1 (0.2)	1 (0.4)	2 (0.4)
RR (msec)	≤600	26 (5.9)	24 (5.5)	23 (5.2)	17 (7.3)	37 (7.7)
	≤500	1 (0.2)	3 (0.7)	1 (0.2)	1 (0.4)	2 (0.4)
	≥1200	27 (6.1)	25 (5.7)	26 (5.8)	20 (8.5)	22 (4.6)
	≥1500	2 (0.5)	0	0	1 (0.4)	0

[a] For Study 08, only patients who had not previously participated in a naloxegol trial, approximately 90% of the study population, are included. Results for rollover patients are presented in Module 5.3.5.2, Study 08 clinical study report, Tables 11.3.8.2.3 and 11.3.8.2.8.

[b] In the 12-week pool, 3 patients in the naloxegol 12.5 mg group and 2 patients in the naloxegol 25 mg group did not have PR values. In Study 08, 1 patient in each treatment group did not have PR values.

bpm Beats per minute; ECG Electrocardiogram; HR Heart rate; msec Millisecond; N Number of patients in safety population with data; NGL Naloxegol; PCI Potentially clinically important.

Source: Module 5.3.5.3, Appendix 2.7.4.7, Tables 4.1.5.3 and 4.1.5.9; and Module 5.3.5.2, Study 08 clinical study report, Tables 11.3.8.2.3 and 11.3.8.2.8.

Electronically copied and reproduced from Summary of Clinical Safety, p 77, Table 21

Reference ID: 3504437

7.4.5 Special Safety Studies/Clinical Trials

No special clinical safety studies other than those discussed above were submitted.

7.4.6 Immunogenicity

N/A

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Overall, patients treated with naloxegol 25 mg reported more adverse events than did patients treated with naloxegol 12.5 mg. This is discussed in previous sections of this review.

7.5.2 Time Dependency for Adverse Events

No particular explorations for time dependency of adverse events were conducted.

7.5.3 Drug-Demographic Interactions

No particular explorations for drug-demographic interactions related to adverse events were conducted.

7.5.4 Drug-Disease Interactions

No particular explorations for drug-disease interactions were conducted.

7.5.5 Drug-Drug Interactions

Naloxegol is a substrate of CYP3A4 enzyme and a substrate of P-gp transporter. See the naloxegol labeling and the clinical pharmacology review for details regarding potential interaction of naloxegol and other drugs.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Patients with cancer were not admitted to the Phase 3 studies. The Applicant did not provide any clinical or adverse event data regarding human carcinogenicity in this application.

7.6.2 Human Reproduction and Pregnancy Data

Based on reproductive toxicology studies, the Applicant proposes that naloxegol be a Pregnancy category (b) (4) However, the pharm/tox reviewer, Dr. Ng, proposes Pregnancy Category C. See the final label for the agreed upon pregnancy category. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

7.6.3 Pediatrics and Assessment of Effects on Growth

The naloxegol Phase 3 program only included adult patients. The Applicant has submitted a PPSR. The PPSR was reviewed by the Pediatric and Maternal Health Staff (PMHS). Dr. Ethan Hausman, PMHS clinical reviewer, completed a consult regarding the proposed naloxegol pediatric program which can be found in DARRTS (04 April 2014).

PMHS Conclusion/Recommendations (excerpt from the review by Dr. Hausman):

> *Pediatric studies for OIC associated with chronic opioid exposure for chronic cancer-related pain and chronic non-cancer-related pain are unlikely to be feasible. Therefore, PMHS recommends that a full waiver of studies in pediatric patients 0 through 17 years be granted.*

MO Comment:
I agree with the PMHS conclusion that the pediatric program (ages 0-17 years) for naloxegol should be given a full waiver.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Currently, naloxegol is classified by the US Drug Enforcement Administration (DEA) as a Schedule II Substance on the basis of chemical similarity to noroxymorphone. A de-control petition has been submitted by the Applicant and will be reviewed by the DEA and the FDA Controlled Substance Staff (CSS).

7.7 Additional Submissions / Safety Issues

Multiple *post-hoc* analyses were requested by the FDA during communications with the Applicant both prior to and after submission of the NDA. These have been discussed throughout this review.

8 Postmarket Experience

This NME is currently not marketed in the United States or any other country.

9 Appendices

9.1 Literature Review/References

Literature references are provided in footnotes in this review.

9.2 Labeling Recommendations

The Movantik label submitted by the Applicant with the NDA was generally of poor quality with many revisions required to make it compliant with labeling regulations. See the final approved label for final labeling recommendations.

9.3 Advisory Committee Meeting

A meeting of the Anesthetic and Analgesic Drug Products
Advisory Committee Meeting is scheduled subsequent to the completion of this review (June 11-12, 2014) to discuss the need for a pre-market CV safety study in the peripheral mu-opioid receptors antagonist class of drugs. See the advisory committee meeting minutes for full details.

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/s/

AISHA P JOHNSON
05/09/2014

ANIL K RAJPAL
05/11/2014
I concur with Dr. Johnson.

Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products

DCRP Consult NDA 204760

DATE:	Initial Desired Completion date: 10 Feb 2014 Completion Date Revised (AC rescheduled to May 2014) Review Completion Date: 25 February 2014
FROM:	Preston M. Dunnmon, M.D., Medical Officer Division of Cardiovascular and Renal Products, HFD-110
THROUGH:	Norman Stockbridge, M.D., Ph.D., Division Director Division of Cardiovascular and Renal Products, HFD-110
TO:	Brian K. Strongin, RPM Division of Gastroenterology and Inborn Errors Products
NAME OF DRUG:	Naloxegol (formerly NKTR-118)
SPONSOR:	Astra Zeneca
FORMULATION:	Tablet
DOSE:	25 mg

DEVELOPMENT INDICATION: opioid induced constipation (OIC) in patients taking opioids for chronic, non-cancer pain

DOCUMENTS AVAILABLE FOR REVIEW:
NDA 204760 Safety Summaries
NDA 204760 CV Safety Review
NDA 204760 Toxicology Written Summary
NDA 204760 Pharmacology Written Summary
DCRP Consult for IND 78781 (04/18/2013)

Executive Summary and Assessment

There is no definitive CV safety signal from naloxegol's preclinical data, ECG data and TQT study, clinical vital sign data (changes in SBP, DBP, and HR), or MACE outcomes (stoke, MI, CV death, hospitalization for unstable angina, hospitalization for CHF). Indeed, adjudicated MACE outcomes from the Phase III trials were as follows (sponsor table 15):

NDA 204760

Reference ID: 3467518

Table 15 **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)**

	Placebo-controlled pool (Studies 04/07 and 05)			52-week safety study (Study 08)	
Category	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.

Source: Module 5.3.5.3, Appendix 2.7.4.7, Table 4.3.3.5; and Module 5.3.5.2, Study 08 clinical study report, Table 11.3.6.1.2.

From this table, the MACE rates per 100 patient years of exposure in the placebo-controlled trials were 1.5 for placebo (2/444 patients), 1.6 for naloxegol 12.5 mg (2/441 patients), and 0.8 for naloxegol 25 mg (1/446 patients).

That being said, it is noted that of the seven deaths that occurred in the entire program (Phase I through Phase III)

- Five of the seven were from (non-pulmonary embolus) cardiovascular causes
  - Four of these five of these subjects were taking naloxegol, and
  - Three of these five subjects, all who had taken naloxegol, experienced acute myocardial infarctions that resulted in death.

However, the implications of these observations from these small data sets, if any, are unknown.

CV adverse events occurred more frequently on NGL at either dose tested in patients experiencing both a CV adverse event and a GI adverse event in the 12-week controlled

pivotal studies 04 and 05 (0.5%, 1.6%, and 1.8% respectively for placebo, NGL 12.5 mg, and NGL 25 mg). However, looking at these cases, most were non-serious reports of hypotension, hypertension, palpitations, or hot flashes/flushing. One patient experienced angina twice, and one patient experienced extrasystoles. This trend was seen once again in the data for study 08, where all 8/8 patients experiencing a GI AE and a CV AE were taking NGL 25 mg. One of these patients experienced a pericardial effusion and one developed AFib, however the remainder involved flushing and hypertension. Taken together, these results suggest that while withdrawal can be associated with CV adverse events, none of those documented involved ischemic catastrophes in these rather small studies.

That being said, these drugs induce physiologic stress in some patients, whether this is due to direct actions of the drug, peripheral/regional withdrawal effects, or central withdrawal effects. Physiologic stress results in increased myocardial work and increased myocardial oxygen demand, and any drug, device, or procedure that induces physiologic stress has the potential for causing destabilization in patients with tenuous coronary perfusion and/or important stenotic valvular heart disease. These are basic principles of medicine that apply to many approved therapies, and for which clinical judgment of the treating physician is important. In this regard, it is noted that one of the naloxegol-treated subjects who died was a 73 year old who suffered an MI on study Day 16 that led to surgery for aortic valve replacement and coronary artery bypass grafting.

It is unclear what if any relevance that the side effect profile of IV naloxone has to the clinical safety profile of this oral PEGylated derivative. However, given the lack of clinical experience with naloxegol in post-operative patients, it would be reasonable to at least reference the warning about these patients from the IV naloxone label (i.e., that several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest have been reported in postoperative patients treated with IV naloxone).

Finally, the weaknesses of the datasets available for safety analysis should be borne in mind:

- Lack of specification in submitted documents available for the DCaRP review regarding what if any automated triggers were in place to assure that all potential MACE events and other cardiac SAEs were referred to the event committee for adjudication
- Clinical trials not designed for CV event ascertainment
- Patients not followed through to the end of the studies
- Approximately 1/5 of patients withdrew prematurely from the 12-week data pool

Background

DGIEP has received NDA 204,760 for a μ -opioid antagonist (naloxegol) for the treatment of opioid-induced constipation. Because of prior experience with Entereg (alvimopan), the review Division requested that the Sponsor carefully examine the

occurrence of CV outcome events in naloxegol's development program, and to determine if there exists any temporal relationship between the occurrence of CV events and opioid withdrawal effects (central or peripheral).

In addition to the alvimopan experience, there has been a long clinical experience with naloxone which is indicated for the reversal of opiod depression. Naloxegol is a PEGylated derivative of naloxol (the reduction product of naloxone) that decreases its penetration of the blood brain barrier and reduces its affinity for all opiod receptors. The mu-opioid receptor is less affected by the PEGylation modification, thus increasing naloxegol's relative mu-opiod selectivity. Given the chemical similarity of the naloxone parent molecule, the sections of the IV naloxone label that therefore may be relevant to the cardiac risk assessment of naloxegol are as follows:

- *In vitro* evidence suggests that naloxone antagonizes opioid effects by competing for the mu, kappa, and sigma opiate receptor sites in the CNS, with the greatest affinity for the mu receptor.
- Naloxone is an essentially pure opioid antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other opioid antagonists. When administered in usual doses and in the absence of opioids or agonistic effects of other opioid antagonists, it exhibits essentially no pharmacologic activity.
- Naloxone hydrochloride injection should be administered cautiously to persons, including newborns of mothers, who are known or suspected to be physically dependent on opioids. In such cases, an abrupt and complete reversal of opioid effects may precipitate an acute withdrawal syndrome.
- The signs and symptoms of opioid withdrawal in a patient physically dependent on opioids may include but are not limited to, the following: body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure.
- Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest have been reported in postoperative patients. Death, coma, and encephalopathy have been reported as sequelae of these events. These have occurred in patients most of whom had pre-existing cardiovascular disorders or received other drugs which may have similar adverse cardiovascular effects. Although a direct cause and effect relationship has not been established, naloxone should be used with caution in patients with pre-existing cardiac disease or patients who have received medications with potential adverse cardiovascular effects such as hypotension, ventricular tachycardia or fibrillation, and pulmonary edema. It has been suggested that the pathogenesis of pulmonary edema associated with the use of naloxone is similar to neurogenic pulmonary edema, i.e., a centrally mediated massive catecholamine response leading to a dramatic shift of blood volume into the pulmonary vascular bed resulting in increased hydrostatic pressures.

Of note, immunohistochemical staining demonstrates that mu-, kappa-, and delta- opiod receptors are present in the human heart (Sabanski et al, Heart Vessels Jan 2014, DOI 10.1007/s00380-013-0456-5) (http://link.springer.com/article/10.1007%2Fs00380-013-0456-5). While the authors hypothesize a role for these receptors in neural transmission and regulation of myocardial cell function, the clinical consequences of their activation and/or antagonism on the heart are unknown.

Consult Questions

The cardiac adverse event data was on naloxegol was collected as part of routine safety monitoring in the clinical trials, and is not from a dedicated safety outcome study. Accordingly, the review division requests that DCaRP provide an evaluation of the cardiac safety of this product, to include:

- An assessment of whether there appears to be a signal for cardiac adverse events associated with the use of naloxegol (including the type and extent of the signal if present).

- An assessment of whether there is a causal relationship between cardiac events that occurred and opioid withdrawal.

To address these questions by the review division, DCaRP reviewed the submitted data and analyses to assess for the following:

- Evidence of cardiotoxicity in the pre-clinical animal data (e.g. conduction/rhythm disturbances, cardiac histopathology findings, or unexplained death of the experimental animals)
- Distribution studies in animals to assess for the degree of blood brain barrier (BBB) penetration and thus the possibility of naloxegol induction of central opiod withdrawal
- TQT study findings to assess for a risk of potentially lethal drug-induced ventricular arrhythmias
- Phase I and Phase II clinical cardiac safety
- Phase III clinical cardiac safety to include
    - Effects of naloxegol on SBP, DBP, and HR
    - Naloxegol associated adverse events, premature discontinuations, MACE, and death
    - Cardiac adverse events occurring concomitantly with adverse events having preferred terms (PT) attributable to opioid withdrawal.

Overall preclinical toxicology findings/conclusions for naloxegol (from the sponsor's written toxicology summary)

- Repeated dose toxicity has been investigated after oral administration of NKTR-118 for up to 6 months in rats and 9 months in dogs. The target organ identified was the liver, but the findings (increased liver weights, hepatocellular hypertrophy

[rat only], and increased cholesterol [also in mice]) were slight and reversible upon cessation of dosing. The chronic rat (6 months) and dog (9 months) toxicity studies identified a NOAEL of 200 mg/kg/day for both species. Based on the systemic exposure (Cmax and AUC(0-24)), a high margin of safety (≥120-fold) is available to support the maximum proposed dose of 25 mg qD for further development (Phase 3)

- There were no adverse effects observed on blood pressure and ECG parameters in the toxicology studies in dogs at doses up to 200 mg/kg and 500 mg/kg, respectively. No significant cardiac histopathology findings were noted.

- Naloxegol had no effect on CV parameters in a rat isolated heart assay or on contractility parameters in a dog isolated myocyte assay at 10 and 100 uM, respectively.

- Naloxegol was also inactive at human ether-ago-go (hERG) and 7 other cardiac ion channels. The *in vitro*IC50 for hERG inhibition was >300 μM.

- In an ongoing dog telemetry study, the sponsor reports that BP, heart rate (HR), left ventricular pressure, lead II ECG, and body temperature were monitored by telemetry in 4 male Beagle dogs for approximately 1 hour pre-dose and up to 20 hours post-dose of naloxegol (5 mg/kg, 25 mg/kg, 75 mg/kg, and 200 mg/kg). Naloxegol 5 mg/kg reportedly had no effect on CV parameters. There was a transient prolongation of PR interval following 25 and 75 mg/kg. At the 3 higher doses, non-dose-related moderate decreases were observed at 0.5 hours post-dose in arterial systolic and diastolic BP (SBP and DBP; maximal effect from -9 to-12% vs vehicle; recovery within 2.5 hours), left ventricular systolic pressure (-7 to -13%; recovery within 2.5 hours), and indices of cardiac myocardial contractility (LVdp/dt+: -19 to 22%) and relaxation (LVdp/dt-: -15 to -19%) (recovery within 4 to 8 hours). HR was increased at ≥75 mg/kg dose (+28%). The maximum increase in HR occurred at different time points compared to the decrease in BP or contractility. No additional effects were noted on ECG parameters or body temperature. In addition, no observable adverse effects were noted in the animals at any dose. The no observed effect level (NOEL) of 5 mg/kg for CV effects corresponds to a maximal plasma drug concentration (Cmax) of 0.152 μmol/L (total), 0.071 μmol/L (unbound), which is approximately equal to the exposure at the maximum dose used in the Phase III studies (25 mg).The clinical relevance of the preliminary findings of the dog telemetry study are uncertain.

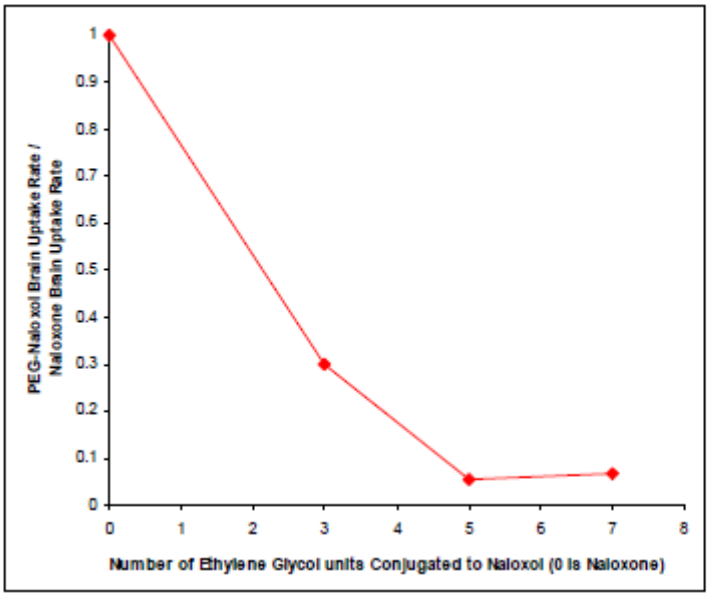
- Results of the individual animal studies are summarized in Appendix 1.

Distribution (from the sponsor's written PK summary, page 10)

The effect of PEG length (PEGn where n = 0 to 7) on brain uptake rate of a series of PEG-naloxol conjugates was investigated using a rat (male Sprague-Dawley) *in situ* brain

perfusion model (RD00001811.00). As the size of the PEG moiety increased, the brain uptake rate significantly decreased relative to that of the parent molecule, naloxone (Figure 2). The effect of PEG length on reducing brain uptake rate was maximal at ≥5 ethylene glycol units, indicating that conjugates of this length or greater would be required to minimize the occurrence of CNS opioid antagonism.

Figure 2: Effect of PEG Chain Length on Blood-Brain Barrier Transport



Naloxone readily entered the brain at a rate greater than that of the fast permeation reference drug antipyrine (60.2 and 28.2 pmol/g brain/sec, respectively), consistent with its demonstrated ability to reverse opioid drug effects in the CNS (Table 3 below):

Table 3: Brain Uptake Rate of Naloxone, NKTR-118 and Permeation Standards in Sprague-Dawley Rats[1]

Drug	Mean Brain Uptake Rate (pmol/g brain/sec)
Naloxone	60.2±13.7
NKTR-118	4.1±1.4
Antipyrine (high permeation standard)	28.2±14.3
Atenolol (low permeation standard)	5.2±2.2

1 male

Effect of PEGylation on *In Vitro* Receptor Binding

Competitive inhibition studies (RD00001536.00) were performed on cloned human μ-opioid receptors expressed in CHO cells using displacement of [3H]naloxone by NKTR-118 or naloxone. Similar studies were performed using displacement of [3H]naloxone at

cloned human κ-opioid receptors or [3H]DPDPE at cloned human δ−opioid receptors. The sponsor reports the following results from these studies:

- NKTR-118 exhibited relatively high affinity binding at μ-opioid receptors, but with a 20-fold reduction in binding affinity (as indicated by increased Ki values) for NKTR-118 compared with naloxone
    - NKTR-118 displayed a Ki of 33.8 nM at μ-opioid receptors, whereas naloxone produced a Ki of 1.7 nM

- Reduction in binding affinity for NKTR-118 was also observed at cloned human κ-opioid and δ-opioid receptors
    - NKTR-118 produced a Ki value of 186.5 nM at the κ-opioid receptor, compared with a Ki of 4.0 nM for naloxone, and a Ki value of 53.5 nM at the δ−opioid receptor, compared with a Ki of 10.3 nM for naloxone

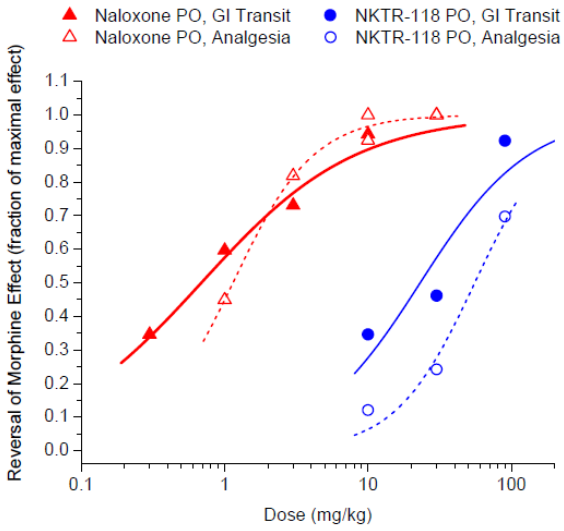
- Thus, NKTR-118 retains its greatest potency at μ-opioid receptors, but displays an altered selectivity profile such that the order of affinity is $\mu > \delta > \kappa$, whereas that for naloxone it is $\mu > \kappa > \delta$

Evaluation of Sprague-Dawley Rat Pharmacology Study Results to Estimate the Resolution Between CNS and GI Opioid Receptor Antagonism (from the sponsors phrmacol-written summary pages 7-8)

To be useful as a peripheral opioid receptor antagonist, NKTR-118 must antagonize μ-opioid receptors located in the myenteric plexus of the gastrointestinal tract without causing clinically important reversal of CNS opioid-mediated analgesia. Data from both rat studies on CNS and peripheral pharmacological effects of NKTR-118 were pooled to determine whether there was resolution between these desired (GI antagonism) and undesired (CNS antagonism) effects (RD00001766.00).

Visual inspection of the pooled Sprague-Dawley Rat dose-response data showed that the curves for naloxone overlap, indicating that doses of naloxone that reverse morphine-induced slowing of GI transit also reverse morphine analgesia to a similar extent (Figure 4). The sponsor reports that this is consistent with several reports in the clinical literature indicating that while oral naloxone relieves OIC in patients, it simultaneously reverses analgesia such that the drug is not clinically useful for this indication (Liu et al., 2002). In contrast, NKTR-118 reversed morphine-induced slowing of GI transit at doses lower than those that completely reversed morphine analgesia, providing evidence of resolution between desired peripheral GI and undesired central CNS morphine antagonism.

Figure 4: **Dose-Response Relationship for Reversal of Morphine Effects in the GI Tract and CNS for Naloxone and NKTR-118**



Reviewer's Comment: The brain distribution and receptor selectivity information above regarding the effect of the naloxegol's PEGylation looks initially compelling. However, I note the absence of SD bars around the data points, and going back to the study reports from which the BBB penetration data was generated, it appears as though this information was generated from approximately 3 animals. The table for receptor selectivity is footnoted as "1 male". It is interesting to note the sponsor's conclusions from this data:

- *"…conjugation with PEG7 did not abolish the peripheral opioid receptor antagonist properties of naloxone"*
- *The rat study of reversal of morphine effects on GI transit shows that NKTR-118 can completely antagonize the effect of morphine on the GI tract and that the potency was about 33-fold less than that of naloxone (ED50: about 23 mg/kg for NKTR-118 versus ED50: 0.7 mg/kg for naloxone)*
- *"NKTR-118 retains the (central) antagonist properties of naloxone, but is significantly less potent than naloxone at reversing morphine analgesia."*
- *rat pharmacology studies indicate that NKTR-118 reverses morphine-induced slowing of GI transit at doses lower than those that reverse morphine analgesia, demonstrating resolution between desired and undesired opioid antagonist effects. The ratio ED50 for analgesia reversal and for gastrointestinal transit is about 1.5-fold higher for NKTR-118 than for naloxone.*

This somewhat explains the less than overwhelming differential in GI versus Analgesia opiod receptor antagonism pooled data for naloxegol in figure 4 above. The naloxegol doses tested were 10, 30, and 90 mg/kg, versus 10 mg/kg of naloxone. Note that at the 10 mg/kg dose of naloxegol, there was an approximately 10% reversal of morphine's effect on analgesia, and a 30% reversal of neloxegol's effect on GI motility. The differential effects became even more narrow at higher doses.

Human Data

5.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	25 mg	
Maximum tolerated dose	1000 mg in healthy volunteers	
Principal adverse events	Across all Phase I studies adverse events reported in >5% of the total number of subjects who received at least one dose of naloxegol included nausea, dizziness, headache and somnolence.	
Maximum dose tested	Single Dose	1000 mg in healthy volunteers
	Multiple Dose	250 mg twice daily for 7 days in healthy volunteers 50 mg once daily for 4 weeks in OIC patients
Exposures Achieved at Maximum Tested Dose	Single Dose	4717 ng/mL (27%) and 9624 ng.h/mL (21%)
	Multiple Dose	1014 ng/mL (30%) and 2840 ng.h/mL (36%)
Range of linear PK	Approximately linear up to 250 mg with twice daily dosing	
Accumulation at steady state	1.46 (16%) with twice daily dosing & 1.08 (35%) with once daily dosing at 25 mg.	
Metabolites	No metabolite circulating at >10% of total drug-related material	
Absorption	Absolute/Relative Bioavailability	Absolute bioavailability not available Relative bioavailability: 100% (relative to solution formulation) ; bioequivalence demonstrated between solution & tablet formulations
	Tmax	• 1.0 h (0.2-5.0) commercial formulation (Study 18)
Distribution	Vz/F	1740 L (60%) commercial formulation (Study 18)
	% bound	4.2%
Elimination	Route	• Hepatic clearance is likely primary route • Renal (6%)
	Terminal t½	• 7.0 h (59%) commercial formulation (Study 18)

Phase I and Phase II Clinical Safety Data

The Phase I studies were not pooled with the Phase IIb/III studies because the safety profile of opioid-naive healthy volunteers and subjects with hepatic or renal impairment may not be representative of the safety profile in patients with OIC taking chronic opioid analgesics, who may have comorbidities and other disease risk factors.

The Phase IIb study had a similar target patient population to the Phase III studies of naloxegol; eligible patients had a confirmed diagnosis of OIC, non-cancer-related pain, and reported a history of <3 spontaneous bowel movements/week. However, patients were randomized in sequential cohorts to receive either placebo or naloxegol 5, 25, or 50 mg (as compared to 12.5 or 25 mg in the Phase III studies) for 4 weeks (as compared to 12-weeks in the confirmatory Phase III studies). A dose escalation committee reviewed safety and tolerability after each cohort and made recommendations regarding progressing to the next higher dose. Due to the occurrence of AEs of abdominal pain that resulted in discontinuation in 9/37 patients receiving 50 mg naloxegol, the 50 mg dose level was not pursued in the Phase III clinical program. Although some patients received one of the naloxegol doses used in the Phase III program (25 mg; N=31), data from the Phase IIb study are generally summarized separately from the Phase III studies because of the differences in design and treatment duration as compared to the pivotal studies.

TQT Study Summary of Findings

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 Figure 4, indicating that assay sensitivity was established. In this randomized, blinded, four-period crossover study, 51 healthy subjects received NKTR-118, placebo, and a single oral dose of moxifloxacin 400 mg. The overall summary of findings is presented in the following table:

Table 1: The Point Estimates and the 90% CIs 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.

The supratherapeutic dose (150 mg) produces mean Cmax values 7.7-fold the mean Cmax 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 Cmax as much as 9.6-fold. The Sponsor states that they plan to contraindicate co-administration of strong CYP3A4 and Pgp inhibitors. A significant relationship between naloxegol concentration and $\Delta\Delta$QTcF was detected, although the predicted effect at the concentrations observed in this study is small (~ 2 ms).

Heart rate was assesses in this TQT study using the same statistical approach as was used for the QTcF analysis. As shown in table Table 11 and Table 12 below, the largest upper limit of the 90% CI's for the HR mean differences between NKTR-118 25 mg and placebo and NKTR-118 150 mg and placebo are 3.2 bpm and 1.6 bpm, respectively:

Table 11: Analysis Results of ΔHR and ΔΔHR for Treatment Group A: NKTR-118 25 mg x 1 day

	ΔHR: NKTR-118			ΔHR: Placebo			ΔΔHR			
Time	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0.5	51	0.2	0.5	48	-0.3	0.5	48	0.4	0.7	(-0.8, 1.7)
1	50	-0.7	0.5	48	-1.3	0.5	48	0.6	0.7	(-0.6, 1.8)
1.5	51	-0.2	0.4	48	-0.9	0.5	48	0.7	0.6	(-0.3, 1.8)
2	50	0.4	0.5	47	-0.6	0.5	47	1.0	0.7	(-0.1, 2.1)
3	50	0.1	0.5	48	0.3	0.5	48	-0.1	0.7	(-1.4, 1.1)
4	51	0.9	0.7	48	0.2	0.7	48	0.7	1.0	(-1.0, 2.4)
6	50	7.7	0.7	48	7.5	0.8	48	0.2	1.1	(-1.6, 1.9)
8	51	4.7	0.7	47	3.1	0.7	47	1.6	1.0	(0.0, 3.2)
12	51	8.9	0.8	48	7.8	0.8	48	1.1	1.1	(-0.8, 2.9)
24	50	3.5	0.6	48	3.5	0.6	48	-0.0	0.9	(-1.5, 1.4)

Table 12: Analysis Results of ΔHR and ΔΔHR for Treatment Group B: NKTR-118 150 mg x 1 day

	ΔHR: NKTR-118			ΔHR: Placebo			ΔΔHR			
Time	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0.5	49	-0.4	0.5	48	-0.3	0.5	48	-0.1	0.8	(-1.4, 1.1)
1	49	-0.8	0.5	48	-1.3	0.5	48	0.4	0.7	(-0.7, 1.6)
1.5	48	-0.6	0.5	48	-0.9	0.5	48	0.3	0.7	(-0.8, 1.4)
2	48	-1.1	0.5	47	-0.6	0.5	47	-0.6	0.7	(-1.7, 0.6)
3	48	-0.4	0.5	48	0.3	0.5	48	-0.6	0.8	(-1.9, 0.6)
4	49	-0.9	0.7	48	0.2	0.7	48	-1.1	1.0	(-2.8, 0.6)
6	49	5.8	0.8	48	7.5	0.8	48	-1.7	1.1	(-3.5, 0.1)
8	49	2.7	0.7	47	3.1	0.7	47	-0.4	1.0	(-2.0, 1.2)
12	49	7.2	0.8	48	7.8	0.8	48	-0.6	1.1	(-2.5, 1.2)
24	49	3.5	0.6	48	3.5	0.6	48	-0.1	0.9	(-1.5, 1.4)

The outlier analysis results for HRfrom the TQT study are presented in Table 13 below, demonstrating that there was 1 (2.0%) subject who experienced HR greater than 100 bpm in the NKTR-118 150 mg arm:

Table 13: Categorical Analysis for HR

Treatment Group	N	HR < 100 bpm	HR >=100 bpm
NKTR-118 25 mg	49	49 (100%)	0 (0.0%)
NKTR-118 150 mg	51	50 (98.0%)	1 (2.0%)
Placebo	48	48 (100%)	0 (0.0%)

There were no deaths, SAEs, or discontinuations of the investigational product due to AEs in the study.

Phase III Clinical Safety Data

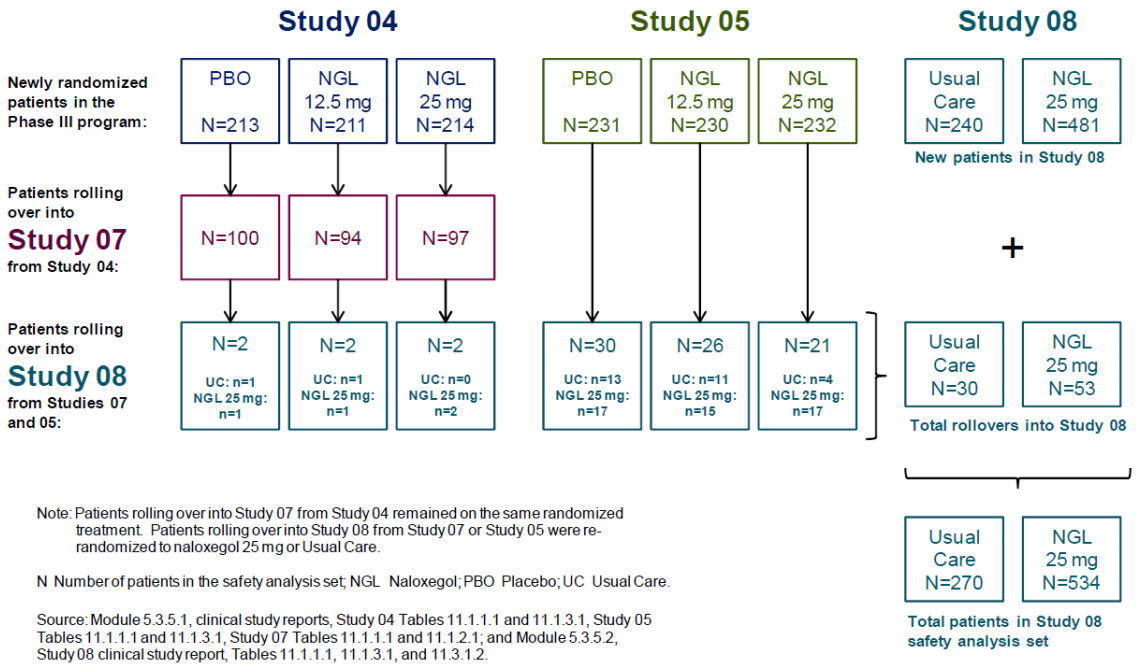
In the Phase IIb and III naloxegol clinical studies, 1497 unique patients were exposed to naloxegol at 1 or more doses (33 to 5 mg, 446 to 12.5 mg, 999 to 25 mg, and 35 to 50 mg) and included in the safety analyses. For the 25 mg dose, 464 patients were exposed for at least 24 weeks, 317 were exposed for at least 51 weeks, and 96 were exposed for at least 52 weeks. In addition, 438 volunteers were exposed to naloxegol in the Phase I studies (at doses of 5 to 1000 mg).

The integrated safety summary for this product presented information related to safety from all completed clinical studies, but with specific attention to 4 Phase III studies in patients with OIC taking opioid analgesics who had non-cancer-related pain: Studies D3820C00004 (Study 04) and D3820C00005 (Study 05) provide placebo-controlled efficacy and safety data over a period of 12-weeks and are combined in the '12-week pool', D3820C00007 (Study 07) was a 12-week safety extension of Study 04, and Study D3820C00008 (Study 08) was a 52-week open-label safety study comparing naloxegol to a Usual Care (ie, flexible laxative treatment determined by the Investigator) control group.

A fifth Phase III trial, study 06, was conducted in patients with OIC and cancer-related pain, but the study was terminated prematurely due to recruitment challenges. Only 13 patients were exposed to naloxegol in study 06, and there were no deaths, SAEs, or DAEs (AEs resulting in discontinuation). Therefore, the data from study 06 was not integrated or addressed in safety analyses.

A graphical representation of the patients contributing to the Phase III integrated safety analysis is shown in the figure below (from the sponsor's ISS, page 16):

Figure 1 Enrolment of patients into Study 08 (safety analysis sets)



Note: Patients rolling over into Study 07 from Study 04 remained on the same randomized treatment. Patients rolling over into Study 08 from Study 07 or Study 05 were re-randomized to naloxegol 25 mg or Usual Care.

N Number of patients in the safety analysis set; NGL Naloxegol; PBO Placebo; UC Usual Care.

Source: Module 5.3.5.1, clinical study reports, Study 04 Tables 11.1.1.1 and 11.1.3.1, Study 05 Tables 11.1.1.1 and 11.1.3.1, Study 07 Tables 11.1.1.1 and 11.1.2.1; and Module 5.3.5.2, Study 08 clinical study report, Tables 11.1.1.1, 11.1.3.1, and 11.3.1.2.

Primary Analysis Sets:

- 12-week pool (Studies 04 and 05) - the 2 randomized, double-blind, placebo controlled, parallel-group confirmatory efficacy and safety studies within the Phase III development program in patients with non-cancer related pain and OIC

- 52-week safety study (study 08) - an open-label study in which patients who completed Study 05 or Study 07, as well as patients who had not previously participated in a naloxegol study, were eligible to participate. Patients in Study 08 received either naloxegol 25 mg QD or Usual Care (2:1 randomization).

Supportive/other Safety Pools

- 24-week integrated dataset (Studies 04 and 07) - After completing participation in Study 04, enrolled patients were eligible to enroll in an extension study (Study 07) in which they continued to receive their randomly assigned treatment in a blinded, placebo-controlled fashion for an additional 12-weeks. To supplement the open-label data from Study 08 and further understand the safety profile of naloxegol during longer-term exposure, data from Study 04 and Study 07 were integrated to

provide placebo-controlled safety data with up to 24 weeks of planned exposure. Rollover into Study 07 was optional; therefore there was potential selection bias, with rollover patients likely to have a lower propensity for experiencing AEs and/or a higher propensity for experiencing a positive response to IP, compared to patients who chose not to participate. In addition, sites that were initiated after a certain date for Study 04 did not participate in Study 07. Rollover patients were counted once, in the appropriate treatment group.

- Placebo-controlled pool (Studies 04, 05, and 07)
- Phase IIb study
- Phase IIb/III pool – requested by FDA
- Study 06
- Phase I pool

Strategy for Evaluating CV Safety

All serious CV events (and selected non-serious CV AEs of interest) occurring in the Phase III clinical studies of naloxegol were adjudicated by an independent external CV event adjudication committee (CV-EAC). In addition, to support assessment of potential cardiac risks, serial digitalized ECGs were collected (in triplicate) 2 hours after administration of the first dose of IP to correlate with naloxegol Tmax and at all subsequent study visits, and were read centrally. Patients were also observed for changes in blood pressure (BP) and pulse 1 hour after administration of the first dose of IP (as well as at the end of the 4-hour post-first-dose observation period, although these latter measurements were not entered into the database unless considered clinically relevant, but were taken only to inform Investigator decisions).

Sources of Data for the CV-EAC

The process for selecting CV events for adjudication was as follows:

- The Investigator was to report all deaths and pre-specified MACE, as well as any other events deemed by the Investigator to be appropriate for adjudication.
- AstraZeneca and Quintiles:
    - Reported all CV SAEs
    - Performed a medical review to identify non-serious cases that might have been missed by the Investigators and sent a query to the Investigator concerning appropriateness for adjudication; in such cases, AstraZeneca reserved the right to report an event to the CV-EAC even if the Investigator did not consider it appropriate for adjudication, and maintained a highly conservative threshold for submission of events.

Reviewer's Comment: Cannot locate CV-EAC charter in section 5.3.5.3 to assess automated triggers for EAC referral.

Clinical safety methods

For each study and pool, the safety analysis set was to comprise all randomized patients who received at least 1 dose of study drug. However, 15 patients were excluded from the 12-week pool and 36 patients were excluded from the Study 08 safety analysis set. The following patients were excluded:

- Patients who were randomized multiple times at different centers, including:
    - 15 patients in the 12-week pool (1% of the randomized patients; see Module 5.3.5.3, Appendix 2.7.4.7, Table 4.1.1.3)
    - 16 patients in Study 08 (1.6% of the 840 randomized patients; see Module 5.3.5.2, Study 08 CSR, Table 11.1.2.1)

- The 24 (2.9%) patients in Study 08 who were randomized at centers 8703 and 8939, where data integrity issues were identified (see Module 5.3.5.2, Study 08 CSR, Section 5.6 for details). Four of these 24 patients were also randomized at multiple sites.

The sponsor notes that Among the 36 unique excluded patients in the naloxegol treatment groups (5 on 12.5 mg and 31 on 25 mg), 16 had AEs during the treatment period, most of which were isolated reports: urinary tract infection was reported for 3 patients and the following AEs were reported for 2 patients: diarrhea, nasopharyngitis, back pain, laceration, anemia, headache, cough. There was 1 SAE (on 25 mg; Patient E4705004, limb traumatic amputation) and no DAEs. There was also 1 SAE in a patient in the Usual Care treatment group (Patient E8703006, peripheral vascular disorder, post-treatment). All data were retained in the database and included in the patient data listings in the CSRs. The sponsor reports that exclusion of these patients from the safety analysis sets did not affect the characterization of the safety profile of naloxegol.

Potential signs of CNS opioid withdrawal were assessed using the mHS in the Phase III clinical development program. The mHS is a clinician observer-rated scale in which patients are rated with respect to the following symptoms as observed at the time of the assessment: yawning, lacrimation, rhinorrhea, perspiration, tremor, mydriasis, piloerection, and restlessness. The signs are quantified on a scale of 0 (none), 1 (mild), 2 (moderate), and 3 (severe). The mHS was chosen by the sponsor because this scale is focused on non-GI withdrawal signs; GI signs may be confounded by the activity of naloxegol, as the sponsor believes was seen in the Phase IIb study, in which the Clinical Opiate Withdrawal Scale (COWS) was used. The sponsor reports the following two points that were relevant to the use of this withdrawal assessment scale:

- The mHS was administered periodically in the Phase III studies, including at 2 hours post-first-dose of study drug. Raters had to meet pre-specified criteria for clinical experience, underwent training on proper scoring using the mHS, and received certification provided by (b) (4) based upon pre-specified criteria for scoring competency. (ISS page 28)

- While there is no published or established threshold for a clinically important change in the total mHS score, a change of ≥3 was considered, in consultation with external subject matter experts, to be a conservative and appropriate cutoff for identifying patients with potential withdrawal symptoms. (ISS page 82)

Reviewer's Comment: From a CV risk perspective, the COWS has the benefit of including resting pulse rate, which the mHS does not, thus potentially limiting ascertainment of pulse elevations as adverse events. However, the assessment of MACE as defined by this sponsor as MI, non-fatal stroke, non-fatal MI, hospitalization for heart failure, and hospitalization for unstable angina, should not be impacted by this difference between the withdrawal scales. It is noted that the requirement of ≥ 3 mHS points was arbitrary and without literature validation.

With respect to pain assessment as a measure of potential naloxegol-induced withdrawal, the NRS scale was incorporated, which rates pain from 0 (no pain) to 10 (worst pain imaginable). The 11-point NRS was used in the naloxegol clinical development program because it has been recommended as the preferred response format for use in clinical trials (Dworkin et al 2005). An increase of ≥2 in NRS score relative to baseline was selected as an appropriate cutoff for identifying individual patients with PCI increases in pain (whereas a cutoff of 1 was used in the CSRs for mean values), based on consultation with external experts.

Reviewer's comment: It should be noted in the Summary of Clinical Safety that the NRS has primarily been used to assess the efficacy of pain-relieving medications, rather than to measure increases in pain that might result from treatment with an opioid receptor antagonist, and a recommended cutoff for PCI changes in the latter context has not been established (ISS page 27-28)

Two other elements of the sponsor's safety analysis were also arbitrarily chosen:

- *"The criteria used to define these potential indicators of opioid withdrawal syndrome were chosen, in consultation with external experts in opioid withdrawal, as clinically relevant and conservative criteria for identifying patients who may have experienced generalized opioid withdrawal".*

- *Whether or not a treatment imbalance is 'notable' is based on a subjective assessment by AstraZeneca of both the magnitude of the difference in incidences and the potential for harm related to the endpoint. (Response doc 8 Oct 2013 page 12).*

Missing data and premature discontinuations

Patients who discontinued prematurely from a Phase III study after randomizing and receiving at least 1 dose of study drug were not required to be followed up to the planned study duration (i.e., 12-weeks, 24 weeks, or 52 weeks in the confirmatory, rollover, or long-term safety studies, respectively). These patients were asked to return to the study center for an early termination (ET) visit. This ET visit was scheduled as soon as possible after the patient discontinued from the study. Any patient who discontinued and had clinically significant or abnormal results for any safety assessment had an additional follow-up visit 1 week after discontinuation and at appropriate intervals thereafter, as medically indicated and determined by the investigator. The sponsor's ISS states that information regarding all AEs was collected during the 2-week post-treatment period, and information regarding SAEs was collected for up to 30 days after the end of the randomized treatment period.

Changes from baseline to post-baseline were calculated as the post-baseline value minus the baseline value. If either the baseline or post-baseline value was missing for a particular parameter, the change from baseline value was also missing.

In Kaplan-Meier analyses of time-to-event data, patients who did not have an event were censored at their study completion visit (on-study assessment) or at their last dose of study drug (on-treatment assessment). In the calculation of exposure-adjusted event rates, all patients, including those who discontinued prematurely, contribute their actual duration of exposure or follow-up.

Reviewer's Comment: In short, patients who discontinued from the study prematurely were censored from the collection of further efficacy and safety endpoints after they withdrew.

Exposure and premature withdrawal from Phase III Trials

In the 12-week pool,

- 17.8% of the placebo patients, 20.0% of the patients on naloxegol 12.5 mg, and 22.1% of the patients on naloxegol 25 mg withdrew from the studies prematurely
- The most common reasons for treatment discontinuation in the placebo, naloxegol 12.5 mg, and naloxegol 25 mg groups were AE (5.1%, 4.4%, and 10.2%, respectively), subject decision (5.8%, 8.9%, and 5.8%, respectively), and loss to follow-up (2.9%, 4.0%, and 3.3%, respectively)

In Study 08,

- 28.8% of the Usual Care patients and 36.8% of the patients taking naloxegol 25 mg withdrew from the study prematurely
- As in the 12-week pool, the most common reasons for treatment discontinuation were subject decision (13.5% and 12.4% in the Usual Care and naloxegol 25 mg groups, respectively), AE (1.8% and 9.9%, respectively), and loss to follow-up (6.8% and 6.4%, respectively).

Demographics of Phase III OIC

With respect to demographics, the sponsor reports that the Phase III naloxegol program enrolled an OIC population generally representative of patients receiving long-term opioid treatment for non-cancer pain. Accordingly, the Phase III study population was predominantly White, female (approximately two-thirds), and 50 to 65 years old, and approximately 95% were enrolled at study sites in the US. Approximately half of the patients had BMI >30. The most commonly specified primary reasons for opioid use were back pain (approximately 60% of the patients), 'other', arthritis, and fibromyalgia; most patients in the 'other' category reported various pain conditions, most of which were of musculoskeletal origin (eg, 'left leg injury', 'degenerative disc disease', 'post-laminectomy syndrome'). Patients in the placebo group were taking a lower opioid dose on average than patients in the naloxegol groups (mean dose of 127.4 meu in the placebo group compared to 146 and 139.7 meu, respectively, in the naloxegol 12.5 and 25 mg groups).

Phase III Vital Sign Analyses

The sponsor analyzed mean changes from baseline for SBP, DBP, and HR in both the double-blind pool and the 52-week safety study both at 1 hour post-first-dose and at any time during the study. There were no clinically important differences between the treatment groups, as shown in the table below (ISS table 11.3.8.1.1, appendix 2.7.4.7 Tables 4.2.7.5; confidence intervals were widely overlapping, data not shown):

Mean Vital Sign Changes from Baseline					
Parameter	Placebo-controlled pool (Studies 04, 05, 07)			52-week safety study (Study 08 newly randomized)	
	Pl	NGL 12.5 mg	NGL 25 mg	Usual Care	NGL 25 mg
SBP mean change from baseline (mmHg)					
1 hr-post-dose 1				1.5	2.1
week 1				0.9	0.6
Last on Rx	0	-0.3	1.7	0.1	2.3
DBP mean change from baseline (mmHg)					
1 hr-post-dose 1				0.2	0.5
week 1				0.2	0.1
Last on Rx	-0.3	0.1	0.5	-0.9	0.5
HR mean change from baseline (bpm)					
1 hr-post-dose 1				-1.1	-2.6
week 1				0.4	0.8
Last on Rx	1.6	3.0	1.4	2.0	1.0

The sponsor analyzed relevant categorical shifts for SBP, DBP, and HR in both the 12-week pool and the 52-week safety study both at 1 hour post-first-dose and at any time during the study . Differences between the treatment groups were minor and not consistent, as shown in the table below (ISS Table 19):

Table 19 Summary of PCI vital signs abnormalities observed in ≥1 patient in any treatment group (12-week pool and Study 08)

		12-week pool (Studies 04 and 05)			52-week safety study (Study 08)[a]	
Parameter	**Criterion**	**Placebo**	**NGL 12.5 mg**	**NGL 25 mg**	**Usual care**	**NGL 25 mg**
Number (%) of patients with PCI values 1 hour post-first-dose of study drug						
N		443	439	446	231	477
SBP (mmHg)	≤100 and ↓ ≥20	1 (0.2)	3 (0.7)	3 (0.7)	0	0
	≤80	0	1 (0.2)	0	0	0
	≥160 and ↑ ≥20	2 (0.5)	2 (0.5)	4 (0.9)	2 (0.9)	3 (0.6)
	≥180	1 (0.2)	0	4 (0.9)	0	1 (0.2)
DBP (mmHg)	≤50 and ↓ ≥10	2 (0.5)	0	1 (0.2)	1 (0.4)	0
	≤45	1 (0.2)	0	1 (0.2)	0	1 (0.2)
	≥95 and ↑ ≥10	5 (1.1)	8 (1.8)	6 (1.3)	2 (0.9)	5 (1.0)
Pulse (bpm)	≤50 and ↓ ≥20	1 (0.2)	0	0[b]	0	0
	≥100 and ↑≥20	1 (0.2)	0	1 (0.2)[b]	1 (0.4)	1 (0.2)
Number (%) of patients with PCI values at any time during the treatment period						
N		444	441	446	234	481
SBP (mmHg)	≤100 and ↓ ≥20	18 (4.1)	27 (6.1)	17 (3.8)	14 (6.0)	28 (5.8)
	≤80	0	2 (0.5)	0	2 (0.9)	3 (0.6)
	≥160 and ↑ ≥20	14 (3.2)	17 (3.9)	13 (2.9)	18 (7.7)	18 (3.7)
	≥180	5 (1.1)	1 (0.2)	7 (1.6)	1 (0.4)	4 (0.8)
DBP (mmHg)	≤50 and ↓ ≥10	4 (0.9)	2 (0.5)	7 (1.6)	5 (2.1)	2 (0.4)
	≤45	3 (0.7)	0	2 (0.4)	0	1 (0.2)
	≥95 and ↑ ≥10	44 (9.9)	34 (7.7)	30 (6.7)	23 (9.8)	35 (7.3)
	≥120	0	0	0	0	3 (0.6)
Pulse (bpm)	≤50 and ↓ ≥20	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.2)
	≤40	1 (0.2)	0	0	2 (0.9)	0
	≥100 and ↑≥20	14 (3.2)	11 (2.5)	10 (2.2)	13 (5.6)	24 (5.0)
	≥120	1 (0.2)	1 (0.2)	1 (0.2)	0	2 (0.4)

[a] For Study 08, only patients who had not previously participated in a naloxegol trial, approximately 90% of the study population, are included. Results for rollover patients are presented in Module 5.3.5.2, Study 08 clinical study report, Tables 11.3.8.1.3 and 11.3.8.1.8.

[b] N=445 for this assessment.

Reviewer's comment: While overall, the changes in SBP and DBP were minor, it is noted that the most extreme elevations of both noted at any time during the treatment period were numerically higher in the NGL 25 mg arm of the 12-week pool, or the NGL 25 mg arm of the 52-week safety study. However, the absolute numbers of these events were all very small, and they often trended in the opposite direction from the next highest SBP/DBP elevation category. HR elevations were similar between treatment groups.

Summary of Phase III Adverse Events

*Definition Note:

- The ISS used the pre-specified PTs within the standardized Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) list of PTs related to drug withdrawal and a post-hoc assessment of PTs related to the mHS

- Subsequent Assessments of opioid withdrawal and CV risk used an expanded list of preferred opioid withdrawal non-GI terms from OOWS, COWS, SOWS and other terms agreed to by the Agency in the NDA submission, provided in response to the Type C Meeting Minutes dated 22 May 2013, where the FDA requested additional analyses of the naloxegol data pertaining to opioid withdrawal and CV effects.

- For all patients in Study 07 and rollover patients in Study 08, AEs with onset during the previous study that were ongoing at baseline of the follow-up study were recorded as medical history in the follow-up study and were not counted as AEs unless they worsened.

For both the 12-week pool of the two pivotal safety studies (04 and 05) and the 52-week extension study (08), there were numerically higher percentages of AEs in patients taking NGL 25 mg compared to either placebo or usual care, respectively, as seen in the sponsor's ISS table 8 below:

Table 8 Number (%) of patients who had ≥1 AE in any category during the treatment period (12-week pool and Study 08)

	12-week pool (Studies 04 and 05)			52-week safety study (Study 08)	
AE category	Placebo (N=444)	NGL 12.5 mg (N=441)	NGL 25 mg (N=446)	Usual care[a] (N=270)	NGL 25 mg (N=534)
Any AE	227 (51.1)	231 (52.4)	283 (63.5)	194 (71.9)	428 (80.1)
Any AE with outcome = death	0	0	0	1 (0.4)	0
Any SAE (including events with outcome = death)	20 (4.5)	20 (4.5)	14 (3.1)	30 (11.1)	46 (8.6)
Any DAE	21 (4.7)	20 (4.5)	46 (10.3)	NA	50 (9.4)

[a] Patients randomized to Usual Care were treated with approved over-the-counter and/or prescription laxative(s) either as monotherapy or in any combination, according to the Investigator's clinical judgment. These patients were not taking IP and therefore could not discontinue IP.

AE Adverse event; DAE AE leading to discontinuation of investigational product; IP Investigational product; N Total number of patients; n Number of patients in category; NA Not applicable; NGL Naloxegol.

Source: Module 5.3.5.3, Appendix 2.7.4.7, Table 4.1.2.2; and Module 5.3.5.2, Study 08 clinical study report, Table 11.3.2.1.2.

Of note, while there were numerically fewer SAEs reported with NGL 25 mg in both the 12-week pool and long term study 08, the rate of adverse events leading to

discontinuation in the 12-week pool was almost twice as high for NGL 25 mg as for placebo.

Deaths

There were a total of 7 deaths in naloxegol clinical program: 5 in the Phase III studies, 1 in the Phase II study, and I in the Phase I studies. Of the 6 deaths in OIC patients, 1 occurred in the Usual Care group in Study 08 (0.4%), 3 occurred in patients in naloxegol 12.5 mg groups (0.7%), and 2 occurred in patients in naloxegol 25 mg groups (0.2%, 1 in Phase III, 1 in Phase IIb). Four of the five deaths that occurred in the Phase III program were adjudicated as CV deaths. The patient from the Phase I trial who died had an MI, then died post-operatively after CABG. The Phase II death followed a pulmonary embolus in a patient with a h/o DVTs. Neither the investigators nor AstraZeneca consider any of these individual cases to be related to study treatment.

Table 10 Key information regarding AEs with outcome=death, during the treatment period or post-treatment follow-up (Phase III studies)

Study/ Treatment group	Patient	Sex	Age (years)	Investigator description of AE	Preferred term	Time from start of treatment to onset of AE (days)	Time from last dose to onset of AE (days)	Time from start of treatment to death (days)	Time from last dose to death (days)	Causality per Investigator
Study 04										
NGL 12.5 mg	E4003038	F	55	Advanced stage nonsmall cell lung cancer	Non-small cell lung cancer	109	19	113	23	Not related
NGL 12.5 mg	E4068050	M	73	Complication of AVR and CABG surgery	Cardiac valve replacement complication	19	4	49	34	Not related
Study 05 There were no deaths in this study										
Study 07										
NGL 12.5 mg	E4073006	M	54	Ischemic heart disease secondary to coronary artery disease	Myocardial ischaemia	146	6	146	6	Not related
Study 08										
Usual Care[a]	E5228010	F	30	Death	Death	95	1	95	1	Not related
NGL 25 mg	E8843004	F	39	Idiopathic epilepsy	Idiopathic generalized epilepsy	111	20	111	20	Not related

Details of the five deaths from the phase III studies are as follows:

- 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.

- 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 with complications of pneumonia, sepsis, and renal failure. The SAE of cardiac valve

replacement complication on Day 19 resulted in the patient's death on Day 49. This event was adjudicated as a CV death (see Section 2.1.7.2).

- Study 07 Patient E4073006 was a 54-year-old male in the naloxegol 12.5 mg group with diabetes. He was in a serious road traffic accident on Day 146 (Day 60 of Study 07), after a "blackout" due 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. An autopsy showed that the patient died of myocardial ischemia, secondary to coronary artery disease. This event was adjudicated as a CV death (see Section 2.1.7.2).

- 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 the current study, the patient died in her sleep, cause of death unknown, and no additional details were available. This event was adjudicated as a CV death (see Section 2.1.7.2).

- Study 08 Patient E8843004 was a 39-year-old female in the naloxegol 25 mg group. She was reported by the investigator to have a SAE of idiopathic generalized epilepsy on Day 111 that resulted in the patient's death. There was no previous history of epilepsy for this patient and the patient 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 the patient stopped taking IP on Day 92; the reason for IP discontinuation could not be determined. This event was adjudicated as a CV death (see Section 2.1.7.2).

The single death in the Phase IIb study, patient 43003, was 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 1 death in the Phase I studies of naloxegol (see Module 5.3.5.3, Appendix 2.7.4.7, Table 4.4.2.3). In Study 09, Subject E0001005 (severe renal impairment group), a 61-yearold, 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 diagnosis 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.

All Phase III Adjudicated MACE Events in Placebo-controlled Pool and Study 08

Combined Phase III Adjudicated MACE events are summarized in the following table (sponsor analysis, ISS page 109):

Table 15 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)

	Placebo-controlled pool (Studies 04/07 and 05)			52-week safety study (Study 08)	
Category	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.

Source: Module 5.3.5.3, Appendix 2.7.4.7, Table 4.3.3.5; and Module 5.3.5.2, Study 08 clinical study report, Table 11.3.6.1.2.

In the placebo-controlled studies, the MACE rate per 100 patient years of exposure was 1.5 for placebo (2/444 patients), 1.6 for naloxegol 12.5 mg (2/441 patients), and 0.8 for naloxegol 25 mg (1/446 patients).

CV-SAEs Reported for ≥2 Patients in any Treatment Group During the Treatment Period or Post-treatment Follow-up (Studies 04/05, 07, and 08)

Syncope was reported as an SAE in 2/441 (0.5%) of patients in the 12-week pool on NGL 12.5 mg and 1/534 (0.2%) of patients from Study 08 on NGL 25 mg. There were no syncope SAEs in patients taking placebo in the 12-week pool or in the usual care arm of study 08.

Atrial fibrillation was reported as an SAE in 1/270 (0.4%) of patients in the usual care arm of Study 08 and 2/534 (0.4%) of patients from the NGL 25 mg arm of Study 08. There were no cases of AFib in the 12-week pool or the Study 07 extension to the 12-week pool.

CV-DAEs Reported for ≥2 Patients in any Treatment Group during the Treatment Period or Post-treatment Follow-up (Studies 04/05, 07, and 08)

The only CV adverse events leading to discontinuation that occurred in at least two patients in any treatment group in the treatment period of post-treatment follow-up were isolated cases of hypotension. Hypotension was reported as a DAE in 1/441 (0.2%) of patients in the NGL 12.5 mg arm of the 12-week pool, in 1/446 (0.2%) of patients in the NGL 25 mg arm of the 12-week pool, and in 1/97 (1.0%) of patients in the NGL 25 mg arm of study 07. There were no hypotension DAEs in study 08.

Other Significant CV-AEs Reported for ≥1 Patient in any Treatment Group During the Treatment Period or Post-treatment Follow-up (Studies 04/05, 07, and 08)

ECG QT prolonged was reported as an AE in 1/444 (0.2%) of patients in the 12-week pool on placebo, in 1/446 (0.2%) of patients in the 12-week pool on NGL 25 mg, in 4/270 (1.5%) of patients from Study 08 on usual care, and in 5/534 (0.9%) of patients from Study 08 on NGL 25 mg.

ECG T wave inversion was reported as an AE in 1/444 (0.2%) of patients in the 12-week pool on placebo, and in 2/534 (0.4%) of patients from Study 08 on NGL 25 mg.

ECG ST segment depression was reported as an AE in 2/534 (0.4%) of patients from Study 08 on NGL 25 mg.

BP/HR AEs Reported for ≥1 Patient in any Treatment Group During the Treatment Period or Post-treatment Follow-up (Studies 04/05, 07, and 08)

AEs related to blood pressure for the double-blind pool and study 08 are summarized in the table below:

Table 16 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: Module 5.3.5.3, Appendix 2.7.4.7, Table 4.3.3.4; and Module 5.3.5.2, Study 08 clinical study report, Table 11.3.6.3.1.

In the double-blind pool, the incidence of decreased BP adverse events was similar between the placebo and NGL 12.5 arms, and somewhat higher in the NGL 25 mg arm. Of note, the opposite trend was seen in study 08, with approximately twice the percentage of subjects experiencing decreased BP adverse events in the usual care arm as compared to the NGL 25 mg arm.

AEs of increased BP appeared dose related in the placebo-controlled pool (04, 05, and 07), but were more common in the usual care arm of open-label study 08 than in the NGL 25 mg group.

Overall Withdrawal Adverse Events, alone and with CV Adverse Events

The sponsor's interpretation of their naloxegol data is summarized by their statement in section 4.4.3 of the ISS, page 82, in which Astra Zeneca states the following:

> *"A comprehensive review of all relevant data indicates that there was no consistent or definitive evidence of opioid withdrawal associated with naloxegol"*

However, examination of the adverse event data suggests otherwise. Specifically, from the sponsor's response 8 Oct 2013 to an FDA IR regarding opioid withdrawal events and CV risk assessment, the 12-week data pool demonstrated that the incidence of adverse event preferred terms potentially related to opiod withdrawal during treatment was dose responsive in the 12-week pool, and elevated in the NGL 25 mg arm of the 52-week

safety study (study 08) relative to the usual treatment arm of study 08, as is seen in the table below from that document:

Table 1 **Number (%) of patients with at least 1 PT potentially related to opioid withdrawal syndrome during the treatment period (12-week pool and Study 08)**

	12-week pool (Studies 04 and 05)			52-week safety study (Study 08)	
	Placebo (N=444)	NGL 12.5 mg (N=441)	NGL 25 mg (N=446)	Usual care (N=270)	NGL 25 mg (N=534)
Any PT	**84 (18.9)**	**106 (24.0)**	**150 (33.6)**	**70 (25.9)**	**253 (47.4)**
Any non-GI PT	**31 (7.0)**	**35 (7.9)**	**58 (13.0)**	**49 (18.1)**	**131 (24.5)**
Hyperhidrosis	1 (0.2)	2 (0.5)	13 (2.9)	1 (0.4)	17 (3.2)
Anxiety	5 (1.1)	7 (1.6)	7 (1.6)	4 (1.5)	17 (3.2)
Arthralgia	5 (1.1)	4 (0.9)	5 (1.1)	16 (5.9)	33 (6.2)
Pyrexia	2 (0.5)	3 (0.7)	5 (1.1)	6 (2.2)	14 (2.6)
Drug withdrawal syndrome	1 (0.2)	2 (0.5)	5 (1.1)	0	2 (0.4)
Hot flush	2 (0.5)	2 (0.5)	4 (0.9)	3 (1.1)	6 (1.1)
Muscle spasms	3 (0.7)	3 (0.7)	3 (0.7)	8 (3.0)	17 (3.2)
Palpitations	1 (0.2)	3 (0.7)	3 (0.7)	1 (0.4)	2 (0.4)
Tremor	2 (0.5)	1 (0.2)	3 (0.7)	1 (0.4)	2 (0.4)
Rhinorrhea	0	1 (0.2)	3 (0.7)	1 (0.4)	4 (0.7)
Myalgia	0	0	3 (0.7)	1 (0.4)	3 (0.6)
Depression	4 (0.9)	3 (0.7)	2 (0.4)	10 (3.7)	14 (2.6)
Insomnia	3 (0.7)	1 (0.2)	2 (0.4)	5 (1.9)	15 (2.8)
Flushing	1 (0.2)	1 (0.2)	2 (0.4)	0	3 (0.6)
Cold sweat	0	1 (0.2)	2 (0.4)	0	1 (0.2)
Yawning	1 (0.2)	0	2 (0.4)	0	3 (0.6)
Feeling jittery	1 (0.2)	2 (0.5)	1 (0.2)	0	1 (0.2)
Chills	1 (0.2)	1 (0.2)	1 (0.2)	0	11 (2.1)
Irritability	0	1 (0.2)	1 (0.2)	0	2 (0.4)
Tachycardia	1 (0.2)	0	1 (0.2)	0	3 (0.6)
Restlessness	1 (0.2)	0	0	0	4 (0.7)
Sneezing	0	0	0	2 (0.7)	2 (0.4)
Muscle twitching	0	0	0	0	2 (0.4)
Selected GI PT[a]	**62 (14.0)**	**86 (19.5)**	**127 (28.5)**	**39 (14.4)**	**190 (35.6)**
Abdominal pain	25 (5.6)	43 (9.8)	71 (15.9)	9 (3.3)	95 (17.8)
Diarrhea	19 (4.3)	25 (5.7)	41 (9.2)	16 (5.9)	69 (12.9)
Nausea	20 (4.5)	29 (6.6)	36 (8.1)	11 (4.1)	50 (9.4)
Vomiting	13 (2.9)	10 (2.3)	20 (4.5)	15 (5.6)	27 (5.1)
Abdominal pain upper	7 (1.6)	8 (1.8)	17 (3.8)	3 (1.1)	27 (5.1)
Abdominal pain lower	0	1 (0.2)	2 (0.4)	3 (1.1)	9 (1.7)

Note: PTs reported for ≥2 patients in any treatment group are included in the table, sorted by highest incidence on naloxegol 25 mg, then naloxegol 12.5 mg, then placebo in the 12-week pool; followed by naloxegol 25 mg, then Usual Care in Study 08.
Percentages are based on the number of patients in the safety set for each treatment group.
Patients with >1 event in the same category are counted only once in that category. Patients with events in >1 PT are

While the differences were primarily due to GI adverse event preferred terms (PT) that may have been caused by the direct action (peripheral withdrawal) of naloxegol, non-GI adverse event PTs suggestive of withdrawal were also higher for NGL 25 mg than for placebo in the 12-week pool and for usual care in the 52-week pool. In the placebo-controlled pool which included study 07, the results were similar, per the following table from the same document:

Table 1.3.1 Summary of AEs potentially related to Opioid Withdrawal including GI-related AEs, On-trt, S004, S007 and S005 (Safety set)

Category Preferred term	Number (%) of patients Placebo (N=444)	NKTR-118 12.5 mg (N=441)	NKTR-118 25 mg (N=446)
Number of pts with at least 1 AE potentially related to Opioid Withdrawal including specific GI-related AEs	87 (19.6)	111 (25.2)	155 (34.8)
Number of pts with at least 1 AE potentially related to Opioid Withdrawal excluding GI-related AEs	33 (7.4)	36 (8.2)	65 (14.6)
HYPERHIDROSIS	1 (0.2)	2 (0.5)	13 (2.9)
ARTHRALGIA	5 (1.1)	4 (0.9)	9 (2.0)
ANXIETY	5 (1.1)	8 (1.8)	7 (1.6)
PYREXIA	2 (0.5)	3 (0.7)	6 (1.3)
DRUG WITHDRAWAL SYNDROME	1 (0.2)	2 (0.5)	6 (1.3)
MUSCLE SPASMS	5 (1.1)	3 (0.7)	5 (1.1)
HOT FLUSH	2 (0.5)	2 (0.5)	4 (0.9)
MYALGIA	0	0	4 (0.9)
PALPITATIONS	1 (0.2)	3 (0.7)	3 (0.7)
TREMOR	2 (0.5)	1 (0.2)	3 (0.7)
RHINORRHOEA	0	1 (0.2)	3 (0.7)
DEPRESSION	4 (0.9)	4 (0.9)	2 (0.4)
INSOMNIA	3 (0.7)	1 (0.2)	2 (0.4)
FLUSHING	1 (0.2)	1 (0.2)	2 (0.4)
COLD SWEAT	0	1 (0.2)	2 (0.4)
YAWNING	1 (0.2)	0	2 (0.4)
FEELING JITTERY	1 (0.2)	2 (0.5)	1 (0.2)
CHILLS	1 (0.2)	1 (0.2)	1 (0.2)
HEART RATE INCREASED	1 (0.2)	1 (0.2)	1 (0.2)
IRRITABILITY	0	1 (0.2)	1 (0.2)
LACRIMATION INCREASED	0	1 (0.2)	1 (0.2)
TACHYCARDIA	1 (0.2)	0	1 (0.2)
DRUG DEPENDENCE	0	0	1 (0.2)
DRUG EFFECT DECREASED	0	0	1 (0.2)

Likewise, the sponsor states the following in this response to the FDA IR (page 12):

> *There was no notable treatment imbalance in the 12-week pool with respect to increases in opioid dose, Numeric Rating Scale (NRS) for pain intensity score, or modified Himmelsbach Scale (mHS) score during the study, indicating a lack of association between naloxegol and these potential indicators of opioid withdrawal syndrome (see Table 2). If naloxegol were associated with opioid withdrawal per se, one would expect to see a notable imbalance in these measures in the safety population, regardless of the incidence of selected GI PTs. (Whether or not a treatment imbalance is 'notable' is based on a subjective assessment by AstraZeneca of both the magnitude of the difference in incidences and the potential for harm related to the endpoint.)*

Table 2 that the sponsor reference is reproduced below for convenience, and demonstrates a higher incidence of these withdrawal indicators for the NGL 25 dose than for placebo. The fact that the magnitude of the increase was relatively small may have been an artifact of the arbitrary cutoffs that were used for the NRS and the mHS:

Table 2 **Number (%) of patients in the overall safety population, by category (12-week pool)**

	Placebo (N=444)	Naloxegol 12.5 mg (N=441)	Naloxegol 25 mg (N=446)
≥10% increase from baseline in mean weekly opioid dose during the study	51 (11.5)	51 (11.6)	58 (13.0)
≥30% increase from baseline in mean weekly opioid dose during the study	24 (5.4)	17 (3.9)	28 (6.3)
≥2 point increase from baseline in mean weekly NRS average pain at any time during the study	37 (8.3)	35 (7.9)	43 (9.6)
≥3 point increase from baseline in mHS score at any time during the study	13 (2.9)	14 (3.2)	16 (3.6)

12-week pool (studies 04 and 05) withdrawal adverse events, alone and with CV adverse events

In the 12-week pool, DAEs potentially related to withdrawal occurred in a dose responsive fashion, driven primarily by the GI adverse events that could have been direct actions of the drug (peripheral opiod withdrawal), as seen in table 3 below:

Table 3 **Number (%) of patients with at least 1 DAE potentially related to opioid withdrawal syndrome (12-week pool and Study 08)**

	12-week pool (Studies 04 and 05)			52-week safety study (Study 08)	
	Placebo (N=444)	NGL 12.5 mg (N=441)	NGL 25 mg (N=446)	Usual care (N=270)	NGL 25 mg (N=534)
Any DAE	**10 (2.3)**	**10 (2.3)**	**29 (6.5)**	**NA[a]**	**29 (5.4)**
Non-GI DAE	**6 (1.4)**	**1 (0.2)**	**10 (2.2)**		**13 (2.4)**
Hyperhidrosis	1 (0.2)	0	4 (0.9)		3 (0.6)
Myalgia	0	0	2 (0.4)		1 (0.2)
Depression	0	1 (0.2)	1 (0.2)		2 (0.4)
Drug withdrawal syndrome	1 (0.2)	0	1 (0.2)		0
Yawning	1 (0.2)	0	1 (0.2)		0
Chills	0	0	1 (0.2)		3 (0.6)
Drug dependence	0	0	1 (0.2)		0
Drug effect decreased	0	0	1 (0.2)		0
Feeling jittery	0	0	1 (0.2)		0
Rhinorrhea	0	0	1 (0.2)		0
Restlessness	1 (0.2)	0	0		1 (0.2)
Flushing	1 (0.2)	0	0		0
Night sweats	1 (0.2)	0	0		0
Palpitations	1 (0.2)	0	0		0
Tachycardia	1 (0.2)	0	0		0
Tremor	1 (0.2)	0	0		0
Arthralgia	0	0	0		2 (0.4)
Anxiety	0	0	0		1 (0.2)
Pyrexia	0	0	0		1 (0.2)
Selected GI DAE[b]	**5 (1.1)**	**9 (2.0)**	**25 (5.6)**		**17 (3.2)**
Diarrhea	3 (0.7)	4 (0.9)	14 (3.1)		11 (2.1)
Abdominal pain	1 (0.2)	4 (0.9)	13 (2.9)		9 (1.7)
Nausea	1 (0.2)	5 (1.1)	5 (1.1)		3 (0.6)
Abdominal pain upper	0	0	5 (1.1)		2 (0.4)
Vomiting	1 (0.2)	2 (0.5)	4 (0.9)		5 (0.9)
Abdominal pain lower	0	0	0		2 (0.4)

However, the sponsor does acknowledge that considering AEs related to drug withdrawal that did not result in study discontinuation, "… there was a numerical treatment imbalance in the number of patients with concurrent non-GI PTs potentially related to opioid withdrawal syndrome as seen in the table below:

Table 5 **Number (%) of patients with a selected GI PT during the treatment period, by category (12-week pool)**

	Placebo (N=444)	Naloxegol 12.5 mg (N=441)	Naloxegol 25 mg (N=446)
Patients with a selected GI PT[a]	62 (14.0)	86 (19.5)	127 (28.5)
Patients with at least 1 of these PTs and:			
≥10% increase from baseline in mean weekly opioid dose within 2 weeks of an event	4 (0.9)	6 (1.4)	12 (2.7)
≥30% increase from baseline in mean weekly opioid dose within 2 weeks of an event	1 (0.2)	4 (0.9)	7 (1.6)
≥2 point increase from baseline in mean weekly NRS average pain at any time during the study	7 (1.6)	9 (2.0)	18 (4.0)
≥2 point increase from baseline in weekly average NRS pain score within 2 weeks of an event	5 (1.1)	4 (0.9)	9 (2.0)
≥3 point increase from baseline in mHS score at any time during the study	4 (0.9)	6 (1.4)	8 (1.8)
≥1 reported PT potentially related to opioid withdrawal syndrome, excluding GI PTs, at any time[b]	10 (2.3)	15 (3.4)	36 (8.1)
≥1 other reported PT potentially related to opioid withdrawal, excluding GI PTs, that started within 2 weeks of the GI PT	6 (1.4)	13 (2.9)	31 (7.0)
≥2 other reported PT potentially related to opioid withdrawal, excluding GI PTs, that started within 2 weeks of the GI PT	0	2 (0.5)	9 (2.0)

The number of patients who also had ≥1 reported non-GI PT potentially related to opioid withdrawal syndrome within 2 weeks of the time of onset of the GI PT was 6/62 in the placebo group, 13/86 in the naloxegol 12.5 mg group, and 31/127 in the naloxegol 25 mg group. The number of patients who also had ≥2 non-GI PTs potentially related to opioid withdrawal syndrome within 2 weeks was 0/62, 2/86, and 9/127, respectively. Of the 9 patients on naloxegol 25 mg, 5 had hyperhidrosis; none had a clinically important change in vital signs or ECG around the time of the events."

In looking at patients experiencing any PT potentially related to withdrawal syndrome, similar trends are note, per the table below:

Table 6 **Number (%) of patients with any PT potentially related to opioid withdrawal syndrome during the treatment period, including selected GI PTs, by category (12-week pool)**

	Placebo (N=444)	Naloxegol 12.5 mg (N=441)	Naloxegol 25 mg (N=446)
Patients with any PT potentially related to opioid withdrawal syndrome, including selected GI PTs[a]	84 (18.9)	106 (24.0)	150 (33.6)
Patients with at least 1 of these PTs and:			
≥10% increase from baseline in mean weekly opioid dose within 2 weeks of an event	6 (1.4)	9 (2.0)	16 (3.6)
≥30% increase from baseline in mean weekly opioid dose within 2 weeks of an event	4 (0.9)	4 (0.9)	8 (1.8)
≥2 point increase from baseline in mean weekly NRS average pain at any time during the study	9 (2.0)	11 (2.5)	21 (4.7)
≥2 point increase from baseline in weekly average NRS pain score within 2 weeks of an event	7 (1.6)	5 (1.1)	11 (2.5)
≥3 point increase from baseline in mHS score at any time during the study	4 (0.9)	6 (1.4)	9 (2.0)
≥1 reported PT potentially related to opioid withdrawal syndrome, excluding GI PTs, at any time[b]	12 (2.7)	17 (3.9)	40 (9.0)
≥1 other reported PT potentially related to opioid withdrawal, excluding GI PTs, that started within 2 weeks of the GI PT	8 (1.8)	14 (3.2)	35 (7.8)
≥2 other reported PT potentially related to opioid withdrawal, excluding GI PTs, that started within 2 weeks of the GI PT	1 (0.2)	2 (0.5)	11 (2.5)

Finally, drilling down on the patients who experienced both a GI PT adverse event and a CV PT adverse event, the absolute numbers are smaller, but again, there are numerically more of these with NGL 25 mg in the 12-week pool, as shown in the table below:

Table 7 **Number (%) of patients with both a selected GI PT and a CV PT during the treatment period (12-week pool)**

	Placebo (N=444)	Naloxegol 12.5 mg (N=441)	Naloxegol 25 mg (N=446)
Patients with a selected GI PT[a]	62 (14.0)	86 (19.5)	127 (28.5)
Patients with at least 1 selected GI PT and:			
A CV PT[b] at any time	5 (1.1)	8 (1.8)	12 (2.7)
A CV PT within 2 weeks of the selected GI PT[c]	2 (0.5)	7 (1.6)	8 (1.8)

Importantly, none of the patients with both a selected GI event and a CV AE had any AE that met diagnostic criteria for major adverse CV events (MACE) [CV death, acute myocardial infarction, or stroke] or other CV events of interest (as defined for the naloxegol Phase III program: hospitalization for unstable angina and heart failure requiring hospitalization) at any time during the study. A listing of the patients having a

CVPT within two weeks of a selected GI PT (plus one additional case that occurred in study 07), are shown in the listing below, along with the cardiac symptoms that were reported:

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Table 8 **List of patients who had both a selected GI PT and a CV PT within 2 weeks (placebo-controlled Studies 04, 05, and 07)**

Treatment group	Patient number	Age/Sex	CV PT (MedDRA PT)	CV PT start/stop dates	Selected GI PT (MedDRA PT)	GI PT start/stop dates
Placebo	E5228020	53/F	Hot flush	Day 17/ongoing	Nausea	Day 3/ongoing
Placebo	E5250015	80/F	Tachycardia	Day 57/Day 78	Abdominal pain	Day 50/Day 55
NGL 12.5 mg	E4019014[a]	45/M	Hypotension	Day 165/Day 169	Diarrhea Abdominal pain	Day 164/Day 167 Day 164/Day 167
NGL 12.5 mg	E4026024	60/M	Hypotension	Day 1/ongoing	Abdominal pain lower	Day 1/Day 2
NGL 12.5 mg	E4056032	37/F	Hypotension Orthostatic hypotension	Day 35/Day 37 Day 35/Day 50	Nausea	Day 35/Day 35
NGL 12.5 mg	E4056042	49/M	Hypertension	Day 2/ongoing	Nausea	Day 2/Day 20
NGL 12.5 mg	E5245017	37/M	Palpitations	Day 6/Day 10	Abdominal pain	Day 6/ongoing
NGL 12.5 mg	E4010007	62/M	Ventricular extrasystoles	Day 1/ongoing	Abdominal pain	Day 7/Day 102
NGL 12.5 mg	E5218011	57/F	Flushing Palpitations	Day 1/Day 8 Day 17/Day 58	Abdominal pain Nausea	Day 1/ongoing Day 6/Day 86
NGL 12.5 mg	E5330001	51/F	Hypertension	Day 18/Day 21	Nausea	Day 9/Day 21
NGL 25 mg	E4089004[b]	49/F	Palpitations	Day 58/Day 58	Nausea	Day 58/Day 58
NGL 25 mg	E5228007	60/M	Hypotension	Day 1/Day 7	Abdominal pain Diarrhea	Day 2/Day 9 Day 5/Day 5
NGL 25 mg	E5237016	69/F	Hypertension	Day 1/Day 96	Abdominal pain	Day 1/Day 83
NGL 25 mg	E5246014	54/M	Hypertension	Day 15/Day 43	Diarrhea Diarrhea	Day 8/Day 10 Day 12/Day 12
NGL 25 mg	E5246022	53/M	Flushing	Day 1/Day 5	Abdominal pain	Day 1/Day 4
NGL 25 mg	E5334001	61/F	Hot flush	Day 2/Day 32	Diarrhea Diarrhea	Day 2/Day 2 Day 14/Day 14
NGL 25 mg	E5209005	61/M	Angina pectoris Angina pectoris	Day 15/Day 15 Day 22/Day 22	Abdominal pain	Day 1/Day 2

Table 8 **List of patients who had both a selected GI PT and a CV PT within 2 weeks (placebo-controlled Studies 04, 05, and 07)**

Treatment group	Patient number	Age/Sex	CV PT (MedDRA PT)	CV PT start/stop dates	Selected GI PT (MedDRA PT)	GI PT start/stop dates
NGL 25 mg	E5526005	45/M	Palpitations	Day 43/Day 43	Diarrhea	Day 54/Day 55

[a] The events for Patient E4019014 were reported in Study 07.

[b] In addition to CV and GI AEs, Patient E4089004 also reported a non-GI PT potentially related to opioid withdrawal syndrome of hyperhidrosis on Day 58 (resolved Day 58).

CV Cardiovascular CV Cardiovascular; GI Gastrointestinal; MedDRA Medical Dictionary for Regulatory Activities; NGL Naloxegol; PT preferred term.

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Reference ID: 3467518

The nature of the CV AEs reported was generally non-serious: 4 AEs related to hypotension, 4 AEs related to hypertension, 4 AEs related to palpitations, 3 AEs related to hot flashes/flushing, 2 AEs of angina (in a single patient), and 1 AE each of the following: orthostatic hypotension and extrasystoles. (There were 19 CV AEs of potential interest reported for the 16 unique patients).

Twelve of these 16 patients did not have an AE that qualified for review by the independent external CV Event Adjudication Committee. Three patients had AEs that were adjudicated but did not meet the criteria for any of the pre-established diagnostic categories, while 1 patient reported an AE that was categorized by the CV Event Adjudication Committee as an 'other chest pain'.

The 4/16 patients with AEs that the sponsor identified that were of greatest potential clinical importance (ie, SAEs, DAEs, or severe events) were summarized as follows:

- E4056032: Reports of mild/moderate intensity DAEs of hypotension/orthostatic hypotension and coincident mild intensity DAE of nausea, reported after over 1 month on study drug. Details from the time of the reported events were not given; possibly confounding is the history of hypertension and treatment with several antihypertensives. The AE of hypotension was sent for CV adjudication but did not meet any of the pre-defined diagnostic categories.

- E5330001: Moderate intensity SAE of symptomatic hypertension coincident with a mild intensity AE of nausea about 3 weeks after randomization. Workup revealed previously unreported hypertensive CV disease in addition to a likely confounding history of hypertension. Note is made of change to antihypertensive regimen shortly before this SAE, which also may be confounding. The AE of hypertension was sent for CV adjudication but did not meet criteria for any of the predefined diagnostic categories.

- E4089004: Multiple coincident transient (1 day duration) AEs (hyperhidrosis, palpitations, nausea, cellulitis, peptic ulcer disease, shortness of breath) and single SAE (non-cardiac chest pain) after about 2 months on study drug; met adjudication criteria for "hospitalization for other chest pain". Past history of non-cardiac chest pain, MI and peptic ulcer disease are likely contributory. Note is made of concomitant methadone. Negative cardiac workup. No pattern suggestive of generalized opioid withdrawal or clinically important changes in vital signs/ECG was noted during the study. The event met adjudication diagnostic criteria for "other chest pain".

- E5209005: 61-year-old male with a history of multiple serious CV risk factors, including ongoing angina, which likely confound assessment of this report. Moderate intensity AE of abdominal pain was reported from study Day 1 to 2, not coincident in time with subsequent AE reports of severe intensity AE of angina

(reported only after 2 more weeks of treatment). The anginal event was sent for CV adjudication but did not meet any pre-defined diagnostic categories.

Study 08 (52-week, Open-label) Withdrawal Adverse Events, alone and with CV Adverse Events

As was seen with the 12-week data, a numerical excess of patients having both GI and CV adverse events was noted in the 52-week study 08, as seen in the table below:

Table 9 Number (%) of patients with both a selected GI AE and a CV AE during the treatment period (Study 08)

	Usual Care (N=270)	Naloxegol 25 m (N=534)
Patients with a selected GI PT during the treatment period[a]	39 (14.4%)	190 (35.6%)
A CV PT[b] at any time	5 (1.9%)	20 (3.7%)
A CV PT within 2 weeks of the selected GI PT[c]	0	8 (1.5%)

A listing of the 8 cases where a patient experienced a CV PT within 2 weeks of a selected GI PT is demonstrated in the listing below:

Table 10 List of patients who had both a selected GI PT and a CV PT within 2 weeks (Study 08)

Treatment group	Patient number	Age/Sex	CV PT (MedDRA PT)	CV PT start/stop dates	Selected GI PT (MedDRA PT)	GI PT start/stop dates
NGL 25 mg	E8705022[a]	49/F	Hot flush	Day 1/Day 29	Abdominal pain upper	Day 1/Day 29
NGL 25 mg	E8731002	55/F	Hypertension	Day 90/ongoing	Nausea	Day 90/Day 90
NGL 25 mg	E8783003	53/M	Flushing Flushing	Day 1/Day 1 Day 3/Day 5	Abdominal pain Abdominal pain	Day 1/Day 1 Day 3/Day 5
NGL 25 mg	E8794027	56/F	Pericardial effusion	Day 190/ongoing	Abdominal pain	Day 190/ongoing
NGL 25 mg	E8886014	47/F	Flushing	Day 16/ongoing	Abdominal pain	Day 16/ongoing
NGL 25 mg	E5267004	48/M	Hypertension	Day 27/Day 64	Abdominal pain	Day 20/Day 25
NGL 25 mg	E8810008[b]	57/M	Hypertension	Day 9/Day 92	Abdominal pain	Day 2/ Day 8
NGL 25 mg	E8921029	61/F	Atrial fibrillation	Day 15/ongoing	Nausea	Day 1/Day 1

Of these 8 patients who had both a CV PT and a selected GI PT within a 2-week period, all eight were taking NGL 25 mg. Within this group, 5/8 had GI and CV events that were directly overlapping in time (ie, coincident). Most of the CV events were reported within about 2 weeks of randomization (5/8 patients) and the sponsor notes "…were confounded by the presence of 1 of more baseline factors in their medical history or presentation (5/8 patients)."

Reviewer's Comment: a history of CV disease is not a confounder when an CV AE occurs. It is exactly this vulnerable population that is of interest when assessing the safety profile of this drug.

The nature of the CV AEs reported was varied and generally non-serious: 4 AEs related to hot flashes/flushing (1 patient experienced flushing on 2 separate occasions), 3 AEs related to hypertension, 1 AE of pericardial effusion, and 1 AE of atrial fibrillation. (There were 9 CV AEs of potential interest reported for the 8 unique patients).

Six of these 8 patients did not have a CV AE that qualified for review by the independent external CV Event Adjudication Committee. The other 2 patients reported an AE that was adjudicated but was not judged to meet criteria for any of the pre-established diagnostic categories.

The 2/8 patients with AEs identified by the sponsor to be of greatest potential clinical importance are discussed briefly below:

- E8731002: Moderate intensity AE of nausea coincident with mild intensity AE of hypertension reported after about 3 months' exposure to study drug. Nausea self-resolved after 1 day while hypertension was ongoing throughout the study. The patient had a documented history of (untreated) hypertension, which may be contributory. The hypertension event was not adjudicated.

  Note is made of a subsequent SAE/DAE of syncope, which occurred much later (Day 249) in the study and in the absence of a GI AE. Past history of hypotension was noted - as well as initiation of lisinopril on Day 161 - both of which were possibly contributory. The syncopal event did not meet any pre-defined adjudication diagnostic category.

- E8921029: 61-year-old female with mild intensity AE of nausea on study Day 1 (self-resolved on the same day), which was not coincident with a subsequent mild DAE/SAE of atrial fibrillation on study Day 15, confirmed by ECG. Multiple baseline CV risk factors were noted. The atrial fibrillation did not meet pre-defined criteria for any adjudication category.

Dec 31, 3013 FDA-Requested Reanalysis of Withdrawal Event and SAEs

On Dec 31, 2013, the sponsor provided a listing of patients experiencing three or more opioid withdrawal term AEs (using an expanded list of PTs*)* who also discontinued from one of the 12-week studies or experienced on SAE. The table below summarizes the patient numbers, study ID, reason for withdrawal or nature of SAE (first digit of patient ID = study number):

ID	Rx	Outcomes and Symptoms (PTs)
E4003034	Plb	Discontinued - abdominal distension, abdominal pain
E4104006	Plb	Discontinued – restlessness, yawning, night sweats, tremor
E4053034	NGL-12.5	SAE - hyperglycemia
E4056009	NGL-12.5	Discontinued – patient decision
E5271006	NGL-12.5	Discontinued - nausea
E5320002	NGL-12.5	Discontinued – abdominal cramping and abdominal pain
E4074011	NGL-25	Discontinued – abdominal pain
E4083001	NGL-25	Discontinued – • Severe: whole body pain, left arm pain, muscle aches, non-cardiac chest pain, sweats • Moderate – narcotics not effective; "treatment not as effective due to the blood brain barrier being crossed"
E4083002	NGL-25	SAE – pyrexia, abdominal pain, sigmoid colitis
E4089004	NGL-25	SAE – non-cardiac chest pain
E5206010	NGL-25	Discontinued – abdominal pain, severe
E5206024	NGL-25	Discontinued – abdominal cramping, nausea, vomiting
E5239005	NGL-25	Discontinued –, diarrhea, watery eyes, cold sweats, tremor, restless
E5241042	NGL-25	Discontinued – abdominal pain, jittery
E5243001	NGL-25	Discontinued – neck/back pain, irritable, same as missing opioids, but had not missed meds
E5267036	NGL-25	Discontinued – drug withdrawal, vomiting, abdominal pain, withdrew after first dose
E5267047	NGL-25	SAE – drug withdrawal, abdominal pain, dehydration - severe

E5283018	NGL-25	SAE – staph wound infection
E5288007	NGL-25	Discontinued – abdominal pain, nausea, vomiting, diarrhea
E5293001	NGL-25	Discontinued – nausea, vomiting, diarrhea

Both in Study 4 and 5 the number of patients with ≥3 PTs potentially related to OWS was higher in the naloxegol 25 mg treatment group compared with placebo (4.7%, 1.9% and 2.3% in Study 4 and 8.6%, 3.0% and 1.3% in Study 5 for the naloxegol 25 mg, 12.5 mg and placebo treatment groups, respectively).

Assessments

Thoughtful consideration of the CV safety of these agents is warranted, given that:

- Immunohistochemical staining demonstrates that mu-, kappa-, and delta- opiod receptors are present in the human heart (Sabanski et al, Heart Vessels Jan 2014, DOI 10.1007/s00380-013-0456-5) .(http://link.springer.com/article/10.1007%2Fs00380-013-0456-5), yet their function(s) in the heart is unknown.
- Mu-opioid antagonism can stimulate smooth muscle contraction and peristalsis in the gut, so it is reasonable to consider whether it might have a similar effect on smooth muscle in coronary artery walls, thereby resulting in a potentially deleterious vasomotor effect on coronary perfusion.
- An imbalance in CV events was observed in alvimopan study SB-767905/14. After going to AC, alvimopan was ultimately approved with a boxed warning and only for short term use in an in-patient setting (via REMS-ETASU).

In addition to a potential direct effect on cardiovascular vasomotor tone, other potential mechanisms by which CV safety could be negatively impacted by these agents include the secondary physiologic stress of peripheral (GI) and/or central withdrawal in patients with a marginal coronary perfusion status and/or important stenotic valvular heart disease. Of relevance to this point are the sponsor's own PK/PD conclusions, that:

- *"NKTR-118 retains the (central) antagonist properties of naloxone, but is significantly less potent than naloxone at reversing morphine analgesia", and*

- *"The ratio ED50 for analgesia reversal and for gastrointestinal transit is about 1.5-fold higher for NKTR-118 than for naloxone."*

The fact that the ratio of the ED_{50} for analgesia reversal and for gastrointestinal transit is only about 1.5-fold higher for NKTR-118 than for naloxone explains the clinical course of subject E4083001, who was prematurely withdrawn from study 04 due to severe whole body pain, left arm pain, muscle aches, non-cardiac chest pain, and sweats, with the

investigator reporting that his/her narcotics were not effective with naloxegol, and that "treatment not as effective due to the blood brain barrier being crossed".

Yet whether these withdrawal effects are completely peripheral or also have some central component is moot – the point is that patients are experiencing GI and non-GI symptoms of withdrawal that likely induce physiologic stress that could be poorly tolerated by a patient with marginal coronary artery perfusion and/or important stenotic valvular heart disease at baseline. In this regard, it is noted that one of the naloxegol-treated subjects who died was a 73 year old who suffered an MI on study Day 16 that led to surgery for aortic valve replacement and coronary artery bypass grafting.

With this background, and following our review of CV safety in NDA 204760, we address your consult questions as follows:

1. **Regarding the requested assessment of whether there appears to be a signal for cardiac adverse events associated with the use of naloxegol (including the type and extent of the signal if present), the following are relevant:**

    - There is no discernable CV safety signal from the preclinical data that we can identify, nor were adverse effects noted on blood pressure or ECG parameters in toxicology studies in dogs up to 200 mg/kg and 500 mg/kg, respectively.

    - No significant QTc prolongation effect of NKTR-118 was detected in the TQT study.

    - There were no important drug-induced changes in mean vital signs or categorical vital sign changes during follow-up, but the confidence intervals of the means were large and widely overlapping.

    - There was no discernable MACE signal in the 12-week studies or in the 52-week open label follow-on study.

    - Syncope occurred in 2 patients on NGL 12.5 in the 12-week pool, and one patient on NGL 25 from the 52-week open-label study, but in no placebo or usual care patients. These could be chance findings, but deem future observation.

    - CV adverse events occurred more frequently on NGL at either dose tested in patients experiencing both a CV PT and a GI PT in the 12-week pool (0.5%, 1.6%, and 1.8% respectively for placebo, NGL 12.5 mg, and NGL 25 mg). However, looking at these cases, most were non-serious reports of hypotension, hypertension, palpitations, or hot flashes/flushing. One patient experienced angina twice, and one patient experienced extrasystoles. This trend was seen once again in the data for study 08, where all 8/8 patients experiencing a GI PT and a CV PT were taking NGL 25 mg. One of these

patients experienced a pericardial effusion and one developed AFib. Taken together, these results suggest that while withdrawal can be associated with CV adverse events, none of those documented involved d ischemic catastrophes in these rather small studies.

- Finally, from of the 20 patients experiencing $\geq$ 3 opioid PTs of withdrawal who also discontinued from the 12-week studies or experienced an SAE, 18 of the 20 were taking NGL at some dose, but none experienced MACE, and none suffered other cardiac events.

In interpreting these findings, it must be kept in mind that ascertainment of a clinical CV safety signal may have been limited by the fact patients who prematurely withdrew were censored and not followed for CV events until the end of the studies (17.8% of the placebo patients, 20.0% of the patients on naloxegol 12.5 mg, and 22.1% of the patients on naloxegol 25 mg withdrew from the blinded studies prematurely). Furthermore, the CEC charter does not appear to be uploaded to the NDA, so it was unclear what if any automated triggers were put in place as a backup to the manual reporting system for adverse events, to assure that all potential MACE outcomes were referred for adjudication to the CEC. Finally, these trials were not designed for the ascertainment of MACE and other CV SAEs.

In conclusion, while no MACE safety signal is identified for this NDA, the resolving power of the trials reviewed to identify cardiac safety concerns is likely limited to at least some degree by the abovementioned design elements.

2. An assessment of whether there is a causal relationship between cardiac events that occurred and opioid withdrawal.

In these small studies, no MACE signal is identified. Whether the other less serious events (e.g. hypotension, hypertension, flushing, palpitations, angina) were primarily caused by naloxegol, or were reactive to abdominal pain caused by the direct GI effects of the drug, cannot be determined.

Other DCaRP Comments/Recommendations

It is unclear what if any relevance that the side effect profile of IV naloxone has to the clinical safety profile of this oral PEGylated derivative. However, given the lack of clinical experience with naloxegol in post-operative patients, it would be reasonable to at least reference the warning about these patients from the IV naloxone label (i.e., that several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest have been reported in postoperative patients treated with IV naloxone).

Appendix 1: Preclinical Toxicology Study Results

7-Day Oral Toxicity Study in Sprague-Dawley Rats (non-GLP study LS-2007-005)

Oral administration of NKTR-118 in Sprague-Dawley rats at the doses used in this study (100, 500, and 1000 mg/kg/day body weight) resulted in reduced body weight and food consumption at 1000 mg/kg/day and some effects on the adrenals and liver at 500 and 1000 mg/kg/day. The NOEL and NOAEL were established to be 100 mg/kg/day by body weight. There were no pre-terminal deaths and no findings reported related to CV safety.

14-Day Oral Toxicity Study in Beagle Dogs (GLP study SL-2007-004)

The dosing strategy for this 14 day oral tox study in Beagle Dogs was as follows (from Table 3, toxicology written summary, page 6):

Table 3: 14-Day Oral Toxicity Study in Beagle Dogs

Group Number	Group Designation	Dose Level (mg/kg/day)	Dose Concentration (mg/mL)	Number of Animals	
				Male	Female
1	Control	0	0	3	3
2	Low Dose	200	50	3	3
3	High Dose	500	125	3	3

Relevant findings from this study with respect to CV safety are as follows:

- Two animals died during this study
- One low dose female (200 mg/kg/day) was sacrificed on Day 1 and one high dose female (500 mg/kg/day) was found dead on Day 9.
- Based on the pathology results the death of the two animals was attributed to incorrect dosing (dose administered to the lung) and was not considered to be related to NKTR-118.
- The sponsor concluded that once daily dosing by oral gavage administration to the Beagle dog at doses of 200 and 500 mg/kg/day over 14 consecutive days was not associated with any dose limiting toxicity. The NOAEL was established to be 500 mg/kg/day.

28-Day Oral Toxicity Study in Sprague-Dawley Rats Followed by a 14-Day Recovery Period (GLP study LS-2007-011)

The study design of this 28/14 day oral tox study in rats was as follows (from Table 4, toxicology written summary, page 7):

Table 4: 28-Day Oral Toxicity Study in Sprague-Dawley Rats

Group Number	Group Designation	Dose Level (mg/kg/day)	Number of Animals	
			Male	Female
G1	Vehicle Control	0	10	10
G2	Low Dose	50	10	10
G3	Mid Dose	150	10	10
G4	High Dose	500	10	10
G1R	Vehicle Control Recovery	0	5	5
G4R	High Dose Recovery	500	5	5
G1TK	Vehicle Control	0	2	2
G2TK	Low Dose	50	9	9
G3TK	Mid Dose	150	9	9
G4TK	High Dose	500	9	9

There were no pre-terminal deaths in this study, and the sponsor reports no significant findings relevant to CV safety. Clinical chemistry analysis showed treatment-related significantly higher cholesterol levels at the mid and high doses (150 and 500 mg/kg/day) in males and at the high dose (500 mg/kg/day) in females and higher triglyceride levels at all the tested doses (50 to 500 mg/kg/day) in males. These cholesterol and triglyceride changes normalized after discontinuation of drug. The NOAEL was identified as 500 mg/kg/day.

<u>14-Day Oral Toxicity Study Followed by a 14-Day Recovery Period in Beagle Dogs (GLP study LS-2005-031)</u>

The design of this 14 day oral tox study in beagle dogs was as follows (from the LS-2005-031 FSR):

Dose Group	No. Animals	Dose Level (mg/kg)	Dose Concentration (mg/mL)	Necropsy
Vehicle Control	3M/3F	0	0	Day 15
Low Dose	3M/3F	25	6.25	Day 15
Mid Dose	3M/3F	75	18.75	Day 15
High Dose	3M/3F	200	50	Day 15

Electrocardiographic (ECG) evaluations found no adverse effects in any treatment groups for either male or female dogs. Blood pressure (BP) values for both male and female dogs were observed to be within normal statistical parameters throughout the study. No target organs of toxicity were identified in this study. The no observed adverse effect level (NOAEL)) for PEG-Naloxegol orally administered once daily for 14 days to male and female Beagle dogs was considered to be ≥ 200 mg/kg.

28-Day Oral Toxicity Study Followed by a 14-Day Recovery Period in Beagle Dogs (GLP study LS-2007-012)

The study design of this 28/14 day oral tox study in beagle dogs was as follows (from Table 5, toxicology written summary, page 8):

Table 5: 28-Day Toxicity Study in Beagle Dogs

Group Number	Group Designation	Dose Level (mg/kg/day)	Main Number of Animals		Recovery Number of Animals	
			Male	Female	Male	Female
1	Vehicle Control	0	4	4	2	2
2	Low Dose	50	4	4	NA	NA
3	Mid Dose	150	4	4	NA	NA
4	High Dose	500	4	4	2	2

This study included ECG acquisitions and respiratory rate assessments. No pre-terminal deaths were reported for this study. There was an increase in heart rate at week 4 that was not thought to be treatment related but rather due to excitement since heart rate changes were also observed in controls. Dogs treated with 500 mg/kg/day had increased depletion of lymphocytes from the thymus. The sponsor concluded that the NOAEL was 150 mg/kg/day.

Toxicokinetics from this 28/14 GLP study in beagle dogs showed:

- NKTR-118 was readily absorbed and reached peak plasma NKTR-118 concentrations within 0.25 hr following oral administration
    - The mean Cmax on Day 1 of dosing was 3109.2, 10735, and 72571 ng/mL in males and 3042.0, 12842, and 62735 ng/mL in females, following 50, 150, and 500 mg/kg/day daily oral NKTR-118 administrations, respectively
    - The mean AUC(0 24 hr) on Day 1 dosing was 3320.0, 12641, and 74102 hr•ng/mL in males and 2717.5, 13724, and 70866 hr•ng/mL in females following 50, 150, and 500 mg/kg/day daily oral NKTR-118 administrations, respectively
    - The increase of mean peak plasma NKTR-118 concentrations with increase in NKTR-118 dose was greater than dose-proportional in both males and females as assessed on Days 1 and 28

    - There was greater than dose-proportional increase in AUC(0-24 hr) when dose was increased in male and female animals on both assessment days
    - There was no plasma NKTR-118 accumulation upon repeated dosing for 28 days
- NKTR-118 was rapidly metabolized to its glucuronide metabolite and peak plasma glucuronide metabolite concentrations appeared in the plasma within 1 hr following oral NKTR-118 administration
    - The mean Cmax on Day 1 dosing was 20419, 67330, and 196350 ng/mL in males and 9544.8, 72275, and 152300 ng/mL in females following 50, 150, and 500 mg/kg/day daily oral NKTR-118 administrations, respectively
    - The mean AUC(0-24 hr) on Day 1 dosing was 24419, 94157, and 430750 hr•ng/mL in males and 13346, 95309, and 321890 hr•ng/mL in females following 50, 150, and 500 mg/kg/day daily oral NKTR-118 administrations, respectively
    - There was greater than dose-proportional increase in mean plasma NKTR-118-Glucuronide Cmax and AUC(0-24 hr) when dose was increased in both male and females on both assessment days
    - Day 28 mean plasma C24 hr values were found to be relatively unchanged when compared to mean plasma C24 hr values observed on Day 1
    - Plasma NKTR-118-Glucuronide accumulation was not observed at any of the doses tested upon repeated oral dosing of oral NKTR-118.

3 Month Oral Dose Ranging Study in Rat (GLP study LS-2007-028)

Five groups of Sprague-Dawley rats, each consisting of 10 males and 10 females, were dosed with NKTR-118 orally, once daily, for at least 94 days. The dose levels were 0 (vehicle control), 50, 400, 600 and 800 mg/kg/day. Additional groups were included for toxicokinetics.

Five unscheduled deaths occurred during the course of the study. Two toxicity males, one given 50 and the other 800 mg/kg/day, were sacrificed in a moribund condition on Days 78 and 60 of the dosing phase, respectively. One toxicokinetic male and female, each given 400 mg/kg/day, were sacrificed in a moribund condition on Days 19 and 78 of the dosing phase. One female given 600 mg/kg/day was sacrificed in a moribund condition on Day 61 of the dosing phase. The moribund condition of these animals and the macroscopic observations were not considered NKTR-118 related.

The sponsor concluded that oral administration of NKTR-118 in Sprague-Dawley rats at 50, 400, 600 and 800 mg/kg/day for 94 days resulted in no test article-related mortalities and no CV-related safety issues.

3 Month Oral Dose Ranging Study in Mice (GLP study LS-2007-056)

Five groups of mice, each consisting of 10 males and 10 females, were dosed with NKTR-118 orally, once daily, for at least 90 days. The dose levels were 0 (vehicle control), 50, 400, 600 and 800 mg/kg/day. Additional groups were included for toxicokinetics.

A total of nine toxicity animals, two males and two females given 800 mg/kg/day and four males and one female given 600 mg/kg/day, were found dead or sacrificed at unscheduled intervals. Four of the unscheduled deaths in toxicity animals were considered attributed to the gavage procedure and not to the test article. The causes of death or moribundity for the other unscheduled mortalities (one male and two females at 800 mg/kg/day and two males at 600 mg/kg/day) were not apparent histologically. All toxicity animals given ≤400 mg/kg/day NKTR-118 survived until the final sacrifice.

Leukocyte and serum protein effects suggested an inflammatory response and were consistent with the microscopic findings indicating increased granulopoiesis in both sexes at ≥400 mg/kg/day, but no organ-specific toxicity or CV safety issues were identified.

6-month +1-month Recovery Oral Toxicity Study in Rat (GLP study LS-2007-040)

Four groups of Sprague-Dawley rats, each consisting of 15 males and 15 females, were dosed with NKTR-118 orally, once daily, for at least 26 weeks. The dose levels were 0 (vehicle control), 50, 200 and 800 mg/kg/day. Additional groups were included for toxicokinetics and to assess recovery at 4 weeks after cessation of dosing.

A total of seven toxicity animals died during the course of the study. None of the deaths were considered test article-related. Two control females, one female given 200 mg/kg/day, and one female given 800 mg/kg/day were found dead shortly after blood collection on Days 23, 86, 23, and 23 of the dosing phase, respectively. These deaths were considered accidental and unrelated to test article administration. Other deaths included one male given 800 mg/kg/day found dead on Day 46 of the dosing phase, one control male found dead on Day 4 of the recovery phase, and one control female found dead on Day 127 of the dosing phase. Additionally, one toxicokinetic female given 50 mg/kg/day was sent to necropsy after the final toxicokinetic blood collection on Day 182 of the dosing phase.

The sponsor concluded that there oral administration of NKTR-118 in Sprague-Dawley rats at 50, 200 and 800 mg/kg/day for 26 weeks resulted in no NKTR-118-related mortalities and there were no CV safety issues.

9-month +1-month Recovery Oral Toxicity Study in Dog (GLP study LS-2007-041)

Four groups of Beagle dogs (Groups 1 to 4), each consisting of 6 males and 6 females, were dosed with NKTR-118 orally, once daily, for at least 39 weeks. The dose levels were 0 (vehicle control), 50, 200 and 500 mg/kg/day. Additional control and high dose animals (four/sex in Groups 1 and 4) were included to assess recovery at 4 weeks after cessation of dosing.

Parameters evaluated included survival, clinical observations, body weight, food consumption, ophthalmic and electrocardiogram examinations, clinical pathology, toxicokinetics of NKTR-118 and NKTR-118-Glucuronide (Day 1 and Weeks 4, 13, 26 and 39), organ weights, and macroscopic and microscopic pathology.

All animals survived until their scheduled sacrifice. There were no effects attributed to NKTR-118 in the body weight, food consumption, ophthalmic or electrocardiographic examination, or macroscopic or microscopic data.

The slightly higher mean cholesterol values observed primarily in the 200 and 500 mg/kg/day animals at most collection intervals during the dosing phase were considered to be an effect of NKTR-118 administration. The cholesterol values decreased in the 500 mg/kg/day dogs by recovery Day 29, indicating the reversibility of the change with cessation of treatment. The increased cholesterol values were of small magnitude, not considered adverse, may have correlated with the liver weights, but lacked a microscopic correlate.

Oral administration of NKTR-118 in Beagle dogs at 50, 200 and 500 mg/kg/day for 39 weeks resulted in adverse clinical signs of tremors, ataxia and hypoactive behavior at 500 mg/kg/day. The NOAEL was considered to be 200 mg/kg/day. Other than the small cholesterol elevations, no other CV safety issues were identified.

Safety Pharmacology and Ongoing Dog Telemetry Study

Cardiovascular endpoints assessed in all dog studies. There were no adverse effects observed on blood pressure and ECG parameters (including heart rate and QTcv, single time-point/registration occasion) in dogs at doses up to 200 mg/kg/day and 500 mg/kg/day, respectively.

Naloxegol had no effect on CV parameters in a rat isolated heart assay or on contractility parameters in a dog isolated myocyte assay at 10 and 100 uM, respectively. Naloxegol was also inactive at human ether-ago-go (hERG) and 7 other cardiac ion channels. The *in vitro*IC50 for hERG inhibition was >300 μM.

In an ongoing dog telemetry study, the sponsor reports that BP, heart rate (HR), left ventricular pressure, lead II ECG, and body temperature were monitored by telemetry in 4 male Beagle dogs for approximately 1 hour pre-dose and up to 20 hours post-dose of

naloxegol (5 mg/kg, 25 mg/kg, 75 mg/kg, and 200 mg/kg). Naloxegol 5 mg/kg had no effect on CV parameters. There was a transient prolongation of PR interval following 25 and 75 mg/kg. At the 3 higher doses, non-dose-related moderate decreases were observed at 0.5 hours post-dose in arterial systolic and diastolic BP (SBP and DBP; maximal effect from -9 to-12% vs vehicle; recovery within 2.5 hours), left ventricular systolic pressure (-7 to -13%; recovery within 2.5 hours), and indices of cardiac myocardial contractility (LVdp/dt+: -19 to 22%) and relaxation (LVdp/dt-: -15 to -19%) (recovery within 4 to 8 hours). HR was increased at ≥75 mg/kg dose (+28%). The maximum increase in HR occurred at different time points compared to the decrease in BP or contractility. No additional effects were noted on ECG parameters or body temperature. In addition, no observable adverse effects were noted in the animals at any dose. The no observed effect level (NOEL) of 5 mg/kg for CV effects corresponds to a maximal plasma drug concentration (Cmax) of 0.152 μmol/L (total), 0.071 μmol/L (unbound), which is approximately equal to the exposure at the maximum dose used in the Phase III studies (25 mg).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PRESTON M DUNNMON
03/09/2014

THOMAS A MARCINIAK
03/10/2014

NORMAN L STOCKBRIDGE
03/10/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204,706 **Applicant: AstraZeneca** **Stamp Date: 16 September 2013**

Drug Name: Naloxegol **NDA/BLA Type: NDA**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: 07-IN-NX003 Study Title: Double-blind, randomized, placebo-controlled, Multiple ascending dose in patients with opioid induced constipation, using naloxegol solution Sample Size: 185 Arms: 5mg, 25 mg, 50mg Location in submission:	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 D3820C000	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

Reference ID: 3397702

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Indication: opioid induced constipation 652 patients were randomized with confirmed OIC and on stable opioid regimen, and received the following treatment: naloxegol 12.5 mg n=217, 25 mg n=218 and placebo n= 217. Treatment duration= 12 weeks Pivotal Study #2 D3820C0005 Indication: opioid induced constipation 700 patients were randomized with confirmed OIC and on stable opioid regimen, and received the following treatment: naloxegol 12.5 mg n=233, 25 mg n=234 and placebo n= 233. Treatment duration = 12 weeks.				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			

[1] For chronically administered drugs, the ICH guidelines recommend ecd 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted

Reference ID: 3397702

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X, see comment			Whether cardiovascular effects should be evaluated pre-marketing is the subject of an upcoming advisory committee meeting regarding this class of drugs
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial	X			

as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Disclosure information?				
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Medical Officer Date

Clinical Team Leader Date

Reference ID: 3397702

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AISHA P JOHNSON
10/29/2013

ANIL K RAJPAL
10/29/2013