

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

**Meeting of the Gastrointestinal Drugs Advisory Committee (GIDAC)
To Evaluate Entereg (Alvimopan) for the Acceleration of Recovery Time to Upper
and Lower Gastrointestinal Recovery Following Partial Large or Small Bowel
Resection Surgery with Primary Anastomosis**

January 23, 2008

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January 23, 2008**

Division of Gastroenterology Products

OVERVIEW

The purpose of this meeting is to obtain advice from the Committee regarding the efficacy and safety of Alvimopan (ENTEREG®) for the proposed indication: “to accelerate the time to upper and lower gastrointestinal (GI) recovery following partial large or small bowel resection surgery with primary anastomosis.” Currently there are no drugs approved for this indication. Post operative ileus is a disorder characterized by temporary impairment of gastrointestinal tract motility; without complete blockage of the GI tract, following abdominal surgery. The proposed dose is 12 mg of alvimopan prior to surgery and twice daily until discharge through 7 post-operative hospital days for a maximum of 15 doses. It is not intended to be used as an outpatient product for this indication.

Efficacy:

Five studies submitted for efficacy in POI were randomized, double-blind, placebo-controlled, parallel-group, multi-center trials in patients who were scheduled to have one of the following surgeries: 1) partial large or small bowel resection (BR) surgery with anastomosis (i.e., surgical connection of two severed parts of the bowel to form a continuous channel); and 2) Total Abdominal Hysterectomy (TAH). Since the efficacy was not demonstrated in the TAH surgery subpopulation in the original NDA submission, the sponsor decided to narrow their proposed indication as described above.

The primary endpoint (GI2) is a composite endpoint defined as the time from the end of surgery to the time of recovery of the upper GI tract (toleration of solid food) and the lower GI tract (first bowel movement). The secondary efficacy endpoints in these studies included 1.) Discharge order written (DOW) and 2.) Ready defined as the time from the end of surgery to the time ready for hospital discharge based solely on the recovery of GI function as determined by the surgeon.

The Agency is interested in the Committee’s impression regarding the clinical meaningfulness of these endpoints. Specifically, what is the minimum time that would be clinically meaningful?

Safety:

A detailed report of the safety data submitted to this NDA is provided in subsequent sections of this background package. The majority of Dr. He’s review focuses on the Safety Database as it relates to patients treated with alvimopan in the POI studies. This

short-term use has not been associated with increased cardiovascular ischemic events, although study patients were not followed to ascertain all cardiovascular events, especially events occurring after hospital discharge.

Alvimopan was being concurrently developed for the treatment of Chronic Opioid Induced Constipation or Bowel Dysfunction (OIC or OBD) by GSK. This patient population was exposed to a lower dose of alvimopan (the most commonly used dose was 0.5 mg bid) for an extended period of time (6-12 months). While the OBD indication has not been submitted for review at this time and is still under development, the safety database was reviewed by GSK and it revealed the following imbalances between alvimopan and placebo in controlled trials: cardiovascular events, bone fractures and neoplasm. Our review focused on these adverse events which are presented in Dr. Dannis' review. The data are presented to inform the review of safety for the proposed indication and are useful in identifying potential issues in the long-term use of this drug. We are interested in the Committee being aware of these data in order to focus the discussion of risk-benefit and the proposed Risk Management Plan for the POI indication only.

Regarding safety, we are interested in the Committee's opinion regarding the short-term use of alvimopan. Are there safety concerns? Will the potential cardiovascular risk be minimized sufficiently by the proposed Risk Management Plan? Can longer term use and outpatient use of alvimopan be prevented by limiting sales by wholesaler to hospitals only? What other aspects of such a plan need to be included? The review of this plan provided by the Office of Surveillance and Epidemiology is included in this package.

Finally, it will be important for the Committee to give the Agency feedback on the overall balance of the risks and benefits as they apply to the proposed POI indication.

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Food and Drug Administration
Center for Drug Evaluation and Research

The Gastrointestinal Drugs Advisory Committee (GIDAC) Meeting

January 23, 2008

BACKGROUND MATERIALS

Clinical Evaluation Part 1: Efficacy and General Safety

Established Name	Alvimopan
(Proposed) Trade Name	ENTEREG [®]
Therapeutic Class	μ-opioid receptor antagonist
Applicant	Adolor Corporation
Formulation	Oral capsule
Application Type	NDA
Submission Number	21-775
Proposed Indication	“To accelerate the time to upper and lower GI recovery following partial large or small bowel resection surgery with primary anastomosis”.
Prepared by	Ruyi He, M.D.
Completion Date	December 19, 2007

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1 EXECUTIVE SUMMARY

1.1 Background

This Briefing Document has been prepared for members of Advisory Committee to discuss the safety and efficacy of the new drug application (NDA) 21-775, Entereg (alvimopan) Capsules, for the proposed indication of acceleration of time to upper and lower gastrointestinal (GI) recovery following partial large or small bowel resection (BR) surgery with primary anastomosis.

Alvimopan is a μ -opioid receptor antagonist (without opioid-receptor agonist activity) that is being investigated for the management of postoperative ileus (POI). POI is a disorder characterized by temporary impairment of gastrointestinal (GI) tract motility — without complete blockage of the GI tract — following surgery.

A New Drug Application (NDA 21-775) for alvimopan capsules was originally submitted on 25 June 2004 for the management of POI with the following proposed indication: “alvimopan is indicated to accelerate time to recovery of gastrointestinal function following major abdominal or complex pelvic surgery”. The FDA took an approvable action on 21 July 2005 because of “insufficient proof of efficacy” of alvimopan for the treatment of POI. The FDA recommended that at least one additional adequate and well-controlled study of alvimopan was needed to support approval for the POI indication. In the original NDA submission, no significant safety issues of alvimopan were identified.

The sponsor submitted a Complete Response to the approvable letter on 09 May 2006. In this second-cycle NDA submission, the sponsor narrowed the proposed indication to alvimopan is indicated “to accelerate the time to upper and lower GI recovery following partial large or small bowel resection surgery with primary anastomosis” because both the sponsor and FDA acknowledged that alvimopan did not demonstrate efficacy in the abdominal hysterectomy subpopulation. To satisfy the deficiencies in their original submission, the sponsor submitted in this second-cycle the results of one additional adequate and well controlled POI study in partial small and partial large bowel resection surgery patients.

In May 2006 (during review of the second-cycle submission), the sponsor informed the FDA of a numerically higher incidence of serious cardiovascular (CV) events (e.g., acute myocardial infarction) in the alvimopan treatment group, compared to the placebo group, in one of their ongoing opioid induced bowel dysfunction (OBD) trials [Study SB-767905/014 (Study 14) — a one-year, placebo-controlled, safety study of alvimopan 0.5 mg BID for the treatment of OBD in opioid-experienced patients with chronic non-cancer pain]. The sponsor submitted six-month interim safety analyses of CV events in Study 14 and additional information surrounding CV events in the POI population. A second approvable action was taken by the FDA on 03 November 2006. The second approvable letter requested final 12-month safety findings including analyses of serious CV events

from Study 14; a risk management plan to minimize the possible CV risk of longer-term alvimopan exposure and off-label use; and a safety update.

The sponsor submitted the second Complete Response (the third cycle submission) to the second Approvable Letter on August 9, 2007. In this submission, a numeric imbalance in reports of neoplasms and bone fractures was noted, with a higher incidence in the alvimopan treatment groups than with placebo. The identification of the imbalance in neoplasms in Study 014 led to an interim analysis of the ongoing extension study in cancer pain (Study 684) which showed more deaths occurring in alvimopan treated patients. In response to these preliminary findings GSK elected to discontinue all ongoing clinical trials of alvimopan. FDA placed the alvimopan development program on clinical hold.

This Briefing Document (Part 1) will focus the assessments of efficacy and general safety of alvimopan in the POI population. The Part 2 of the clinical review will focus discussion of specific serious adverse events (e.g., MI, neoplasms and bone fractures) in both OBD and POI population.

1.2 Summary of Clinical Findings

The phase 3 clinical trials to support the efficacy of alvimopan in the treatment of POI in the bowel resection surgery population included the following five POI trials with 1877 patients in the efficacy database [of which 953 (50.8%) and 924 (49.2%) patients received the 12 mg alvimopan dose (the sponsor's proposed alvimopan dose) and placebo, respectively].

The clinical trials to support the safety of alvimopan in the treatment of POI included nine short-term POI trials (i.e., 7.5 days) with 3975 patients in the safety database [of which 2610 (65.7%) and 1365 (34.3%) patients received alvimopan and placebo, respectively] and six longer-term opioid-induced bowel dysfunction (OBD) trials (i.e., \geq 3 weeks) in OBD patients with 2518 patients in the safety database [of which 1728 (68.6%) and 790 (31.4%) patients received alvimopan and placebo, respectively].

The nine POI trials included five efficacy/safety phase 3 trials i.e., Studies 14CL302, 14CL308, 14CL313, SB-767905/001, and 13CL314 — identified as Studies 302, 308, 313, 001, and 314, respectively); one phase 3 trial with primary safety endpoints (i.e., Study 14CL306 identified as Study 306); and three efficacy/safety phase 2 trials (i.e., Studies 13C206, 13C214, and 13C 213— identified as Studies 206, 214, and 213, respectively).

Study Design of the POI Trials

The five phase 3 efficacy POI trials (i.e., Studies 302, 308, 313, 001, and 314) were randomized, double-blind, placebo-controlled, parallel-group, multi-center trials in patients who were scheduled to have one of the following surgeries: 1) Partial large or

small bowel resection (BR) surgery with anastomosis (i.e., surgical connection of two severed parts of the bowel to form a continuous channel); and 2) Total Abdominal Hysterectomy (i.e., TAH, removal of the entire uterus including the cervix through a large, open abdominal incision).

Since efficacy was not demonstrated in the TAH surgery subpopulation in the original NDA submission, the sponsor decided to narrow their proposed POI indication in this second-cycle and include only the BR surgery population.

All five efficacy trials had the following common design features:

- Patients were randomly assigned to receive alvimopan oral capsules or placebo;
- The initial dose was given preoperatively. Subsequent doses were administered twice a day beginning postoperative day 1 until postoperative day 7 or until hospital discharge;
- Patients who were taking chronic opioids before the surgery were excluded; and
- Patients who were scheduled to have laparoscopic surgery or epidural anesthesia were excluded.

Studies 302, 308, 313, and 314 were conducted in the United States and Canada; whereas, Study 001 was conducted in nine European countries, Australia, and New Zealand.

In the five efficacy studies, the original, pre-specified, primary efficacy endpoint was the time to recovery of both upper and lower GI tract motility following surgery. In the four POI studies submitted in the first-cycle NDA (i.e., 302, 308, 313, and 001) the time to recovery of the upper and lower GI tracts was a **three-component composite endpoint** called **GI3** and in the one POI efficacy study submitted in the second-cycle NDA (i.e., 314) the time to recovery of the upper and lower GI tracts was a **two-component composite endpoint** called **GI2**.

- **GI3** was defined as the time from the end of surgery to the time of recovery of the upper GI tract (toleration of solid food) and the lower GI tract [(the first flatus or the first bowel movement (whichever occurred first)); and
- **GI2** was defined as the time from the end of surgery to the time of recovery of the upper GI tract (toleration of solid food) and the lower GI tract (first bowel movement).

The secondary efficacy endpoints in the five important efficacy studies included the following measurements of the length of hospitalization:

- Discharge order written (**DOW**) was defined as the time from the end of surgery to the time that the hospital discharge order was written; and

- **Ready** was defined as the time from the end of surgery to the time ready for hospital discharge solely based on the recovery of GI function, as determined by the surgeon.

The primary efficacy endpoints were adequate because they evaluated the recovery of both upper and lower GI tract motility following surgery. However, **GI2** evaluates the recovery of GI tract more accurately than **GI3** and therefore is a better POI efficacy endpoint, because the three-component **GI3** endpoint includes the time to flatus, which may be difficult to assess and may not adequately assess the recovery of the lower GI tract. Moreover, **DOW** and **Ready** were the two most important pre-specified secondary endpoints in the four efficacy trials because these endpoints could demonstrate a clinically meaningful benefit — shorter hospitalization.

Efficacy Results of POI Trials

Table 1 delineates the efficacy results of **GI2** in BR surgery patients in the five POI efficacy studies. The hazard ratios (HRs) of **GI2** for the 12 mg alvimopan dose compared to the placebo dose in Studies 302, 308, 313, 001, and 314 were 1.40, 1.37, 1.63, 1.30, and 1.53, respectively. The change in time to achieve **GI2** for the 12 mg alvimopan group compared to the placebo group increased from the 25th to the 50th to the 75th percentiles in all five important POI trials. It is appropriate to assess GI tract recovery at the 75th percentile given the nature of POI in BR patients — these patients are not likely to have GI tract recovery during the initial postoperative period.

Table 1: GI2 in days in BR patients in the POI studies

Study	Treatment Group ¹	N ²	50 th Percentile in days	Change from placebo in days	75 th Percentile in days	Change from placebo in days	Hazard Ratio (95% CI)	p-value ³
302	Placebo	99	4.8	0.7	5.9	0.8	1.40 (1.04-1.89)	0.029
	Alvimopan 12 mg	98	4.1		5.1			
308	Placebo	142	4.9	0.5	6.3	0.9	1.37 (1.06-1.76)	0.017
	Alvimopan 12 mg	139	4.4		5.4			
313	Placebo	142	4.9	0.9	6.3	1.2	1.63 (1.26-2.10)	<0.001
	Alvimopan 12 mg	160	4.0		5.1			
001	Placebo	229	4.0	0.1	5.7	0.8	1.30 (1.07-1.58)	0.008
	Alvimopan 12 mg	238	3.9		4.9			
314	Placebo	312	4.0	0.7	5.5	0.9	1.53 (1.29-1.82)	<0.001
	Alvimopan 12 mg	317	3.3		4.6			

1 The 6 mg alvimopan dose is not shown in Studies 302, 308, 313, and 001 because the proposed alvimopan dose is 12 mg.

2 N is the number of patients in the efficacy database in the BR patients (the TAH patients were not included).

3 The p-value of the results of Study 314 is bolded because GI2 was the pre-specified primary efficacy endpoint. GI2 was not the primary efficacy endpoint in Studies 302, 308, 313, and 001.

The change in days to achieve GI2 at the 75th percentile for the 12 mg alvimopan dose compared to placebo in Studies 302, 308, 313, 001, and 314 were 0.8, 0.9, 1.2, 0.8, and 0.9 days, respectively. Thus, BR surgery patients who received 12 mg of alvimopan had recovery of their GI tract motility about one day earlier than BR surgery patients who received placebo at the 75th percentile.

Table 2 displays the efficacy results of the time to achieve **DOW**, an important measure of hospital discharge, in BR patients in the four U.S. POI efficacy/safety trials. Since there are significant differences in hospital discharge practices in Europe, compared to the United States, the results of **DOW** from the one European POI efficacy/safety trial (i.e., Study 001) was not included in this table. The HRs of **DOW** for the 12 mg alvimopan dose compared to the placebo dose in Studies 302, 308, 313, and 314 were 1.29, 1.56, 1.42, and 1.40, respectively. The change in times to achieve **DOW** at the 75th percentile for the 12 mg alvimopan dose compared to placebo in Studies 302, 308, 313, and 314 were 0.8, 1.2, 1.5, and 1.0 days, respectively. Thus, BR surgery patients who received 12 mg of alvimopan had discharge orders written about one day earlier than BR surgery patients who received placebo at the 75th percentile in the four U.S. trials.

Table 2: DOW in days in BR patients in the U.S. POI studies

Study	Treatment Group	N*	50 th Percentile in days	Change from placebo in days	75 th Percentile in days	Change from placebo in days	Hazard Ratio (95% CI)	p-value
302	Placebo	99	5.6	0.7	6.8	0.8	1.29 (0.98-1.72)	0.084
	Alvimopan 12 mg	98	4.9		6.0			
308	Placebo	142	5.7	0.7	7.2	1.2	1.56 (1.22-1.98)	<0.001
	Alvimopan 12 mg	139	5.0		6.0			
313	Placebo	142	5.6	0.8	7.5	1.5	1.42 (1.12-1.81)	0.004
	Alvimopan 12 mg	160	4.8		6.0			
314	Placebo	312	5.0	0.3	6.9	1.0	1.40 (1.19-1.65)	<0.001
	Alvimopan 12 mg	317	4.7		5.9			

* N is the number of patients in the efficacy database in the BR patients; the TAH patients were not included.

In conclusion, the 12 mg alvimopan treatment, compared to the placebo treatment, demonstrated:

- Reduction in the time to recovery of upper and lower GI tract motility of about one day;
- Reduction in the length of hospital stay of about one day;
- Correlation of the time to GI recovery endpoints and the time to discharge endpoints; and
- Consistency of the positive efficacy results across several studies.

The reduction in time to GI tract recovery will allow earlier enteral feeding and therefore may improve nutrition and immune system function. Additionally, improved GI tract motility may reduce patient discomfort (e.g., less nausea and vomiting). An earlier hospital discharge may reduce the chance of nosocomial infections (e.g., pneumonia, sepsis) and may reduce post-operative complications (e.g., pulmonary embolism, atelectasis).

Safety Summary

POI Trials

The clinical trials to support the safety of alvimopan in the treatment of POI included nine short-term POI trials (i.e., Studies 206, 214, 213, 302, 306, 308, 313, 001, and 314) with 3975 patients [of which 2610 (65.7%) and 1365 (34.3%) patients received alvimopan and placebo, respectively].

In the nine POI trials, the median duration of exposure was six days for the following treatment groups: the 12 mg alvimopan dose, the 6 mg alvimopan dose, and placebo. In these nine POI trials, the total median alvimopan exposure for the entire trial duration was 120, 54, 12, and 0 mg of alvimopan for the 12 mg alvimopan dose, the 6 mg alvimopan dose, the 1-3 mg alvimopan dose, and placebo, respectively.

In the POI safety database, 13 out of 2610 (0.50%) patients died who received alvimopan and 9 out of 1365 (0.66%) patients died who received placebo.

Common adverse events, drug-related common adverse events, and vital sign and laboratory abnormalities were similar in the alvimopan and placebo treatment groups. Nonfatal serious adverse events (SAEs) were numerically lower in the alvimopan treatment groups compared to the placebo groups (i.e., 11.8% and 18.3% of patients had nonfatal SAEs in the alvimopan and placebo groups, respectively). The difference in nonfatal SAEs was mostly due to a lower percentage of POI and small bowel obstruction reported in the alvimopan group compared to the placebo group. Moreover, the proportion of patients with discontinuations due to adverse events (DAEs) was numerically lower in the alvimopan groups compared to the placebo group (i.e., 7.9% and 11.9% of patients had DAEs in the alvimopan and placebo groups, respectively). The difference in DAEs was mostly due to a lower percentage of POI and vomiting adverse events in the alvimopan group compared to placebo.

The incidence of MI as determined both by AE reporting from clinical trials and by Duke Clinical Research Institute (independent blinded adjudication based on patient-level data) was comparable between alvimopan and placebo treatment groups. For detailed analyses of CV events, neoplasm and fracture events in the POI and OBD populations please see Part 2 of the clinical review.

Chronic Opioid-Induced Bowel Dysfunction

The safety data of alvimopan in OBD patients include more than 1800 patients who received alvimopan in eight clinical studies conducted in the US and elsewhere. In the OBD Phase 3 program, the mean duration of opioid use ranged from approximately 4 to 8 years with an

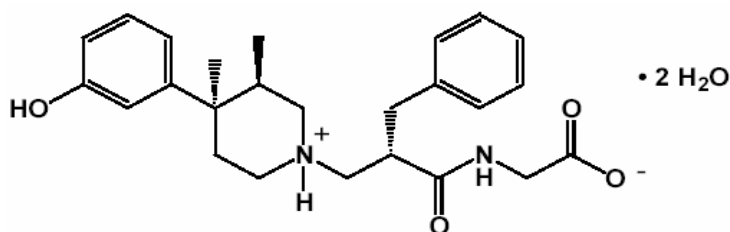
average total daily dose of 108 to > 240 mg morphine equivalents. These opioid-tolerant patients are more sensitive to the effects of alvimopan and therefore low doses have been used in this population (i.e., 0.5 mg BID). In contrast, surgical patients in the POI Phase 3 program were opioid naive and experienced acute postsurgical pain managed with short-term opioid-based IV PCA, with an average total daily dose of 28 mg morphine equivalents; 5- to 10-fold lower than the OBD population. Hence, much higher doses of alvimopan (12 mg BID) are required to antagonize opioid effects on bowel motility in order to shorten the duration of POI.

In May 2006, during the course of the 12-month safety study, Study 014, GSK noted an imbalance of MIs. Following the completion of Study 014 and the unblinding of data in March 2007, the initial analysis of the frequency of AEs by Medical Dictionary for Regulatory Activities (MedDRA) system organ class showed a numerical imbalance in the reports of benign and malignant neoplasms in the alvimopan treatment arm as well as an increase in the incidence of bone fractures compared to placebo. The identification of the imbalance in neoplasms in Study 014 led to an interim analysis of the ongoing extension study in cancer pain (GSK684) which showed more deaths occurring in alvimopan treated patients. For detailed evaluations of MIs, neoplasms, bone fractures and mortality in OBD population, please see Part 2 of the clinical review.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Proposed Trade Name (established name): ENTEREG[®] (alvimopan)



Currently Proposed Indication: To accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis.

Proposed Age Group: Adults

Pharmacologic Class: μ -opioid receptor antagonist

Route of Administration, Description, and Formulation: Oral hard gelatin capsules that are blue and green.

Chemical Class: New molecular entity (NME)

Proposed Treatment Regimen:

Initial dose: Administer one 12 mg alvimopan capsule 0.5 to 5 hours prior to the scheduled start of the surgery on postoperative day (POD) 0.

Next doses: Administer one 12 mg alvimopan capsule BID for a maximum of 7 days (POD 1 to POD 7) while the patient is hospitalized or until discharge from the hospital (whichever is earlier).

Molecular Formula: $\text{C}_{25}\text{H}_{32}\text{N}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$

Chemical Name: [[2(S)-[[4[®]-(3-hydroxyphenyl)-3[®],4-dimethyl-1-piperidiny]methyl]-1-oxo-3-phenylpropyl]amino]acetic acid dihydrate.

2.2 Currently Available Treatment for the Indication

Currently, there are no products that are FDA-approved and marketed in the United States for the treatment of post-operative ileus (POI).

Dexpanthenol (Pandex®, Ilopan®, Panthoderm), a synthetic derivative of pantothenic acid (B complex vitamin), was approved by the FDA in 1948 for the treatment and prevention of adynamic ileus. Currently, this drug product is no longer listed in the orange book and is not marketed in the United States.

Neostigmine (Prostigmin®), a parasympathomimetic agent, was approved by the FDA in 1939 for the treatment or prevention of post-operative non-obstructive abdominal distention (adynamic ileus). Currently, this drug product is no longer listed in the orange book and is not marketed in the United States.

Several FDA-approved drug products are used off-label for the treatment of POI in the United States including metoclopramide (Reglan®), erythromycin, and bethanechol chloride (Urecholine®, Duvoid®).

Availability of Proposed Active Ingredient in the United States

Alvimopan is a new molecular entity (NME) and is not currently marketed in the United States or any other country.

2.3 Presubmission Regulatory Activity

The highlights of the regulatory activity in the United States include the following:

- In August 1998, Adolor Corporation (Adolor) submitted IND# 56,553 for LY246736 Dihydrate, which was renamed to ADL 8-2698 (alvimopan), for the treatment of constipation;
- In March 2001, the DGP and Adolor met for an end-of-phase 2 meeting for the treatment of POI with alvimopan;
- In February 2004, the DGP granted the alvimopan development program (for the treatment of POI) fast track status;
- In February 2004, the DGP and Adolor met for a pre-NDA meeting; and
- In May 2004, the DGP accepted Adolor's proposed plan for the "Pilot 1 Continuous Marketing Application Reviewable Units for Fast Track Products".

2.4 Other Relevant Background Information

Regulatory History during the First-Cycle NDA Review

During the first cycle NDA review process [June 25, 2004 to July 25, 2005 (the PDUFA goal date)] the DGP met with Adolor twice (November 2004 and March 2005).

- In November 2004, the DGP and Adolor met to discuss several issues during the NDA review.

- In the March 2005 meeting between the DGP and Adolor, the DGP stated the following:
 - If “the efficacy benefit of alvimopan can not be demonstrated at the 12 mg dose, it may be difficult to accept the efficacy benefit at the 6 mg dose”;
 - “Study 001 had many similarities with the 3 U.S. efficacy trials including the same complex dosing regimen, the inclusion of the same three doses (placebo, 6 and 12 mg of alvimopan), the same surgical types (BR and rTAH), the same primary endpoint (GI3) and 6 identical secondary endpoints, and the same prohibited medications.” The DGP asked the sponsor to “provide sufficient evidence to demonstrate that differences in regional practices explain the dissimilar results in the trials;”
 - Study 001 (the European POI Study) will be needed for the current NDA review and since Study 001 consisted of a large amount of new clinical data, the study would be a major amendment and therefore, the review clock would be extended from April 25, 2005 to July 25, 2005 (Adolor informed the DGP that Study 001 will be submitted shortly); and
 - The results from the ongoing trial (Study 14CL314) will be needed to complete the evaluation of alvimopan in the treatment of POI.
- On April 8, 2005, Adolor submitted the final study report for Study 001.

Approvable Action of the First-Cycle NDA

On July 7, 2005, an approvable action on the alvimopan NDA for POI was taken. The approvable letter to Adolor stated the following:

1. Provide at least one additional adequate and well-controlled study (in patients scheduled to have partial small or partial large bowel resection) that demonstrates statistically significant superiority of the proposed dosing regimen relative to placebo treatment. The ongoing Study 14CL314 could address this deficiency if statistically superior results for the 12 mg alvimopan dose relative to placebo treatment are demonstrated.
2. Justify the conclusion that the median reduction in time to gastrointestinal recovery relative to placebo treatment would be clinically meaningful to patients undergoing bowel resection surgery, e.g., in terms of shortened hospital stay or other factors.

Post-action Period (after the First Cycle NDA review)

On September 7, 2005, the DGP and Adolor had a post-action meeting to discuss the approvable action on the alvimopan NDA and the DGP had the following comments:

- “Given the design of 14CL314 and experience gained from completed POI trials with similar design, Study 14CL314 appears to be an adequate and well-controlled study from the perspective of population, inclusion and exclusion criteria, sample size, duration, placebo-control, and the primary efficacy endpoint.” However, the DGP was “concerned that the optimum dosing may not yet be established.”

- We expect the label to comment on the results from the gynecologic subpopulation from Studies 302, 306, 308, 313, and 001.

Regulatory History of the Second-Cycle NDA Review

On May 15, 2006, about one week after the second-cycle NDA submission for POI, GlaxoSmithKline (GSK) — Adolor's partner for the OBD indication — informed the DGP that they found a numerical increase in the proportion of patients in Study 14 who developed an acute myocardial infarction (MI) relative to their other alvimopan studies. After an independent GSK Global Safety Board (GSB) determined the need to un-blind Study 14, they discovered six cases of acute MI in the alvimopan arm and no cases of MI in the placebo arm. In addition, GSK stated the following:

- 1) There were no differences in cardiac risk factors between the alvimopan and placebo treatment groups in Study 14;
- 2) The overwhelming majority of patients who had MIs in Study 14 had typical symptoms, EKG changes, and elevated troponins;
- 3) Since there was a 2:1 randomization in Study 14, the actual ratio of MI in the alvimopan arm relative to the placebo arm was 3:0;
- 4) Of the six MIs in Study 14, two occurred at one site in Scotland and two occurred in one site in the United States;
- 5) There were no differences in the baseline CAD risk factors in patients in Study 14 compared to the patients in the other alvimopan OBD studies;
- 6) In their original submission, GSK found that in the phase 2 and phase 3 pooled OBD studies in noncancer patients (Studies 11, 12, 13, and 14) and in cancer patients (Study 8), the rates of MI were 0.63% (11/1760) and 0.37% (3/813) in the alvimopan and placebo treatment groups, respectively. **The relative risk (95% CI) of MI for the alvimopan groups, compared to the placebo group, was 1.69 (0.47-6.05);** and
- 7) Given the increased incidence of MI in the alvimopan groups in the OBD studies, an independent data monitoring committee was established to adjudicate CV cases and establish stopping rules in ongoing Study 14.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

According to Dr. Ramesh Raghavachari, the chemistry reviewer during the first-cycle, "based on the CMC point of view", NDA 21-775 "is recommended for approval." Dr. Raghavachari did not recommend additional phase 4 commitments and according to his review no deficiencies remain in this application.

According to Dr. Ge Zhengfang, the chemistry reviewer for the second-cycle NDA, the new proposed 12 mg alvimopan capsule can be approved provided that the sponsor agrees to certain labeling changes.

3.2 Animal Pharmacology/Toxicology

Please see separate pharmacology/toxicology review for this NDA in this background package.

3.3 Pharmacokinetics

According to Dr. Sue Chih Lee, the pharmacology and biopharmaceutics reviewer, following oral administration to healthy adults, plasma alvimopan concentrations peaked at approximately 2 hours post-dose and thereafter underwent a biphasic decline. No significant accumulation was observed after BID (alvimopan) dosing. The terminal half life ranged from 10 to 14 hours. The pharmacokinetics of alvimopan was approximately linear after single or multiple doses of up to 18 mg and no further increase in exposure was found from 18 mg to 24 mg. Following 12 mg BID (alvimopan) dosing, mean alvimopan C_{max} was 10.98 ± 6.43 ng/mL and mean AUC_{0-12h} was 40.2 ± 22.5 ng*h/mL.”

Alvimopan has one major metabolite (ADL 08-0011). Dr. Sue Chih Lee stated that the concentration “of ADL 08-0011 tended to rise slowly following oral administration of alvimopan capsules. It peaked at approximately 30 hours post-dose, remained relatively constant and then declined rapidly. After 4 ½ days of BID dosing, concentrations of ADL 08-0011 were much higher than those after the first dose but steady state was not reached. The terminal half life ranged from 10 to 18 hours. The AUC of ADL 08-0011 increased less than proportionally with increasing alvimopan doses. Following BID dosing of 12 mg alvimopan for 9 doses, mean ADL 08-0011 C_{max} was 35.73 ± 35.29 ng/mL and mean AUC_{0-12h} was 706.2 ± 789.4 ng*h/mL.”

The absolute bioavailability of alvimopan from oral capsules was 6.0%. Approximately 2% of the administered alvimopan dose is excreted in the urine as the unchanged drug. Renal clearance of alvimopan accounts for approximately 30% of total plasma clearance. Dr. Sue Chih Lee stated that “at this point, there is no evidence that hepatic metabolism is the primary route of alvimopan elimination. Biliary secretion may be important in the elimination of alvimopan; however, there is no direct evidence to confirm this.”

3.4 Pharmacodynamics

Alvimopan is intended to act peripherally (as a μ -opioid-receptor antagonist) without producing significant reversal of the desired, centrally mediated, analgesic effects of opioids. According to Dr. Sue Chih Lee, the “ K_i value for antagonism of [3H]diprenorphine binding to the cloned human μ (opioid) receptors was 0.44 NM for alvimopan and 0.81 NM for ADL 08-0011.”

4 DATA SOURCES

Sources of Clinical Data

The six phase 3 POI trials consisted of four U.S. safety/efficacy trials (14CL302, 14CL308, 14CL313, and 14CL314), one European safety/efficacy trial (SB-767905/001), and one U.S. safety trial (14CL306). Of these six phase 3 POI studies, five (Studies 302, 308, 313, 306, and 001) were originally submitted during the first-cycle NDA submission and one (Study 314) was submitted in the second-cycle NDA. Please see Table 3 for a tabular listing of these important trials.

Table 3: Alvimopan Phase III Studies: the Treatment of POI

STUDY	TITLE	OBJECTIVES	N	TREATMENT GROUPS	DAY(S)
14CL302 (302)	A MC Phase III, DB, PC, Parallel Study of Alvimopan in Opioid-Induced Postoperative Bowel Dysfunction/POI	Demonstrate the effectiveness of alvimopan in the management of POI by accelerating the recovery of GI function in patients undergoing partial colectomy or to TAH (radical or simple).	451	Placebo Alvimopan 6 mg Alvimopan 12 mg	Up to 8 days
14CL306 (306)	A MC, Phase III, DB, PC, Study of Alvimopan in Opioid-induced Postoperative Bowel Dysfunction/POI in Subjects Undergoing sTAH	Demonstrate the safety and tolerability of alvimopan 12 mg administered BID for 7 postoperative days in subjects undergoing sTAH.	519	Placebo Alvimopan 12 mg	Up to 8 days
14CL308 (308)	A MC Phase III, DB, PC, Parallel Study of Alvimopan in Opioid-induced Postoperative Bowel Dysfunction/POI	Demonstrate that alvimopan (6 mg or 12 mg) accelerates recovery of GI function in patients undergoing partial small or large BR with primary anastomosis, rTAH, or sTAH.	666	Placebo Alvimopan 6 mg Alvimopan 12 mg	Up to 8 days
14CL313 (313)	A MC Phase III, DB, PC, Parallel Study of Alvimopan in Opioid-induced Postoperative Bowel Dysfunction/POI	Demonstrate that, in comparison to placebo, alvimopan (6 or 12 mg) accelerates recovery of GI function in patients undergoing partial small or large BR with primary anastomosis or rTAH.	510	Placebo Alvimopan 6 mg Alvimopan 12 mg	Up to 8 days
SB-767905/001 (001)	A MC, R, DB, PC, Parallel Group Study to Evaluate the Efficacy and Safety of 6 and 12 BID Doses of Alvimopan for Treatment of POI in Surgical Subjects.	Determine the efficacy and safety of alvimopan 6 and 12 mg BID for reducing the time to post-operative recovery of GI function in patients undergoing BR. Evaluate the effect of 6 and 12 mg alvimopan on population PK parameters of alvimopan and its main metabolite and health outcomes parameters.	911	Placebo Alvimopan 6 mg Alvimopan 12 mg	Up to 8 days
13CL314 (314)	A Phase 3b, MC, DB, PC, PG Study of Alvimopan for the Management of POI	Demonstrate that alvimopan 12 mg administered 30 to 90 minutes before the scheduled start of surgery and then twice daily until hospital discharge (or for a maximum of 7 days of postoperative treatment) accelerates recovery of GI function in patients undergoing partial small or large BR with primary anastomosis	654	Placebo Alvimopan 12 mg	Up to 8 days

N = number of patients

5 INTEGRATED REVIEW OF EFFICACY

5.1 General Discussion of Endpoints

In the five efficacy studies, the original, pre-specified, primary efficacy endpoint was the time to recovery of both upper and lower GI tract motility following surgery. In the four POI studies submitted in the first-cycle NDA (i.e., 302, 308, 313, and 001) the time to recovery of the upper and lower GI tracts was a **three-component composite endpoint** called **GI3** and in the one POI efficacy study submitted in the second-cycle NDA (i.e., 314) the time to recovery of the upper and lower GI tracts was a **two-component composite endpoint** called **GI2**. **GI2** was an important pre-specified secondary endpoint in Studies 308, 313, and 001 and was a post-hoc endpoint in Study 302.

GI3 was defined as the time from the end of surgery to the time of recovery of the upper GI tract (toleration of solid food) and the lower GI tract [(the first flatus or the first bowel movement (whichever occurred first))].

GI2 was defined as the time from the end of surgery to the time of recovery of the upper GI tract and the lower GI tract. The recovery of the upper GI tract was defined as the time from the end of surgery (the time the last skin staple or suture was placed by the surgeon) to the time of the first toleration of solid food (the time a patient finished meal that required chewing and no significant nausea/vomiting for four hours after the solid meal). The recovery of the lower GI tract was defined as the time from the end of surgery to the first BM.

GI3 may not assess the recovery of the lower GI tract as well as **GI2** because one of the components of **GI3** (assessment of the first flatus) is unreliable. Patients and investigators may not know if patients had flatus during the night; whereas, patients and investigators are more likely to accurately record the time of the first BM.

Secondary endpoints: In Study 314, one of the POI studies, secondary endpoints were the following:

- 1) Time to Ready;
- 2) Time to GI3;
- 3) Time to BM;
- 4) Time to DOW;
- 5) Time to Departure;
- 6) The proportion of GI2 responders* by PSD 3, 4, 5, 6, 7, and 8;
- 7) The proportion of Ready responders* by PSD 3, 4, 5, 6, 7, and 8;
- 8) The proportion of GI3 responders* by PSD 3, 4, 5, 6, 7, and 8;
- 9) The proportion of BM responders* by PSD 3, 4, 5, 6, 7, and 8;
- 10) The proportion of DOW responders* by PSD 3, 4, 5, 6, 7, and 8;
- 11) The proportion of Departure responders* by PSD 3, 4, 5, 6, 7, and 8; and
- 12) The proportion of patients with postoperative NGT insertion.

Responders were defined as patients who achieved the event by the cut-off point and subsequently did not have a prolongation of their hospitalization due to prolonged POI (e.g., POI, paralytic ileus, small intestinal obstruction) or was not readmitted to the hospital for POI (e.g., POI, paralytic ileus, small intestinal obstruction) within seven days of hospital discharge.

Ready and **DOW** were the most important secondary endpoints because these objective endpoints assess a clinically important outcome — reduction in the duration of hospital stay following abdominal surgery. Treatments that demonstrate a reduction in time to **Ready** and **DOW** improve a “serious” aspect (prolongation of hospitalization) of a “serious” disease (POI). We would expect therapies that demonstrate reduction of time to GI recovery also demonstrate reduction of time to discharge.

The duration of hospitalization is better represented by the endpoint **DOW** than the time from surgery to the time that the patient actually leaves the hospital (**Departure**). The latter endpoint may be influenced by transportation difficulties or social issues; rather, than medical problems.

5.2 Study Design

This section details the study design of Study 314. The study design of Studies 302, 308, 313, and 001 were very similar to Study 314.

Title for Study 314: “A Phase 3b, Multi-center, Double-Blind, Placebo-Controlled, Parallel Study of Alvimopan for the Management of Postoperative Ileus”

Study 314 is a randomized, double-blind, placebo-controlled, multi-center (55 sites), parallel, phase III trial of alvimopan in the treatment of POI in patients undergoing partial small or large BR with primary anastomosis in the United States. Patients were randomized in a 1:1 ratio to receive either 12 mg of alvimopan capsules or placebo capsules by mouth with a sip of water at 0.5 to 1.5 hours prior to the scheduled start of surgery and then twice daily beginning post-operative day (POD) 1 until hospital discharge or for a maximum of 7 days of postoperative treatment (until POD 7).

POD was based on a calendar day. POD 0 was the date when a patient had his/her surgery regardless of when the surgery was completed and POD 1 was the next calendar date. In contrast, the post-surgery day (PSD) was the 24-hour period after the end of surgery.

All of the major POI studies (i.e., Studies 302, 308, 313, 001, and 314) were similarly designed: they were randomized, double-blinded, placebo-controlled, multi-centered, parallel-group, phase 3 studies in surgery patients. In all of these studies, patients received the initial study medication prior to the scheduled surgery time and then received BID dosing up until POD 7 or until hospital discharge. Table 4 displays the differences in the study designs of Study 314 compared to the other POI studies (i.e., Studies 302, 308, 313, and 001).

Table 4: Designs differences between Study 314 and the other POI efficacy studies (i.e., Studies 302, 308, 313, and 001)

	Study 314	Studies 302, 308, 313, and 001
Timing of initial study dose	0.5 to 1.5 hours before the start of the scheduled surgery	At least 2 hours before the start of the scheduled surgery
Primary efficacy endpoint	GI2	GI3
Study treatments	Alvimopan 12 mg Placebo	Alvimopan 12 mg Alvimopan 6 mg Placebo
Study population	Only bowel resection surgery	Bowel resection surgery and TAH
Opioid use prior to the study	Were currently taking opioid analgesics or had taken more than 3 doses of opioids within 7 days before the day of surgery	Were currently taking opioid analgesics or had taken opioid analgesics within the previous 2 weeks, excluding a one-time parenteral opioid administered at the time of colonoscopy;

Reference: Adapted from Final Study Report for Study 314

Studies 302, 308, 313, and 314 were performed in the United States and Canada; in contrast Study 001 was performed in Europe, Australia, and New Zealand. Studies 302, 308, 313, and 314 were sponsored by Adolor Corporation; whereas, Study 001 was sponsored by GSK.

Eligibility Criteria of Study 314:

Overall, Study 314 had similar eligibility criteria as the other major POI studies (Studies 302, 308, 313, and 001). All five studies enrolled patients who were scheduled to have laparotomies and excluded patients who were taking significant amounts of opioids prior to their surgeries. Moreover, all of the studies excluded patients who were scheduled to have colectomies, ileostomies, or colostomies.

The main difference in the eligibility criteria of the five major POI studies was in the selection of the surgical types allowed. The sponsor's first four POI studies included both the GI and gynecology surgery populations. Study 302 included three surgical types (sTAH, rTAH, and large BR); Study 308 included all four surgical types (sTAH, rTAH, small BR, and large BR patients); and Study 313 included three surgical types (rTAH, small BR, and large BR). The sponsor's fourth POI study, Study 001, originally included three surgical types (rTAH, small BR, and large BR); however, after amendment #2, Study 001 enrolled only GI surgery patients (i.e., small BR and large BR). Study 314, the sponsor's fifth major study, included only GI surgery patients (i.e., small BR and large BR). Since no efficacy of alvimopan was seen in the gynecologic surgery population, the sponsor decided to focus only on the GI surgery population in the middle of Study 001 and in Study 314.

Table 5 displays the eligibility criteria of Study 314.

Table 5: Eligibility criteria of Study 314

<p>Inclusion Criteria: To be eligible to participate in the study, patients had to have met the following criteria:</p> <ul style="list-style-type: none"> ➤ Male or female and at least 18 years old; ➤ Had an American Society of Anesthesiologists (ASA) Physical Status Score of I-III; ➤ Were scheduled to undergo partial small or large BR with primary anastomosis (performed completely by laparotomy); ➤ Were scheduled to receive postoperative pain management primarily with intravenous patient-controlled analgesia (PCA) opioids; ➤ Were scheduled to have the NGT removed before the first postoperative dose of study medication on POD 1; and ➤ Understood the procedures, agreed to participate in the study program, and voluntarily signed the informed consent form. 	<p>Exclusion Criteria: If patients had the following conditions, they were not eligible to participate in the study:</p> <ul style="list-style-type: none"> ➤ Were currently taking opioid analgesics or had taken more than three doses of opioids within seven days before the day of surgery; ➤ Had complete bowel obstruction; ➤ Were scheduled for a total colectomy, ileal pouch-anal anastomosis, colostomy, ileostomy, any laparoscopic or laparoscopically-assisted procedure, or had a history of gastrectomy, gastric bypass, total colectomy, short bowel syndrome, or multiple previous abdominal surgeries performed by laparotomy; ➤ Had participated in another clinical drug trial within the last 30 days; ➤ Had clinically significant laboratory abnormalities on screening; ➤ Had used illicit drugs or had abused alcohol; ➤ Had a history of surgeries, illness, or behavior (e.g., depression, psychosis) that in the opinion of the investigator might confound the results of the study or pose an additional risk in participating in the study; or ➤ Women who were pregnant (identified by a positive urine test) or lactating, and women who were not postmenopausal least 1 year) and were of childbearing potential and not using method of birth control (i.e., surgical sterilization; intrauterine device; oral contraceptive; diaphragm or condom in combination contraceptive cream, jelly, or foam; or abstinence).
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Reference: Adapted from Clinical Study Report for Study 314, pages 34-36.

Study 302 differed from the other four POI studies because Study 302 excluded patients over 80 years old; patients with Crohn's disease or ulcerative colitis; and patients who were expected to use NSAIDs.

Study 001 differed from the other three studies because Study 001 included patients scheduled to receive postoperative opioids by intravenous patient controlled analgesia (PCA) or intravenous or intramuscular bolus administration by the nursing staff. In contrast, the four U.S. POI studies (i.e., Studies 302, 308, 313, and 314) included patients who were scheduled to receive postoperative opioids only by PCA.

Drugs used in Study 314: Patients were randomly assigned (1:1) to receive 12 mg of alvimopan capsules or identical placebo capsules, given by mouth with a sip of water 0.5 to 1.5 hours prior to the scheduled start of surgery and then twice daily (BID) beginning POD 1

until hospital discharge or until POD 7. For each placebo dose, patients received two placebo capsules. For each 12 mg alvimopan dose, patients received two 6 mg alvimopan capsules. Study medication was intended solely for inpatient hospital administration and was not given to the patients on hospital discharge.

Selection of the dose in Study 314: In Study 314, the sponsor selected the highest doses used in the completed phase 3 trials (the 12 mg dose) because the top two doses in the phase 3 trials (6 mg and 12 mg) appeared equally efficacious in the recovery of upper and lower GI tract motility and the 12 mg alvimopan dose demonstrated no concerning safety signal in the phase 3 trials.

Selection of the dosage regimen in Study 314: The sponsor argued that the initial dose (given 0.5 to 1.5 hours prior to the scheduled surgery) would maximize the efficacy of alvimopan because maximum concentrations of alvimopan would be present in the colonic lumen prior the administration of exogenous opioids during surgery.

The sponsor changed the timing of the initial dose in Study 314 (given 0.5 to 1.5 hours prior to the scheduled surgery) from the timing of the initial dose in the other POI studies (given at least 2 hours prior to the scheduled surgery). The sponsor felt that the new preoperative dosing window was aligned with the timing of administration of routine oral preoperative medications.

The complex dosage regimen (first dose prior to surgery and then a dose BID from POD 1 to POD 7 or until hospital discharge or study termination) was very similar in all five major efficacy phase 3 studies (302, 308, 313, 001, and 314) and all three phase 2 trials (13C206, 13C213, 13C214).

Screening Phase in Study 314: The Screening Phase was Day -30 to Day 0. Within 30 days prior to the study start date, potential patients were evaluated to determine whether they fulfilled entry requirements. In addition, the investigator discussed with patients the nature of the study, its requirements, risks, and restrictions, to obtain informed consent for participation in the study. Patients had physical examinations, vital sign assessments, and laboratory testing during screening.

Schedule of Procedures and Evaluations in Study 314: See Table 6 for a list of the procedures and evaluations during Study 314.

Table 6: Schedule of Procedures and Evaluations in Study 314

Procedure	Screening (Day -30 to 0)	Surgery (Day 0)		POD 1 to 10 ^a	Hospital Discharge or Study Termination	Follow-up Contact ^b
		Pre- surgery	Post- surgery			
Consent	X					
Entry criteria or study eligibility	X	X	X			
Medical history	X	X				
Medication history ^c or concomitant medications	X	X	X	X	X	X
Pregnancy test ^d		X				
Physical examination ^e	X				X	
Vital signs ^f	X				X	
Hematology, serum chemistry, BLTs ^g	X				X	
Administration of study medication ^h		X		X		
Record of scheduled surgery (OR time)		X				
Record of dosing time of 1st preoperative opioid		X				
Record of arrival time to OR		X				
Record of surgery start time and stop time			X			
Record of recovery room start time and stop time			X			
Occurrence of the following events:						
First bowel movement, first time tolerating solids, first flatus				X	X	
Ready for hospital discharge based solely on GI recovery				X		
Hospital discharge order written					X	
Hospital departure					X	
QOL questionnaires ⁱ	X			X	X	
Monitoring of AEs			X	X	X	X

AEs = adverse events, BLTs = biochemical liver tests, GI=gastrointestinal, OR = operating room, POD = postoperative day, QOL = quality of life.

a Assessments were performed mornings and afternoons during hospitalization or for a maximum of 10 PODs while the patient was hospitalized.

b Patients were contacted for follow-up via telephone (or visited, if still hospitalized) 10 to 14 days after the last dose of study medication.

c Medications taken within 14 days of surgery were recorded on the case report form.

d The pregnancy test had to be performed before administration of study medication.

e Physical examinations included measurement of weight; height was measured at the screening visit only.

f Vital signs included blood pressure, heart rate, respiratory rate, and temperature; they were captured once during screening and once at hospital discharge (or study termination).

g Hospital discharge (or study termination) blood samples were obtained at hospital discharge (or study termination) or within 7 days after hospital discharge (or study termination).

h Study medication was administered 30 to 90 minutes before the scheduled start of surgery, then twice daily beginning on POD 1 until hospital discharge or for a maximum of 7 days of postoperative treatment.

i QOL questionnaires were completed as follows: the Gastrointestinal Quality of Life Index was completed once during screening and on PODs 14 and 28; the SF-8 survey and the Cleveland Global Quality of Life Questionnaire were completed once during screening, on POD 2, on POD 5 or at hospital discharge (whichever occurred first), and on PODs 14 and 28; and the Adolor-Inflexxion Recovery Index was completed on POD 2, on POD 5, or at hospital discharge (whichever occurred first), and on PODs 14 and 28.

Reference: Adapted from Clinical Study Report for Study 314, page 41.

Day of Surgery in Study 314: The day of surgery is also identified as POD 0. The patients were randomly assigned to receive 12 mg of oral alvimopan or matching placebo capsules by mouth with a sip of water 0.5 to 1.5 hours prior to the scheduled start of surgery. All other care was determined by the usual surgical routine.

The duration of surgery and the duration of stay in the recovery room were recorded. The surgery start and stop time were defined as the time when the initial incision was made and the time the last suture or staple was placed, respectively. Naso-gastric tubes (NGTs) were to be removed at the end of surgery or no later than the morning of POD 1 (before administration of the study treatment on POD 1).

POD 1 to POD 7 in Study 314: Patients received 12 mg of alvimopan or placebo BID by mouth beginning on POD 1 and continuing until hospital discharge or for a maximum of 7 days of postoperative treatment (while the patient was hospitalized). Patients received routine postoperative care. Patients were encouraged to ambulate the morning of POD 1. Diet was advanced as follows: a liquid diet was offered by the morning of POD 1 and solid food was offered by POD 2 (unless the diet advancement was not warranted by the patient's condition). It was expected that patients would not be discharged until they were able to tolerate solid food (any food that required chewing). A patient was considered to have tolerated solid food if he/she ate most of the meal and did not experience significant nausea and/or vomiting within 4 hours. Successful eating of solid food was recorded four hours after the solid meal was eaten.

Twice a day, the patients were questioned regarding the presence of flatus, the occurrence of BMs, and the tolerability of solid food. In conjunction with the coordinator's assessment, the coordinator reviewed the patient's progress notes to determine the occurrence of GI endpoints documented by hospital staff.

Total daily opioid consumption was recorded upon discharge from the recovery room PODs 1-10, while the patient was hospitalized. The SF-8, CGQL, and Adolor-Inflexxion Questionnaire were administered on POD 2 and POD 5.

The five efficacy phase 3 trials (i.e., Studies 302, 308, 313, 001, and 314) had very similar evaluations and procedures. In all five POI efficacy studies, the last possible day of receiving study treatment was POD 7. In the four U.S. POI efficacy studies (i.e., Studies 302, 308, 313, and 314), the last possible study day was POD 10; in contrast, in the European trial (Study 001), the last possible study day was POD 14.

Discharge/Termination in Study 314: The patients had physical examinations, vital sign measurements, and laboratory testing at hospital discharge or study termination. In addition, GI recovery would be assessed (e.g., flatus, BM, and tolerance of solid food).

Post-Treatment Period in Study 314: If patients were discharged from the hospital, then investigators telephoned patients within 10 to 14 days after the last dose of study medication regarding the use of concomitant medications and AEs. If patients were not reached after three attempts, a certified letter would be sent to the patient.

If patients remained in the hospital then investigators visited them within 10 to 14 days after the last dose of study medication to record concomitant medications and assess AEs. On POD 14 and POD 28, patients would complete the four QOL questionnaires.

The post-treatment follow-up was similar in the five phase 3 efficacy studies. Outpatients were called 5-7 days (or 10-14 days in Study 314) after the last dose of study medication for AE assessments.

In all five studies no follow-up physical exam, ECG, or laboratory test was performed on these outpatients. Since alvimopan's primary metabolite has a long half-life (i.e., 10 to 18 hours) a safety follow-up visit several days after the last alvimopan dose would be useful.

Statistical Methods in Study 314:

- 1) Randomized: All patients who were assigned a randomization number (patients may have or may not have received any study medication);
- 2) Treated: All patients who received at least one study dose;
- 3) Safety: All Treated patients who have any safety evaluation data. This safety population will be used for all safety analyses.
- 4) Modified Intent-to-Treat (MITT): All Treated patients who had the protocol-specified surgery (partial large or small BR) and who had at least one assessment after surgery for BM or tolerability of solids. The MITT population will be the primary population for the efficacy analyses; and
- 5) Efficacy Evaluable (EE): All MITT patients who did not have any major protocol violations.

The MITT population appropriately excluded patients who did not have the protocol-specified surgery (e.g., patients who were not likely to develop POI such as patients who had laparoscopic gallbladder surgery). Additionally, the MITT population appropriately excluded patients who had an ileostomy or a colostomy because BMs (one of the two components of the primary efficacy endpoint) may be difficult to measure in these patients.

For the primary efficacy endpoint, the null hypothesis was that there is was no difference between the alvimopan 12 mg group and the placebo group in GI2 during the 10 day study period. The primary analysis was based on the Cox proportional hazard model. The output from this primary analysis was the hazard ratio (HR) for the 12 mg alvimopan treatment in comparison with the placebo treatment, with corresponding 95% confidence intervals (CIs). The p-value for comparison between the two treatment groups was calculated using the Wald Chi-square test. The cumulative proportions of all patients reaching each event following surgery was plotted as a function of time by using both the Kaplan-Meier product limit method and the Cox proportional hazard model. For the secondary endpoints, the treatment effect on continuous variables was analyzed using an analysis of variance (ANOVA) if normally distributed or the Wilcoxon rank sum test if not normally distributed. Treatment effect on categorical variables was analyzed using logistic regression if sufficient data was available or the Fisher's exact test if sufficient data was not available.

All four phase 3 efficacy trials had similar statistical analysis plans for the primary efficacy endpoint. The sponsor did not include multiplicity adjustments for the numerous secondary endpoints.

5.3 Patients Characteristics

Disposition of patients: In the five important POI efficacy studies, 953 and 942 BR patients were part of the MITT population for the 12 mg alvimopan and placebo treatment groups, respectively (see Table 7).

Table 7: Disposition of BR patients in the five major POI studies

Study	Treatment Groups*	Total number of BR patients
302	Placebo	99
	12 mg alvimopan	98
308	Placebo	142
	12 mg alvimopan	139
313	Placebo	142
	12 mg alvimopan	160
001	Placebo	229
	12 mg alvimopan	239
314	Placebo	312
	12 mg alvimopan	317
Total	Placebo	924
	12 mg alvimopan	953
All BR efficacy patients		1877

Reference: Adapted from Study 314 Final Study Report, ISE, Table 4, Page 19.

The gynecologic surgery patients in Studies 302, 308, 313, and 001 are not included in Table 7 because the sponsor did not desire approval of alvimopan for this population. Study 314 did not include any gynecologic surgery patients. Furthermore, MITT patients who received the 6 mg alvimopan dose in Studies 302, 308, 313, and 001 are not included in Table 7 because the sponsor did not desire approval of this dosage regimen. Study 314 did not have a 6 mg alvimopan dose.

Study 314 contained a large number of BR patients and represents a significant proportion of the overall MITT population (the primary statistical efficacy population). In fact, 33.3% of the patients who received the 12 mg alvimopan dose in the BR population were in Study 314.

Demographics: Table 8 features baseline demographics (including age, race, gender, and BMI) and baseline characteristics of the BR population in the five important POI studies. In these five important POI studies, the mean ages, the proportion of men and women, the race distribution, and BMI of patients in the two treatment groups were similar. Study 001 (the European, Australian, and New Zealand study) had a higher percentage of Caucasians compared to the four U.S. and Canadian studies. In addition, patients in Study 001 had a lower mean BMI than the U.S. and Canadian studies.

Table 8: Demographics of the BR population in Studies 302, 308, 313, 001, and 314

Characteristic	Study 14CL302		Study 14CL308		Study 14CL313		Study 14CL314		Study GSK001	
	Placebo	12 mg	Placebo	12 mg	Placebo	12 mg	Placebo	12 mg	Placebo	12 mg
Total BR MITT subjects	99	98	142	139	142	160	312	317	229	239
Age										
Mean (SD)	63.0 (11.41)	60.4 (14.01)	59.7 (16.32)	61.3 (14.72)	61.4 (14.21)	61.3 (15.07)	59.5 (13.73)	60.2 (14.50)	63.8 (12.04)	64.0 (13.21)
≥ 65 Years, n (%)	45 (45.5)	38 (38.8)	60 (42.3)	65 (46.8)	65 (45.8)	79 (49.4)	121 (38.8)	126 (39.7)	117 (51.1)	129 (54.0)
≥ 75 Years, n (%)	18 (18.2)	19 (19.4)	28 (19.7)	25 (18.0)	28 (19.7)	30 (18.8)	45 (14.4)	46 (14.5)	41 (17.9)	55 (23.0)
Race										
Asian, n (%)	1 (1.0)	0	3 (2.1)	0	0	2 (1.3)	4 (1.3)	5 (1.6)	0	0
Black, n (%)	9 (9.1)	15 (15.3)	18 (12.7)	16 (11.5)	13 (9.2)	13 (8.1)	27 (8.7)	33 (10.4)	0	1 (0.4)
Caucasian, n (%)	89 (89.9)	80 (81.6)	110 (77.5)	113 (81.3)	125 (88.0)	142 (88.8)	265 (84.9)	264 (83.3)	226 (98.7)	236 (98.7)
Hispanic, n (%)	0	3 (3.1)	11 (7.7)	9 (6.5)	3 (2.1)	3 (1.9)	14 (4.5)	14 (4.4)	0	0
Other, n (%)	0	0	0	1 (0.7)	1 (0.7)	0	2 (0.6)	1 (0.3)	3 (1.3)	2 (0.8)
Gender										
Female, n (%)	57 (57.6)	51 (52.0)	71 (50.0)	66 (47.5)	72 (50.7)	83 (51.9)	162 (51.9)	158 (49.8)	104 (45.4)	106 (44.4)
Male, n (%)	42 (42.4)	47 (48.0)	71 (50.0)	73 (52.5)	70 (49.3)	77 (48.1)	150 (48.1)	159 (50.2)	125 (54.6)	133 (55.6)
BMI (kg/m ²)										
n	99	97	142	139	140	157	309	314	225	231
Mean (SD)	28.1 (5.59)	28.3 (5.94)	27.9 (6.89)	27.1 (5.28)	28.6 (6.15)	27.1 (5.56)	28.8 (6.07)	28.0 (6.48)	26.7 (4.61)	26.4 (4.39)
Median	26.6	27.0	26.3	26.8	27.3	26.6	28.0	27.0	26.3	26.0
(min-max)	(17.7-47.0)	(18.4-47.5)	(17.6-67.0)	(17.9-52.5)	(16.8-49.6)	(13.8-45.9)	(17.5-57.0)	(14.2-60.9)	(15.4-46.5)	(14.7-40.4)
< 30 kg/m ² , n (%)	64 (64.6)	64 (65.3)	103 (72.5)	105 (75.5)	94 (66.2)	120 (75.0)	198 (63.5)	215 (67.8)	186 (81.2)	187 (78.2)
≥ 30 kg/m ² , n (%)	35 (35.4)	33 (33.7)	39 (27.5)	34 (24.5)	46 (32.4)	37 (23.1)	111 (35.6)	99 (31.2)	39 (17.0)	44 (18.4)

Reference: Final Study Report for Study 314, ISE, Table 5, Page 21

The racial diversity of the four POI studies in the United States and Canada (Studies 302, 308, 313, and 314) was similar to the racial diversity of the United States; except that the study populations had a lower percentage of Hispanics and a higher percentage of Caucasians. The higher percentage of Caucasian patients in the European, Australian, and New Zealand study (Study 001) probably reflects the baseline racial mixture of these countries.

In addition, the lower BMI of the patients in Study 001, compared to the U.S. and Canadian studies reflects the patient populations in those countries.

The BR subpopulation in Studies 302, 308, 313, and 001 had a lower proportion of female patients compared to the proportion of female patients in entire study population (gynecologic and BR surgery patients). This result is expected since all of the gynecologic surgery patients are female; whereas, the BR patients are female and male.

Surgery characteristics: Table 9 presents the number and proportion of patients who had left large BR, right large bowel, other large bowel, and small bowel resection surgery. Of the 1877 BR surgery patients in the MITT population, 136 (7.2%) and 1741 (92.8%) had small BR and large BR surgery, respectively. The proportion of patients that had large and small BR surgery and the overall surgery duration was similar for each treatment group in the five important POI studies.

Table 9 delineates the time between the first alvimopan dose and the start of surgery. All of the five POI studies display a similar time for both treatment groups. Study 314 had the shortest time between alvimopan dosing and surgery start time.

Table 9: Surgery characteristics for the MITT BR population in the POI studies

Characteristic	Study 14CL302		Study 14CL308		Study 14CL313		Study 14CL314		Study GSK001*	
	Placebo	12 mg	Placebo	12 mg	Placebo	12 mg	Placebo	12 mg	Placebo	12 mg
Total MITT subjects	99	98	142	139	142	160	312	317	229	239
Surgery category, n (%)										
Small BR	NA	NA	16 (11.3)	11 (7.9)	12 (8.5)	23 (14.4)	22 (7.1)	31 (9.8)	12 (5.2)	9 (3.8)
Large BR	99 (100.0)	98 (100.0)	126 (88.7)	128 (92.1)	130 (91.5)	137 (85.6)	290 (92.9)	286 (90.2)	217 (94.8)	230 (96.2)
Left	48 (48.5)	52 (53.1)	77 (54.2)	78 (56.1)	81 (57.0)	80 (50.0)	185 (59.3)	174 (54.9)	99 (43.2)	112 (46.9)
Right	51 (51.5)	46 (46.9)	49 (34.5)	50 (36.0)	49 (34.5)	57 (35.6)	105 (33.7)	112 (35.3)	80 (34.9)	87 (36.4)
Other	0	0	0	0	0	0	0	0	38 (16.6)*	31 (13.0)*
Overall surgery duration (hours)										
n	99	98	142	139	142	160	312	317	229	238
Mean (SD)	2.0 (0.89)	2.0 (1.10)	2.5 (1.26)	2.5 (1.15)	2.2 (1.14)	2.1 (1.04)	2.0 (1.06)	2.0 (1.13)	2.6 (1.02)	2.6 (1.10)
Median	1.9	1.6	2.2	2.2	1.9	1.8	1.8	1.7	2.5	2.5
(min-max)	(0.5-5.1)	(0.5-7.8)	(0.9-8.4)	(0.8-6.6)	(0.4-5.8)	(0.3-7.2)	(0.4-5.9)	(0.4-6.9)	(0.3-5.8)	(0.7-7.3)
Elapsed time btm 1st dose and surgery (hours)										
Mean (SD)	3.2 (1.62)	3.0 (0.89)	3.6 (1.55)	3.6 (1.46)	3.3 (1.28)	3.4 (1.45)	1.4 (0.58)	1.4 (0.68)	2.4 (1.53)	2.3 (0.62)
Median	2.8	2.8	3.2	3.1	3.0	2.9	1.3	1.3	2.3	2.3
(min-max)	(1.3-9.6)	(1.1-6.2)	(1.5-11.8)	(1.4-9.0)	(1.0-10.6)	(1.1-10.5)	(0.2-4.8)	(0.3-4.8)	(-14.8-12.5)	(1.0-4.4)

Reference: Final Study Report for Study 314, ISE, Table 6.

The five efficacy POI studies did not obtain baseline histories of prior ileus (such as POI). Patients with a past medical history of a prior ileus may be more likely to develop another ileus. If the rates of prior ileus are not balanced among study treatment groups, then the results may be confounded. The sponsor should obtain data on prior history of ileus in future POI studies.

Study 001 was the only study that obtained data on the past history of abdominal and/or pelvic surgery. In Study 001, all three treatment groups (alvimopan 6 mg, alvimopan 12 mg and placebo) had similar percentages of prior abdominal and/or pelvic surgeries. The four U.S. and Canadian studies did not collect data on past surgical history. Study 314 had a different elapsed time between the first study drug dose and the surgery start time, compared to the four other POI studies, because the procedures were different. Study 314 instructed investigators to administer the first study drug 0.5 to 1.5 hours prior to the scheduled start of surgery; whereas, the other four trials instructed investigators to administer the first study drug at least two hours prior to the start of surgery.

Primary indication for surgery: In the four U.S. POI efficacy studies, a summary of the primary indications for surgery (for the safety populations) are provided in Table 11. In the five important POI studies, the proportion of patients who had each indication was similar in the 12 mg alvimopan and placebo treatment groups. About 70% of the BR patients in the five POI studies had surgery because of colon or rectal cancer or diverticular disease.

Table 10: Primary Indications for Surgery in the BR Population in the POI Studies

Primary Indication	Study 302 (N=197) n, (%)	Study 308 (N=281) n, (%)	Study 313 (N=302) n, (%)	Study 001 (N=468) n, (%)	Study 314 (N=629) n, (%)	Total (N=1877) n, (%)
Colon or Rectal Cancer	133 (67.5)	151 (53.7)	174 (57.6)	353 (75.4) *	265 (42.1)	1076 (57.3)
Diverticular Disease	38 (19.3)	50 (17.8)	35 (11.6)		100 (15.9)	223 (11.9)
Ostomy Reversal	7 (3.6)	23 (8.2)	20 (6.6)		85 (13.5)	135 (7.2)
Inflammatory Bowel Disease	0 (0)	21 (7.5)	22 (7.3)	40 (8.5)	41 (6.5)	124 (6.6)
Intestinal Polyps	8 (4.1)	15 (5.3)	23 (7.6)		75 (11.9)	121 (6.4)
Rectal Prolapse	3 (1.5)	3 (1.1)	9 (3.0)		10 (1.6)	25 (1.3)
Intestinal Fistula	2 (1.0)	5 (1.8)	6 (2.0)		5 (0.8)	18 (1.0)
Small Bowel Cancer	0 (0)	7 (2.5)	3 (1.0)		4 (0.6)	14 (0.7)
Other Indication	6 (3.0)	6 (2.6)	10 (3.3)	75 (16.0)	44 (7.0)	141 (7.6)

*In Study 001, this number represents all patients who had a BR for a malignancy
Reference: Adapted from Final Study Report for Study 314, ISE, Table 3.1, Page 160; Table 3.3, Page 172; Table 3.4, Page 177; Table 3.5, Page 183; Table 3.6, Page 189; and Table 14.1.13.2, Page 333.

The majority of all the patients in each of the four important efficacy studies had elective surgery for cancer. Therefore, all of the four studies contained patients with high co-morbidity. Study 001 had higher proportion of patients scheduled for cancer surgery compared to the other four studies. This disparity is consistent with the higher mean age seen in Study 001 (about 64 years old) compared to the other studies (about 61 years old): cancer patients tend to be older.

5.4 Efficacy Results:

Pre-specified primary endpoint in Study 314: In Study 314, the pre-specified, two-component, composite, primary efficacy endpoint (**time to GI2**) was the time to recovery of both the upper GI tract (time from the end of surgery to the first toleration of solid food) and the lower GI tract (the time from the end of surgery to the time of the first BM), following partial small or large bowel resection surgery with primary anastomosis. In Studies 308, 313, and 001, GI2 was a pre-specified secondary efficacy endpoint; whereas, in Study 302, GI2 was a post-hoc endpoint.

In Study 314, the alvimopan 12 mg group, compared to the placebo group, achieved a statistically significant difference for the primary efficacy endpoint (time to GI2) with a HR of 1.53 and 95% CI of 1.29-1.82 (p <0.001). For the 12 mg alvimopan dose, the 25th, 50th (median), and 75th percentile change in upper and lower GI tract recovery (time to GI2) from placebo was 9.2, 16.6, and 20.3 hours, respectively (see Table 11).

Table 11: Time to GI2 in Hours in BR Patients

Study	Treatment Group	N*	25 th Percentile (change from placebo)	Median (change from placebo)	75 th Percentile (change from placebo)	Hazard Ratio (95% CI)	p-value
302	Placebo	99	89.5	114.5	141.0		
	Alvimopan 6 mg	99	78.2 (11.3)	98.2 (15.8)	122.5 (18.5)	1.38 (1.01-1.87)	0.042
	Alvimopan 12 mg	98	78.0 (11.5)	97.5 (17)	121.5 (19.5)	1.40 (1.04-1.89)	0.029
308	Placebo	142	94.0	118.3	150.0		
	Alvimopan 6 mg	137	89.0 (5)	106.0 (12.3)	130.1 (19.9)	1.34 (1.04-1.72)	0.025
	Alvimopan 12 mg	139	88.7 (5.3)	104.5 (13.8)	128.7 (21.3)	1.37 (1.06-1.76)	0.017
313	Placebo	142	90.2	117.7	151.4		
	Alvimopan 6 mg	149	79.5 (10.5)	101.2 (16.5)	128.1 (23.3)	1.35 (1.04-1.75)	0.025
	Alvimopan 12 mg	160	76.1 (14.1)	96.0 (21.7)	122.5 (28.9)	1.63 (1.26-2.10)	<0.001
001	Placebo	229	74.7	97.0	136.2		
	Alvimopan 6 mg	237	71.0 (3.7)	91.5 (5.5)	115.5 (20.7)	1.39 (1.15-1.69)	<0.001
	Alvimopan 12 mg	238	71.9 (2.8)	92.6 (4.4)	117.5 (18.7)	1.30 (1.07-1.58)	0.008
314	Placebo	312	73.5	96.6	131.2		
	Alvimopan 12 mg	317	64.3 (9.2)	80.0 (16.6)	110.9 (20.3)	1.53 (1.29-1.82)	<0.001

* The population included only BR patients.

Reference: Final Study Report for Study 314, Table 11, Page 70; Table 5.2.2.1, Page 292; Table 5.2.2.2, Page 295; Table 5.2.2.3, Page 298; and Table 5.2.2.4, Page 301.

The change in times to achieve GI2 at the 75th percentile for the 12 mg alvimopan dose, compared to placebo, in Studies 302, 308, 313, 001, and 314 were 20, 21, 29, 19, and 20 hours, respectively. The HRs of time to GI2 for the 12 mg alvimopan dose compared to the placebo dose in Studies 302, 308, 313, 001, and 314 were 1.40, 1.37, 1.63, 1.30, and 1.53, respectively.

Table 12: Time to GI2 in Days in BR Patients in the POI Studies

Study	Treatment Group	N*	50 th Percentile in days	Change from placebo in days	75 th Percentile in days	Change from placebo in days	Hazard Ratio (95% CI)	p-value
302	Placebo	99	4.8	0.7	5.9	0.8	1.40 (1.04-1.89)	0.029
	Alvimopan 12 mg	98	4.1		5.1			
308	Placebo	142	4.9	0.5	6.3	0.9	1.37 (1.06-1.76)	0.017
	Alvimopan 12 mg	139	4.4		5.4			
313	Placebo	142	4.9	0.9	6.3	1.2	1.63 (1.26-2.10)	<0.001
	Alvimopan 12 mg	160	4.0		5.1			
001	Placebo	229	4.0	0.1	5.7	0.8	1.30 (1.07-1.58)	0.008
	Alvimopan 12 mg	238	3.9		4.9			
314	Placebo	312	4.0	0.7	5.5	0.9	1.53 (1.29-1.82)	<0.001
	Alvimopan 12 mg	317	3.3		4.6			

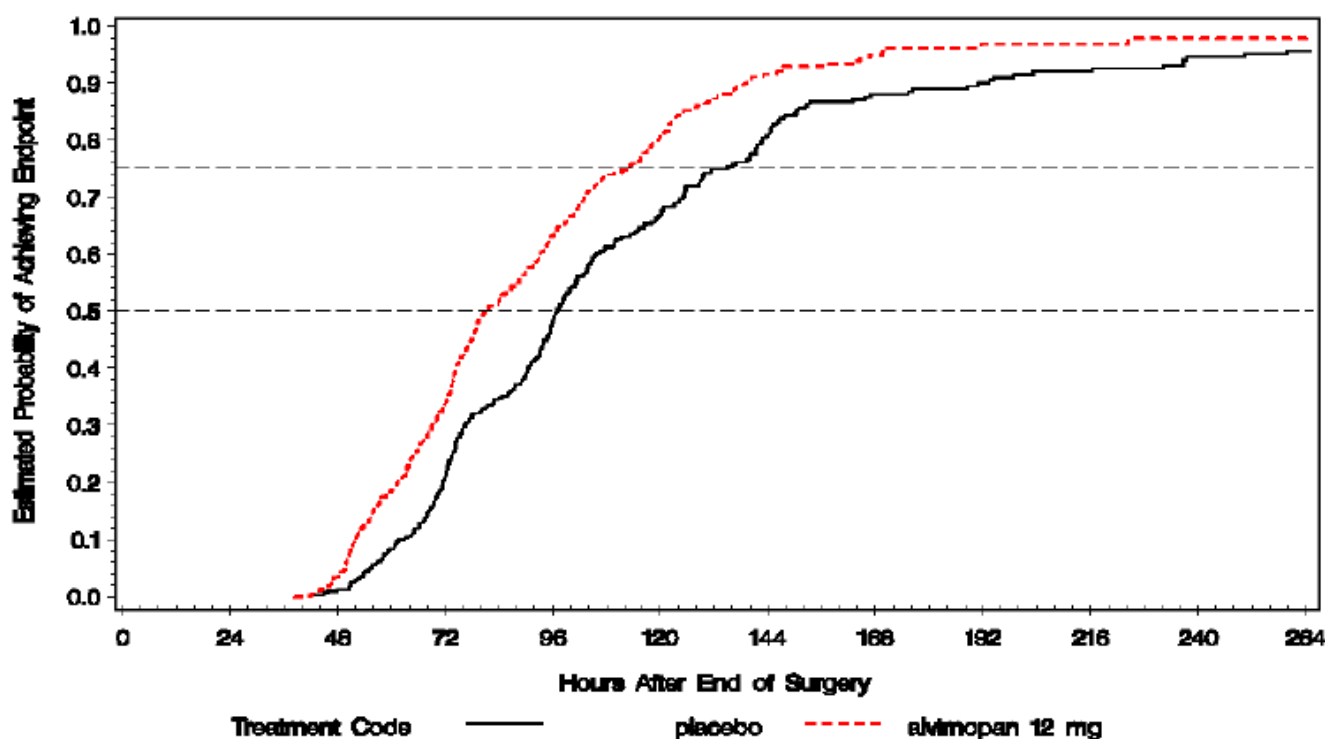
*N is the number of patients in the efficacy database in the BR patients (the TAH patients were not included).

Reference: Final Study Report for Study 314, Table 11, Page 70; Table 5.2.2.1, Page 292; Table 5.2.2.2, Page 295; Table 5.2.2.3, Page 298; and Table 5.2.2.4, Page 301.

For the 12 mg alvimopan group, the change in time to GI2, from the placebo group, increased from the 25th to the 50th to the 75th percentiles in all five important POI studies. Demonstration of a large change in time to GI2 at the 25th percentile is more clinically meaningful than demonstration of a large change in time to GI2 at the 75th percentile. In other words, the earlier a study treatment improves recovery of the upper and lower GI tracts, compared to placebo, the better the treatment. However, demonstration of improvement in time to upper and lower GI tract recovery, compared to placebo, at the 75th percentile can be clinically meaningful. Recovery of the upper and lower GI tracts at the 75th percentile can improve nutrition and therefore may reduce the risk of infection and surgery complications. Patients who received the 12 mg alvimopan dose, compared to patients who received placebo, had their upper and lower GI tract recover about one day earlier at the 75th percentile (about 4.6 to 5.4 days after the end of surgery).

Figure 1 displays the Kaplan-Meier estimates for the time to GI2 (the primary efficacy endpoint) for the 12 mg alvimopan and the placebo treatment groups in Study 314.

Figure 1: Kaplan-Meier Estimates for Time to GI2 in Study 314



Reference: Final Study Report for Study 314, Figure 2, Page 69.

The Kaplan-Meier curves of the time to achieve GI2 demonstrate that after 48 hours, the two treatment groups separate and maintain their separation (i.e., they do not cross) throughout the study period (up until POD 10). The curves demonstrate that after 48 hours, the patients in the alvimopan group achieve GI2 earlier than patients in the placebo group.

Important Pre-Specified Secondary Efficacy Endpoints: In Studies 302, 308, 313, 001, and 314, two of the most important secondary endpoints were time to Ready (the time from the end of surgery to the time ready for hospital discharge based solely on recovery of GI function as defined by the surgeon) and DOW (the time from the end of surgery to the time that the hospital discharge order was written).

Ready: Table 13 and 14 present time to Ready in the BR surgery subpopulation in the five POI trials (i.e., Studies 302, 308, 313, 001, and 314).

Table 13: Time to Ready in Hours in BR patients

Study	Treatment Group	N*	25 th Percentile (change from placebo)	Median (change from placebo)	75 th Percentile (change from placebo)	Hazard Ratio (95% CI)	p-value
302	Placebo	84	91.5	112.8	138.6		
	Alvimopan 6 mg	86	78.8 (12.7)	97.5 (14.8)	117.5 (21.1)	1.60 (1.17-2.19)	0.003
	Alvimopan 12 mg	84	83.8 (7.7)	98.3 (14.5)	118.3 (20.3)	1.52 (1.11-2.09)	0.010
308	Placebo	142	95.3	117.5	147.0		
	Alvimopan 6 mg	137	91.1 (4.2)	111.1 (6.4)	131.5 (15.5)	1.33 (1.04-1.70)	0.021
	Alvimopan 12 mg	139	89.8 (5.5)	109.5 (8)	126.6 (20.4)	1.40 (1.09-1.78)	0.008
313	Placebo	142	88.2	112.5	144.7		
	Alvimopan 6 mg	149	78.3 (9.7)	98.6 (13.9)	129.5 (15.2)	1.30 (1.02-1.67)	0.035
	Alvimopan 12 mg	160	75.4 (12.8)	95.2 (17.3)	120.2 (24.5)	1.54 (1.20-1.96)	<0.001
001	Placebo	229	99.8	137.5	173.4		
	Alvimopan 6 mg	237	94.0 (5.8)	125.3 (12.2)	165.0 (8.4)	1.16 (0.96-1.41)	0.134
	Alvimopan 12 mg	238	94.5 (5.3)	127.2 (10.3)	166.9 (6.5)	1.11 (0.92-1.35)	0.287
314	Placebo	312	70.2	91.3	123.0		
	Alvimopan 12 mg	317	67.0 (3.2)	80.7 (10.6)	101.9 (21.1)	1.38 (1.17-1.63)	<0.001

* The population included only BR patients.

Reference: Final Study Report for Study 314, Table 12, Page 74; Table 5.2.2.1, Page 292; Table 5.2.2.2, Page 295; Table 5.2.2.3, Page 298; and Table 5.2.2.4, Page 301.

Table 14: Time to Ready in Days in BR Patients

Study	Treatment Group ²	N	Median (change from placebo)	75 th Percentile (change from placebo)	Hazard Ratio (95% CI)	p-value
302	Placebo	99	4.7	5.8		
	Alvimopan 12 mg	98	4.1 (0.6)	4.9 (0.9)	1.52 (1.11-2.09)	0.010
308	Placebo	142	4.9	6.1		
	Alvimopan 12 mg	139	4.6 (0.3)	5.3 (0.8)	1.40 (1.09-1.78)	0.008
313	Placebo	142	4.7	6.0		
	Alvimopan 12 mg	160	4.0 (0.7)	5.0 (1.0)	1.54 (1.20-1.96)	<0.001
001	Placebo	229	5.7	7.2		
	Alvimopan 12 mg	238	5.7 (0)	7.0 (0.2)	1.11 (0.92-1.35)	0.287
314	Placebo	312	3.8	5.1		
	Alvimopan 12 mg	317	3.4 (0.4)	4.3 (0.8)	1.38 (1.17-1.63)	<0.001

The change in times to achieve Ready at the 75th percentile for the 12 mg alvimopan dose, compared to placebo in Studies 302, 308, 313, and 314 were 20.3, 20.4, 24.5, and 21.1 hours, respectively. The HRs for the time to Ready endpoint of the 12 mg alvimopan dose, compared to placebo, in Studies 302, 308, 313, and 314 were 1.52, 1.40, 1.54, and 1.38, respectively.

The three time-to-discharge endpoints (i.e., DOW, Ready, and departure) may not represent the efficacy of the study treatments in Study 001. Europeans, Australians, and New Zealanders in Study 001 had quicker GI recovery (i.e., time to GI2 and GI3) than the U.S. and Canadian patients in Studies 302, 308, 313, and 314; however, the patients in Study 001 had longer times to discharge (i.e., time to Ready and DOW) compared to the patients in Studies 302, 308, 313, and 314. Differences in “financial and social pressure related to hospital bed occupancy levels and resource requirements” between Europe and the United States may have affected the results of time to Ready and DOW. Therefore, the four U.S. studies as the primary studies and the one European study will be considered secondary in evaluation of the two secondary endpoints (time to Ready and DOW).

As expected, the times to Ready were greater than the times to GI recovery (i.e., GI2 and GI3) for the treatment groups. One would expect that the upper and lower GI tracts to recover before surgeons believed the patients were ready to be discharged from a GI surgical standpoint. The results of the time to upper and lower GI tract recovery endpoint (i.e., GI2) correlated with the results of the time to discharge endpoint (i.e., Ready). This correlation supports the efficacy of 12 mg alvimopan dose in the treatment of POI.

DOW (a pre-specified secondary endpoint): Table 15 displays the time to **DOW** in the BR surgery subpopulation in the POI trials (i.e., Studies 302, 308, 313, 001, and 314).

Table 15: Time to DOW in Hours in BR patients

Study	Treatment Group	N*	25 th Percentile (change from placebo)	Median (change from placebo)	75 th Percentile (change from placebo)	Hazard Ratio (95% CI)	p-value
302	Placebo	99	112.3	134.1	163.3		
	Alvimopan 6 mg	99	95.9 (16.4)	116.6 (17.5)	139.0 (24.3)	1.56 (1.17-2.08)	0.002
	Alvimopan 12 mg	98	108.6 (3.7)	118.0 (16.1)	143.3 (20.0)	1.29 (0.98-1.72)	0.084
308	Placebo	142	113.0	137.1	171.9		
	Alvimopan 6 mg	137	97.7 (15.3)	120.5 (16.6)	146.3 (25.6)	1.42 (1.12-1.81)	0.004
	Alvimopan 12 mg	139	96.3 (16.7)	119.2 (17.9)	143.8 (28.1)	1.56 (1.22-1.98)	<0.001
313	Placebo	142	97.2	133.3	179.7		
	Alvimopan 6 mg	149	93.8 (3.4)	117.9 (15.4)	159.9 (19.8)	1.24 (0.97-1.58)	0.089
	Alvimopan 12 mg	160	92.4 (4.8)	115.6 (17.7)	144.7 (35)	1.42 (1.12-1.81)	0.004
001	Placebo	229	161.3	192.8	266.3		
	Alvimopan 6 mg	237	158.6 (2.7)	191.5 (1.3)	261.1 (5.2)	1.08 (0.88-1.31)	0.134
	Alvimopan 12 mg	238	158.6 (2.7)	191.5 (1.3)	261.5 (4.8)	1.07 (0.88-1.30)	0.838
314	Placebo	312	95.2	119.9	166.2		
	Alvimopan 12 mg	317	90.3 (4.9)	112.1 (7.8)	141.1 (25.1)	1.40 (1.19-1.65)	<0.001

* The population included only BR patients.

Reference: Final Study Report for Study 314, Table 15, Page 83; Table 5.2.2.1, Page 293; Table 5.2.2.2, Page 296; Table 5.2.2.3, Page 299; and Table 5.2.2.4, Page 302.

The change in times to achieve DOW at the 75th percentile for the 12 mg alvimopan dose, compared to placebo in Studies 302, 308, 313, and 314 were 20.0, 28.1, 35, and 25.1 hours, respectively. The HRs for the time to DOW endpoint of the 12 mg alvimopan dose, compared to placebo, in Studies 302, 308, 313, and 314 were 1.29, 1.56, 1.42, and 1.40, respectively.

Table 16: Time to DOW in Days in BR Patients

Study	Treatment Group	N	Median (change from placebo)	75 th Percentile (change from placebo)	Hazard Ratio (95% CI)	p-value
302	Placebo	99	5.6	6.8		
	Alvimopan 12 mg	98	4.9 (0.7)	6.0 (0.8)	1.29 (0.98-1.72)	0.084
308	Placebo	142	5.7	7.2		
	Alvimopan 12 mg	139	5.0 (0.7)	6.0 (1.2)	1.56 (1.22-1.98)	<0.001
313	Placebo	142	5.6	7.5		
	Alvimopan 12 mg	160	4.8 (0.8)	6.0 (1.5)	1.42 (1.12-1.81)	0.004
001	Placebo	229	8.0	11.1		
	Alvimopan 12 mg	238	8.0 (0)	10.9 (0.2)	1.07 (0.88-1.30)	0.838
314	Placebo	312	5.0	6.9		
	Alvimopan 12 mg	317	4.7 (0.3)	5.9 (1.0)	1.40 (1.19-1.65)	<0.001

Reference: Final Study Report for Study 314, Table 15, Page 83; Table 5.2.2.1, Page 293; Table 5.2.2.2, Page 296; Table 5.2.2.3, Page 299; and Table 5.2.2.4, Page 302.

As expected, the time to DOW at the 25th, 50th, and 75th percentiles was greater than the time to GI recovery (i.e., GI2 and GI3) for the treatment groups. One would expect that the GI tract to recover before a discharge order was written.

As noted above the change in the times to achieve GI2 at the 75th percentile for the 12 mg alvimopan dose, compared to placebo, in Studies 302, 308, 313, and 314 was about 19 to 29 hours. In addition, the change in the times to achieve Ready at the 75th percentile for the 12 mg alvimopan dose, compared to placebo, in Studies 302, 308, 313, and 314 was about 20 to 25 hours. Therefore, the results of the important time to upper and lower GI tract recovery endpoint (i.e., GI2) correlated with the results of two important times to discharge endpoints (i.e., DOW and Ready). These correlations support the efficacy of 12 mg alvimopan dose in the treatment of POI.

Exploratory endpoint (time to GI3) in Study 314: In Study 314, time to GI3 was a post-hoc, three-component, composite endpoint. Time to GI3 was time to recovery of both the upper GI tract (time from the end of surgery to the first toleration of solid food) and the lower GI tract (the time from the end of surgery to the time of the first BM or the first flatus, whichever occurred first), following partial small or large BR surgery with primary anastomosis. In Studies 302, 308, 313, and 001, GI3 was the original, pre-specified primary

efficacy endpoint for the BR surgery and gynecologic surgery populations. The primary efficacy endpoint for Study 001 changed from GI3 to GI2 and the primary population changed from all surgery patients to only BR patients after an amendment midway through the study.

Table 17 displays the time to GI3 in BR surgery patients for Studies 302, 308, 313, 001 and 314. Since the sponsor has not proposed the use of alvimopan in pelvic surgery in this second cycle NDA, Table 17 only includes the BR subpopulation in the POI studies.

In this second cycle NDA, the sponsor proposed the use of the 12 mg alvimopan dose in the treatment of POI; however, the sponsor did not propose the use of the 6 mg alvimopan dose. In the BR surgery subpopulation, of the four phase 3 efficacy studies with GI3 as the original primary efficacy endpoint (Studies 302, 308, 313, and 001), the 12 mg alvimopan treatment group demonstrated statistical significance compared to the placebo group in one study (Study 313) for time to GI3.

Table 17: Time to GI3 (in Hours) in BR Patients

Study	Treatment Group	N*	25 th Percentile (change from placebo)	Median (change from placebo)	75 th Percentile (change from placebo)	Hazard Ratio (95% CI)	p-value
302	Placebo	99	79.0	104.3	127.7		
	Alvimopan 6 mg	99	73.7 (5.3)	94.5 (9.8)	117.6 (10.1)	1.48 (1.10-1.98)	0.009
	Alvimopan 12 mg	98	74.4 (4.6)	96.7 (7.6)	120.2 (7.5)	1.30 (0.96-1.74)	0.086
308	Placebo	142	88.2	113.0	142.3		
	Alvimopan 6 mg	137	78.7 (9.5)	101.0 (12)	124.5 (17.8)	1.23 (0.96-1.57)	0.106
	Alvimopan 12 mg	139	76.9 (11.3)	99.6 (13.4)	121.6 (20.7)	1.32 (1.03-1.69)	0.029
313	Placebo	142	76.1	103.0	140.2		
	Alvimopan 6 mg	149	72.6 (3.5)	96.5 (6.5)	123.0 (17.2)	1.25 (0.97-1.60)	0.084
	Alvimopan 12 mg	160	69.4 (7.1)	92.5 (10.5)	119.2 (21)	1.49 (1.17-1.91)	0.001
001	Placebo	229	65.8	81.3	115.3		
	Alvimopan 6 mg	237	58.8 (7)	74.6 (6.7)	91.1 (24.2)	1.22 (1.01-1.47)	0.042
	Alvimopan 12 mg	238	62.4 (3.4)	76.9 (4.4)	101.2 (14.1)	1.13 (0.94-1.37)	0.200
314	Placebo	312	68.0	82.6	109.5		
	Alvimopan 12 mg	317	55.8 (12.2)	73.5 (9.1)	94.4 (15.5)	1.45 (1.23-1.71)	<0.001

*The population included only BR patients; the gynecologic patients in Studies 302, 308, 313, and 001 were not included in these analyses.

Reference: Final Study Report for Study 314, Table 13, Page 77; Table 5.2.2.1, Page 292; Table 5.2.2.2, Page 295; Table 5.2.2.3, Page 298; and Table 5.2.2.4, Page 301.

For the 12 mg alvimopan group, the results of time to GI3 were not as efficacious as the results of the time to GI2. GI2 is probably a better endpoint than GI3 in the assessment of treatment of POI because of the following two reasons:

- Flatus is an unreliable measurement; and
- Time to first BM, compared to time to first flatus, may be a much better indicator of recovery of the lower GI tract following surgery.

The selection of GI3 for the original, pre-specified, primary efficacy endpoint for the four important POI studies — submitted to the first cycle NDA — may have contributed to the equivocal efficacy results of these four studies.

Exploratory Responder Endpoints in Study 314: Table 18 shows the difference in the proportion of responders for time to achieve GI2, Ready, and DOW by postsurgical day (PSD). Responders were defined as patients who achieved the time-to-event endpoint by a PSD and had no complications of POI (defined as a prolonged hospital stay or a readmission within seven days of the initial discharge due to POI, paralytic ileus, or small intestinal obstruction).

Table 18: Responder Analyses by PSD for the GI2, READY, and DOW Time-to-Event Endpoints in Study 314

	By PSD	Placebo, % (N=312)	Alvimopan 12 mg, % (N=317)	Difference, %
GI2	3	42.6	60.3	17.6
	4	59.0	75.4	16.4
	5	70.2	83.0	12.8
	6	75.6	85.2	9.5
	7	76.9	86.1	9.2
	8	78.5	86.1	7.6
Ready	3	54.2	64.0	9.9
	4	66.0	81.1	15.0
	5	76.0	88.3	12.4
	6	81.4	90.2	8.8
	7	82.7	90.5	7.8
	8	83.3	91.2	7.8
DOW	3	26.0	36.6	10.6
	4	48.4	63.4	15.0
	5	62.8	78.5	15.7
	6	74.0	86.4	12.4
	7	80.8	91.2	10.4
	8	84.3	93.4	9.1

The MITT population was used in these analyses.

Reference: Adapted from the Final Study Report for Study 314, Table 14.2.1.5, Pages 358-359.

The differences between the alvimopan and placebo treatment groups in the proportion of GI2 responders ranged from 7.6% by PSD 8 to 17.6% by PSD 3. The differences between the alvimopan and placebo treatment groups in the proportion of Ready responders ranged from 7.8% by PSD 7 and PSD 8 to 15.0% by PSD 4. The differences between the alvimopan and placebo treatment groups in the proportion of DOW responders ranged from 9.1% by PSD 8 to 15.7% by PSD 5.

For all three time-to-event important endpoints (i.e., GI2, Ready, and DOW), the alvimopan group had a higher percentage of responders, compared to the placebo group for every cut off

point (by PSD 3, 4, 5, 6, 7, and 8). These exploratory efficacy endpoints support the efficacy of 12 mg of alvimopan in the treatment of POI.

Table 19 shows mean length of hospital stay in days (by POD) in the BR population.

Table 19: Mean Length of Hospital Stay in Days (by POD) in the BR Population in the POI Studies

Studies	302	308	313	001	314
Placebo	6.4 (n=99)	6.6 (n=142)	7.4 (n=142)	9.2 (n=229)	6.2 (n=312)
Alvimopan 12 mg	6.1 (n=98)	5.7 (n=139)	6.1 (n=160)	8.9 (n=238)	5.2 (n=317)
Difference	0.3	0.9	1.3	0.2	1.0

Reference: Final Study Report for Study 314, ISE, Table 8, Page 32

Subgroup Exploratory Efficacy Analyses:

The POI studies included three main types of surgery (i.e., large BR, small BR, and TAH). Table 20 showed time to GI2 in hours in large BR and small BR patients

Table 20: Time to GI2 in Hours in Large BR and Small BR Patients

Surgery Type	Study	Treatment Group	N	Median (change from placebo)	Hazard Ratio [#] (95% CI)	p-value [*]
Large Bowel	308	Placebo	126	116	1.28 (0.98,1.68)	0.068
		Alvimopan 12 mg	128	104 (12)		
	313	Placebo	130	116	1.54 (1.17,2.03)	0.002
		Alvimopan 12 mg	137	102 (14)		
	001	Placebo	179	95	1.18 (0.96,1.47)	0.123
		Alvimopan 12 mg	199	94 (1)		
	314	Placebo	290	97	1.47 (1.23,1.75)	<0.001
		Alvimopan 12 mg	286	83 (14)		
Small Bowel	308	Placebo	16	122	3.62 (1.27,10.28)	0.016
		Alvimopan 12 mg	11	95 (27)		
	313	Placebo	12	91	1.81 (0.82,3.98)	0.138
		Alvimopan 12 mg	23	72 (19)		
	001	Placebo	12	97	5.12 (1.59,16.47)	0.006
		Alvimopan 12 mg	9	73 (24)		
	314	Placebo	22	96	2.34 (1.24,4.42)	0.008
		Alvimopan 12 mg	31	72 (24)		

[#]The hazard ratio (HR) of alvimopan to placebo was calculated from a Cox proportional hazards model

^{*}p-values were calculated by the Wald Chi-square tests for pair-wise comparisons between alvimopan and placebo

Reference: Dr. Sonia Castillo's exploratory analysis

Since different surgery types are known to have different rates of recovery of GI motility following surgery, it is important to understand the efficacy of alvimopan in each surgery subgroup. The data indicate that there are similar efficacy results for both large BR and small BR populations. There was no efficacy in the gynecology surgery subgroup (i.e., TAH) in the POI studies that were submitted in the first-cycle. TAH surgery patients were not enrolled in the last POI study (i.e., Study 314) that was submitted in this second-cycle because efficacy was not established in this subgroup.

Table 21 displays the median and mean opioid consumption (in morphine equivalents) prior to surgery, during surgery, and after surgery in the BR surgery patients.

Table 21: Median and Mean (SD) Opioid Consumption[#] in BR Patients

STUDY	TREATMENT GROUPS	n	Median Pre & Intra Operative	Median Postoperative	Mean (SD) Pre & Intra Operative	Mean (SD) Postoperative
302	Placebo	99	38	154	43 (24)	194 (175)
	Alvimopan 12 mg	98	39	174	49 (36)	224 (189)
308	Placebo	142	47	151	50 (29)	182 (145)
	Alvimopan 12 mg	139	44	134	52 (41)	159 (114)
313	Placebo	142	43	121	50 (40)	185 (192)
	Alvimopan 12 mg	160	44	139	30 (44)	166 (129)
001	placebo	198	49	73	54 (39)	104 (120)
	Alvimopan 12 mg	207	50	77	57 (40)	106 (127)
314	Placebo	312	13 +24*	158	17 (15) + 30 (32)*	219 (259)
	Alvimopan 12 mg	317	13 +24*	143	17 (15) + 31 (31)*	185 (188)

[#]The median and mean opioid consumption is in morphine equivalents

*The first number is the opioid use preoperatively and the second number is opioid use intraoperatively

Reference: Adapted ISE, Table 10.2, Pages 488-492; Table 10.3, Pages 494-499; Table 10.4, Pages 500-505; Table 10.5, Pages 506-513; and Table 14.3.6.2, Pages 884-888

The 12 mg alvimopan groups in Studies 308 and 314 appeared to receive more opioids than the placebo groups. However, the placebo group in Study 308 appeared to receive more opioids than the 12 mg alvimopan group. The 12 mg alvimopan and placebo treatment groups appeared to have consumed equivalent amount of opioids. Moreover, the standard deviations of opioid use are very wide. No clear relationship exists between pre, intra, and postoperative opioid use and the efficacy of alvimopan in the treatment of POI (i.e., time to GI2 and time to DOW). Therefore, the efficacy of alvimopan, compared to placebo, in the treatment of POI is not confounded by opioid consumption.

6 INTEGRATED REVIEW OF GENERAL SAFETY

6.1 Deaths

There were 22 deaths which occurred in the POI population. Of the 22 deaths in the POI population, 13 and 9 deaths occurred in patients who received alvimopan and placebo, respectively [13 out of 2610 (0.50%) who received alvimopan and 9 out of 1365 (0.66%) who received placebo]. Of the 13 deaths in the alvimopan treatment groups, 8 and 5 deaths were in the 12 mg and 6 mg alvimopan treatment groups, respectively. Narratives of the POI deaths in the 12 mg alvimopan group, the 6 mg alvimopan group, and the placebo group are displayed in Tables 22, 23, and 24 respectively.

Table 22: Narratives of the Deaths in the 12 mg Alvimopan Group in the POI Trials

	Patient ID#	Cause of Death	Medical History	Surgery Date Surgery Type	Date of Onset ¹ Date of Death
1	14CL302-06-01057	Recurrent respiratory failure due to pneumonia	78 year old white female (with history of colon cancer, breast cancer, atrial fibrillation, diverticulosis, and HTN) had vomiting and SOB on POD 2 and was found to have an aspiration pneumonia and POI. Needed mechanical ventilation. Pneumonia treated and patient was extubated and discharged. Readmitted POD 32 for diarrhea and abdominal pain. Developed pneumonia which required mechanical ventilation and died on POD 57.	5/2/02 Right Large BR	6/9/02 <input type="text"/>
2	14CL302-22-01118 ²	CHF	71 year old white male (with a history of colon cancer, HTN, MI, use of a cardiac assist device and hyperlipidemia). During left large BR surgery was found to have metastatic colon cancer to the entire small bowel mesentery and pelvis and required a colostomy. Discontinued from study medication (only received one dose preoperatively. On POD 5 had CHF and died on POD 12 of CHF.	3/20/02 Left Large BR	3/29/02 <input type="text"/>
3	14CL313-13-13015 ²	Acute MI	64 year old male (with a history of recurrent colon cancer, prostate cancer, renal cell carcinoma, and DM) had a left large BR on POD 0. He was discharged on POD 6 (last dose received on the AM of POD 6). Readmitted for CP on POD 8 [diagnosed with an acute MI (symptoms, positive troponin and CPK) cath showed 100% occlusion of his RCA and he underwent unsuccessful PTCA and stent placement in his RCA]. Post-procedure had ventricular fibrillation and had cardio version. On POD 9 had tachypnea and hypoxia and died on POD 10.	5/14/02 Left Large BR	5/22/02 <input type="text"/>
4	GSK001-273 ²	CVA Peritonitis	70 year old female (with history of recent TIA in 4/03, carotid artery disease, and colon cancer) had large BR because of colon cancer. had a CVA with left hemiparesis on POD 2 (<input type="text"/>). Study medication was withdrawn on POD 5. On POD 9 (<input type="text"/>) had anastomosis leak with peritonitis. Had exploratory laparotomy. Died on POD 16 (<input type="text"/>).	5/13/03 Large BR	5/15/03 <input type="text"/>
5	GSK001-448	Death unknown	63 year old male (with history of AAA) had left large BR for rectal cancer. Postoperative course complicated by mild wound	5/5/04 Left	<input type="text"/>

		cause	infection. Stopped treatment on POD 7. Discharged on POD 13 (). Died during sleep at home on POD 16 (). No autopsy was performed.	Large BR	
6	GSK001-570	Sepsis from peritonitis from anastomosis dehiscence	78 year old male (with a history of colon cancer, DM, and HTN) discontinued from treatment on POD 0 () because had epidural anesthesia. On POD 5 () had tachycardia and tachypnea. Diagnosed with sepsis from peritonitis from anastomosis dehiscence. Had exploratory laparotomy on POD 5 () and had correction of dehiscence. Died on POD 5 ().	10/31/03 Left Large BR	11/5/03 ()
7	14CL314-360240 ²	MI, CHF, and acute renal, liver, and respiratory failure	78 year old female (with history of colon cancer with liver metastasis, left hip arthroplasty, gastric ulcer, osteoarthritis, malnutrition, and HTN) received 12 mg alvimopan and then had a left colon resection and ureteral stent placed. She had an MI, ARF, CHF, and respiratory failure on POD 3 and study medication was discontinued on POD 3. On POD 4, she had acute liver failure. She was discharged to hospice care on POD 6. On POD 9 she died of acute liver and renal failure.	3/3/05 Left Large BR	3/6/06 ()
8	14CL314-220079	GI bleed	73 year old woman (with a history of colon cancer, pacemaker placement, aortic valve replacement, sleep apnea, HTN, osteoporosis, CHF, and hyperlipidemia) had 12 mg of alvimopan on POD 0 (prior to the surgery); however, missed the evening doses on POD 1 and POD 2 due to a staffing error. She did complete the study drug regimen, having her last dose on POD 6 before hospital discharge. As an outpatient, on POD 13, she developed a GI bleed which resulted in her death.	4/10/05 Left Large BR	4/17/05

1 Date of onset – the illness that caused the death was first diagnosed on this date

2 The shaded events were CV deaths

Reference: Adapted from ISS, Volume 211, Table 101, Pages 238-41; Study 001 Report, Section 8.3.1, Table 41, Page 101; Study 001 Report, Section 13, Pages 166, 183, and 191; and Final Study Report for Study 314, Pages 900-1060.

Table 23: Narratives of the Deaths in the 6 mg Alvimopan Group in the POI Trials

	Patient ID#	Cause of Death	Medical History	Surgery Date/ Type	Date of Onset ¹ / Death
1	14CL308-30-01271	Small bowel gangrene	76 year old white female (with a history of recurrent small bowel obstruction and osteoporosis) with a postoperative course complicated by atrial fibrillation, underwent successful cardioversion. Discharged and readmitted POD 9 () for abdominal pain, became unresponsive then revived with CPR. Exploratory laparotomy performed and necrosis of the entire jejunum and ileum was found, gangrene was removed and a duodenal/colonic anastomosis was created. Post surgery had hypotension and acidosis and then died.	8/13/02 Small BR	8/22/02 ()
2	14CL308-31-01182 ²	Recurrent PE	57 white male [with history of metastatic colon cancer to liver, recent pulmonary embolism (6/02), metastatic renal cancer, CRF, and HTN] discharged on POD 7. Readmitted on POD 13 for shortness of breath and dizziness (diagnosed with recurrent PE). Had a cardiac arrest.	7/3/02 Left Large BR	7/16/02 ()
3	14CL313-	Autopsy	47 year old white female [with a past history of morbid obesity,	6/24/02	7/17/02

	05-05005	showed acute purulent peritonitis, severe CAD	DM type II, HTN, hyperlipidemia, CAD (s/p angioplasty), and Crohn's disease with distal terminal ileal stricture and intestinal fistula, and ileocolitis]. Postoperative course complicated by elevated blood pressures. She went home on POD 5 (). On POD 23 () she was found at home unresponsive.	small BR	()
4	14CL313-11-11023	Recurrent Hodgkin's disease	72 year old black male (with history of colon cancer, Hodgkin's disease, DM type II, HTN, CRF, and hyperlipidemia) discharged then readmitted for abdominal pain. Found to have positive blood cultures for Bacteroides fragilis. CT scan showed increased chest/abdominal lymph nodes (probable recurrent Hodgkin's disease) and abdominal abscess. The abscess was drained but he developed ARF (on top of CRF) and acidosis and then died.	4/7/03 Right Large BR	4/21/03 ()
5	001-598	Septic shock	71 year old female (with a history of obesity, HTN, and epilepsy) had BR due to colon-cutaneous fistula. On POD 4 () developed shortness of breath, hypotension, and abdominal tenderness (diagnosed with septic shock). Laparotomy was done and found wound dehiscence and peritonitis due to gram negative bacilli. Study treatment was discontinued on POD 4 (). Her septic shock worsened and she died on POD 20 ().	1/14/04 Left Large BR	1/18/04 ()

1 Date of onset – the illness that caused the death was first diagnosed on this date

2 The shaded events were CV deaths

Reference: Adapted from ISS, Volume 211, Table 101, Pages 238-41; Study 001 Report, Section 8.3.1, Table 41, Page 101; and Study 001 Report, Section 13, Page 192

Table 24: Narratives of the Deaths in the Placebo Group in the POI Trials

	Patient ID#	Cause of Death	Medical History	Surgery Date & Surgery Type	Date of Onset* & Date of Death
1	13C213-005-0009	Pneumonia; respiratory failure, sepsis; ARF on CRF; pancreatitis; and then cardiac arrest	82 year old black male (with a history of colon cancer, HTN, hypercholesterolemia, CAD, CRF, and anemia)	5/4/01 Left Large BR	5/14/05 ()
2	14CL302-69-01406	Gram negative sepsis from postoperative abscess	82 year old black female (with a history of HTN, left ventricular hypertrophy, CHF, atrial fibrillation, AAA, colon cancer, diverticulitis, and lower GI bleed). Postoperative course complicated by hypotension, ARF, and postoperative wound infection. Her ARF and wound infection resolved and she was discharged on (). She was readmitted on () for abdominal abscess and gram negative septic shock. She developed aspiration pneumonia.	11/6/02 Right Large BR	11/21/02 ()
3	14CL308-15-02143	Accidental overdose of oxycodone and cyclobenzaprine	53 year old white female (with a history of HTN, multiple surgeries, and migraines) underwent rTAH for endometrial carcinoma	3/6/03 rTAH	3/9/03 ()
4	14CL308-30-02283	Jejunal obstruction due to metastatic colon cancer	82 year old white male (with a history of recurrent metastatic colon cancer to lungs and kidney, HTN, aortic valve stenosis, and hyperlipidemia) discharged and readmitted with jejunal obstruction. Due to extensive cancer, surgical repair could not clear obstruction.	7/1/03 Small BR	7/8/03 ()

5	001-263	Cause of death not reported	61 year old male (with history of colon cancer) discharged on POD 7. POD 9 () died	11/13/03	()
6	001-889	Peritonitis and septic shock	83 year old female (with history of cirrhosis, malnutrition, and colon cancer) discontinued study medication because of nasogastric tube reinsertion on POD 4 (). On POD 6 () developed wound infection then hypotension. Laparotomy showed abdominal abscess, peritonitis, and anastomotic leakage. Had ileostomy. On POD 8 () she died due to septic shock.	3/12/04 Right Large BR	3/16/04 ()
7	001-1289	Upper GI bleed	82 year old male (with a history of atrial fibrillation) developed a distended abdomen, shortness of breath, tachypnea, and tachycardia and was diagnosis with CHF on POD 5 (). Treatment was discontinued because of reinsertion of nasogastric tube. On POD 7 () because of worsened abdominal distension and tenderness had an exploratory laparotomy and found to have infected free fluid and greater omentum fat necrosis (probably from pancreatitis). His condition was improving, but on POD 39 () had massive UGIB and died on POD 40 ().	7/21/04 Left Large BR	8/29/04 ()
8	14CL314-40191 ²	Arterial thrombus of aorta and superior mesenteric artery	68 year old male (with a history of colon cancer, SVT, iron-deficiency anemia, diverticulosis, GERD) developed C. difficile colitis on POD 4. He completed his last dose of study medication on POD 6 and was discharged from the hospital on POD 6. He was readmitted on POD 9 for lactic acidosis and had pulseless electrical activity and died on POD 9. Postmortem review of the CT scans revealed a thrombus in the thoracic aorta and a probable thrombus in the superior mesenteric artery.	8/18/05 Right Large BR	8/22/06 ()
9	14CL314-110782	Septic shock pulseless electrical activity	41 year old male (with history of diverticulosis with prior perforation, sigmoid colectomy with colostomy with subsequent revision, subdural hematoma, obesity, and GERD) and he received his last dose of study medication on POD 3 before his discharge from the hospital on POD 4. He developed an anastomotic leak on POD 5 which required rehospitalization. On POD 6 he had an exploratory laparotomy and later he developed septic shock. He developed pulseless electrical activity and died on POD 6.	10/21/05 Left Large BR	10/26/05 ()

1 Date of onset – the illness that caused the death was first diagnosed on this date

2 The shaded events were CV deaths

Reference: Adapted from ISS, Volume 211, Table 101, Pages 238-41; Study 001 Report, Section 8.3.1, Table 41, Page 101; Study 001 Report, Section 13, Pages 148, 165, and 202; and Final Study Report for Study 314, Pages 900-1060.

6.2 Serious Adverse Events

Of the 559 nonfatal SAEs in the POI population, 309 and 250 occurred in patients who received alvimopan and placebo, respectively [309 out of 2610 (11.8%) patients had nonfatal SAEs who received alvimopan and 250 out of 1365 (18.3%) patients had nonfatal SAEs who received placebo]. See Table 25 for a listing of the most common nonfatal SAEs in the POI studies.

Table 25: Nonfatal SAEs ($\geq 0.5\%$ of the Population) in the POI Trials

Preferred term	Placebo N=1365 n (%)	Alvimopan			
		1-3 mg N=62 n (%)	6 mg N=898 n (%)	12 mg N=1650 n (%)	Total N=2610 n (%)
Patients with at least one nonfatal SAE	250 (18.3)	7 (11.3)	110 (12.2)	192 (11.6)	309 (11.8)
POI	60 (4.4)	0	11 (1.2)	13 (0.8)	24 (0.9)
Small intestinal obstruction (SBO)	26 (1.9)	0	7 (0.8)	19 (1.2)	26 (1.0)
POI and SBO combined	86 (6.3)	0	18 (2.0)	32 (2.0)	50 (1.9)
Postoperative infection	19 (1.4)	0	10 (1.1)	18 (1.1)	28 (1.1)
Anastomotic leak	15 (1.1)	2 (3.2)	12 (1.3)	11 (0.7)	25 (1.0)
Pulmonary embolism	13 (1.0)	0	9 (1.0)	11 (0.7)	20 (0.8)
Wound dehiscence	6 (0.4)	1 (1.6)	3 (0.3)	15 (0.9)	19 (0.7)
Atrial fibrillation	5 (0.4)	1 (1.6)	5 (0.6)	12 (0.7)	18 (0.7)
Procedure complication	8 (0.6)	0	2 (0.2)	6 (0.4)	8 (0.3)

Reference: Adapted from ISS, Table A.2.6.2, Page 1057

The alvimopan treatment groups, compared to the placebo treatment group, were associated with a lower incidence of nonfatal SAEs. The difference in nonfatal SAEs between the groups was due to a lower incidence of POI and small bowel obstruction (SBO) in the alvimopan groups, compared to the placebo group. The lower frequency of POI/SBO suggests a possible efficacy benefit of alvimopan in the treatment of POI. However, these SAEs were determined by the general surgeon; the terms POI/SBO were not prospectively defined.

The frequency of SAEs due to postoperative infection, wound dehiscence, and pulmonary embolism was similar in the alvimopan and placebo treatment groups.

There were few SAEs in this OBD population in both treatment groups. There were no differences in SAEs in both treatment groups in this OBD population.

6.4 Dropouts and Other Significant Adverse Events

Table 26 delineates the most common reasons for discontinuation in the nine POI studies.

Table 26: The Most Common Reasons for Study Discontinuation in the POI Population

Reason for Discontinuation	Placebo N-1365 n (%)	Alvimopan			
		1-3 mg N=62 n (%)	6 mg N=898 n (%)	12 mg N=1650 n (%)	Total N=2610 n (%)
Total	218 (16.0)	13 (21.0)	138 (15.4)	211 (12.8)	362 (13.9)
AE	76 (5.6)	7 (11.3)	42 (4.7)	68 (4.1)	117 (4.5)
Administrative	3 (0.2)	0 (0)	1 (0.1)	0	1 (<0.1)
Withdrew	32 (2.3)	2 (3.2)	19 (2.1)	25 (1.5)	46 (1.8)
Protocol violation	80 (5.9)	3 (4.8)	54 (6.0)	79 (4.8)	136 (5.2)
Other	27 (2.0)	1 (1.6)	22 (2.4)	39 (2.4)	62 (2.4)

Reference: ISS, Table A.2.1, Page 723.

A lower percentage of patients in the alvimopan groups, compared to the placebo group, discontinued study drug due to an AE. Similar percentages of patients withdrew from the study and had protocol violations in the alvimopan and placebo treatment groups.

Table 27 contains the most frequent treatment-emergent AEs (TEAEs) that resulted in study discontinuation in the POI population.

Table 27: Patients Who Had TEAEs ($\geq 0.3\%$ in Any Group) Causing Discontinuation in the POI Population

Reason for discontinuation	Placebo N-1365 n (%)	Alvimopan			
		1-3 mg N=62 n (%)	6 mg N=898 n (%)	12 mg N=1650 n (%)	Total N=2610 n (%)
Total patients with ≥ 1 TEAE causing discontinuation	162 (11.9)	7 (11.3)	74 (8.2)	125 (7.6)	206 (7.9)
Nausea	42 (3.1)	4 (6.5)	19 (2.1)	39 (2.4)	62 (2.4)
Vomiting	43 (3.2)	1 (1.6)	17 (1.9)	24 (1.5)	42 (1.6)
POI	45 (3.3)	0 (0)	11 (1.2)	20 (1.2)	31 (1.2)
Abdominal distension	11 (0.8)	1 (1.6)	6 (0.7)	8 (0.5)	15 (0.6)
Diarrhea	4 (0.3)	0 (0)	0 (0)	8 (0.5)	8 (0.3)
Dyspepsia	0 (0)	0 (0)	1 (0.1)	8 (0.5)	9 (0.3)
MI	3 (0.2)	0 (0)	1 (0.1)	3 (0.2)	4 (0.1)
Small intestinal obstruction	5 (0.4)	0 (0)	0 (0)	2 (0.1)	2 (0.1)
Flatulence	2 (0.1)	0 (0)	1 (0.1)	3 (0.2)	4 (0.2)
Anastomotic leak	0 (0)	0 (0)	3 (0.3)	2 (0.1)	5 (0.2)
Confusional state	3 (0.2)	0 (0)	0 (0)	2 (0.1)	2 (0.1)
HTN	0 (0)	0 (0)	0 (0)	5 (0.3)	5 (0.2)
Hypotension	4 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)

Patients who had more than one TEAE causing discontinuation in the same category were counted only once. The table is based on the incidence of the total number of patients who experienced these events in descending order.

Reference: ISS, Table A.2.9.1, Page 1166.

The alvimopan treatment groups, compared to the placebo group, had a lower proportion of patients who had TEAEs leading to discontinuation. This lower incidence was due to a lower incidence of vomiting and POI. This suggests a possible efficacy benefit of alvimopan compared to placebo.

Demographics

Table 28 lists the demographics (including age, race, and gender) of the nine POI studies (i.e., Studies 206, 213, 214, 302, 306, 308, 313, 314, and 001) and Table 30 lists the demographics of the eight POI studies that had BR patients (i.e., Studies 206, 213, 214, 302, 308, 313, 314, and 001). Of all the POI patients about 86% and 14% had BR surgery, and gynecologic surgery respectively.

The age, race, and gender demographics are similar in the treatment groups in the BR subpopulation and the race demographics are similar in the treatment groups in the entire POI population.

Table 28: Demographics in the POI Population*

Demographic Factor Statistics	Placebo (N=1365) n (%)	Alvimopan		Total ^a (N=2610) n (%)
		6 mg (N=898) n (%)	12 mg (N=1650) n (%)	
Age (years)				
N	1365	898	1650	2610
Mean (SD)	58 (14.39)	59.4 (14.57)	55.8 (14.82)	57 (14.78)
Median	58	60	55	57
Minimum, maximum	20, 95	19, 91	19, 97	19, 97
< 65 Years	874 (64.0)	525 (58.5)	1139 (69.0)	1712 (65.6)
≥ 65 Years	491 (36.0)	373 (41.5)	511 (31.0)	898 (34.4)
≥ 75 Years	194 (14.2)	151 (16.8)	201 (12.2)	355 (13.6)
Race				
Caucasian	1156 (84.7)	782 (87.1)	1376 (83.4)	2207 (84.6)
Black	132 (9.7)	75 (8.4)	153 (9.3)	238 (9.1)
Asian	16 (1.2)	5 (0.6)	30 (1.8)	36 (1.4)
Hispanic	49 (3.6)	28 (3.1)	72 (4.4)	102 (3.9)
Other	8 (0.6)	4 (0.4)	15 (0.9)	19 (0.7)
Sex				
Female	850 (62.3)	512 (57.0)	1117 (67.7)	1680 (64.4)
Male	515 (37.7)	386 (43.0)	533 (32.3)	930 (35.6)

*The overall POI population includes 206, 213, 214, 302, 306, 308, 313, 314, and 001

Reference: Final Study Report Study 314, ISS, Table 12, Page 33

In the entire POI population, the gender and age demographics are slightly different in the three treatment groups (i.e., 12 mg alvimopan dose, 6 mg alvimopan dose, and placebo dose) because the POI population included Study 306. Study 306 included only female patients who had simple TAH surgery (TAH surgery patients were much younger than BR surgery patients). Since Study 306 had 413 patients on the 12 mg alvimopan dose and 103 patients on the placebo dose (due to a 4:1 randomization), the 12 mg alvimopan dose and placebo doses had lower mean ages and higher percentages of female patients, compared to the 6 mg alvimopan dose.

Table 29: Demographics in the BR Surgery Subpopulation*

Demographic Factor Statistics	Placebo (N=986) n (%)	Alvimopan		Total ^a (N=1681) n (%)
		6 mg (N=663) n (%)	12 mg (N=999) n (%)	
Age (years)				
N	986	663	999	1681
Mean (SD)	61.5 (13.67)	62.1 (13.99)	61.5 (14.22)	61.8 (14.10)
Median	63.0	64.0	63.0	63.0
Minimum, maximum	20, 95	19, 64	19, 97	19, 97
< 65 Years	543 (55.1)	340 (51.3)	545 (54.6)	894 (53.2)
≥ 65 Years	443 (44.9)	323 (48.7)	454 (45.4)	787 (46.8)
≥ 75 Years	178 (18.1)	133 (20.1)	182 (18.2)	318 (18.9)
Race				
Caucasian	867 (87.9)	584 (88.1)	873 (87.4)	1470 (87.4)
Black	73 (7.4)	51 (7.7)	81 (8.1)	136 (8.1)
Asian	9 (0.9)	3 (0.5)	7 (0.7)	11 (0.7)
Hispanic	31 (3.1)	19 (2.9)	33 (3.3)	53 (3.2)
Other	2 (0.2)	2 (0.3)	1 (0.1)	3 (0.2)
Sex				
Female	491 (49.8)	292 (44.0)	484 (48.4)	784 (46.6)
Male	495 (50.2)	371 (56.0)	515 (51.6)	897 (53.4)

*The BR surgery subpopulation includes 206, 213, 214, 302, 308, 313, 314, and 001. Study 306 is not included because all patients in this study had gynecologic surgery.

Reference: Final Study Report Study 314, ISS, Table 35, Page 65

Extent of Exposure (Dose/Duration)

Table 30 lists the extent of exposure in the POI population. In the nine POI trials, the median duration of exposure was six days for the following treatment groups: the 12 mg alvimopan dose, the 6 mg alvimopan dose, and placebo. In these nine POI trials, the total median

alvimopan exposure for the entire trial duration was 120, 54, and 0 mg of alvimopan for the 12 mg alvimopan dose, the 6 mg alvimopan dose, and placebo, respectively.

Table 30: Extent of Exposure in the Overall POI Population*

Parameter Statistics	Placebo (N=1365) n (%)	Alvimopan		
		6 mg (N=898) n (%)	12 mg (N=1650) n (%)	Total [†] (N=2610) n (%)
Total No. of Doses Received				
1	103 (7.5)	68 (7.6)	104 (6.3)	177 (6.8)
2	28 (2.1)	13 (1.4)	29 (1.8)	46 (1.8)
3	23 (1.7)	17 (1.9)	28 (1.7)	46 (1.8)
4	52 (3.8)	45 (5.0)	52 (3.2)	106 (4.1)
5	65 (4.8)	36 (4.0)	45 (2.7)	85 (3.3)
6	132 (9.7)	91 (10.1)	140 (8.5)	247 (9.5)
7	58 (4.2)	39 (4.3)	65 (3.9)	111 (4.3)
8	161 (11.8)	101 (11.2)	183 (11.1)	291 (11.1)
9	59 (4.3)	40 (4.5)	54 (3.3)	97 (3.7)
10	140 (10.3)	119 (13.3)	165 (10.0)	286 (11.0)
11	38 (2.8)	31 (3.5)	38 (2.3)	70 (2.7)
12	116 (8.5)	85 (9.5)	125 (7.6)	213 (8.2)
13	31 (2.3)	18 (2.0)	32 (1.9)	50 (1.9)
14	100 (7.3)	67 (7.5)	110 (6.7)	177 (6.8)
15	257 (18.8)	127 (14.1)	477 (28.9)	604 (23.1)
16	1 (0.1)	0	3 (0.2)	3 (0.1)
17	1 (0.1)	1 (0.1)	0	1 (<0.1)
Total No. of Doses				
N	1365	898	1650	2610
Mean (SD)	9.3 (4.39)	9.1 (4.22)	10.1 (4.46)	9.6 (4.41)
Median	10	9	10	10
Minimum, maximum	1, 17	1, 17	1, 16	1, 17
Treatment Period (Days)				
N	1365	898	1650	2610
Mean (SD)	5.5 (2.19)	5.4 (2.14)	5.8 (2.19)	5.6 (2.19)
Median	6	6	6	6
Minimum, maximum	1, 9	1, 10	1, 9	1, 10
Total Exposure to alvimopan (mg)				
N	1365	898	1650	2610
Mean (SD)	NA	54.4 (25.33)	121.1 (53.57)	95.6 (56.51)
Median	NA	54	120	90
Minimum, maximum	NA	6, 102	12, 192	1, 192

*The overall POI population includes 206, 213, 214, 302, 306, 308, 313, 314, and 001
Reference: ISS, Table 14, Page36

6.5 Common Adverse Events

The frequency of the most common TEAEs in the POI population was similar in the alvimopan and placebo groups. Table 31 displays the most frequent treatment-related TEAEs in the POI population.

Table 31: Common Treatment-related, TEAEs in the POI Population

Preferred Term (1)	placebo	alvimopan				total
	(N=1365)	1-3 mg	6 mg	12 mg	(N=2610)	
	n (%)	(N=62) n (%)	(N=898) n (%)	(N=1650) n (%)	(N=2610) n (%)	
Subjects with at least one AE	362 (26.5)	24 (38.7)*	236 (26.3)	464 (28.1)*	724 (27.7)	
NAUSEA	209 (15.3)	16 (25.8)*	133 (14.8)	263 (15.9)	412 (15.8)	
VOMITING	95 (7.0)	7 (11.3)*	59 (6.6)	83 (5.0)	149 (5.7)	
FLATULENCE	41 (3.0)	2 (3.2)	22 (2.4)	68 (4.1)*	92 (3.5)	
ABDOMINAL DISTENSION	46 (3.4)	2 (3.2)	21 (2.3)	50 (3.0)	73 (2.8)	
CONSTIPATION	32 (2.3)	0	10 (1.1)	50 (3.0)	60 (2.3)	
DIARRHOEA	24 (1.8)	1 (1.6)	29 (3.2)*	36 (2.2)	66 (2.5)	
PRURITUS	27 (2.0)	2 (3.2)*	14 (1.6)	42 (2.5)	58 (2.2)	
DYSPEPSIA	15 (1.1)	2 (3.2)*	6 (0.7)	30 (1.8)	38 (1.5)	
HEADACHE	12 (0.9)	0	12 (1.3)	28 (1.7)	40 (1.5)	
INSOMNIA	15 (1.1)	1 (1.6)	7 (0.8)	26 (1.6)	34 (1.3)	
POSTOPERATIVE ILEUS	13 (1.0)	1 (1.6)	13 (1.4)	15 (0.9)	29 (1.1)	
ASPARTATE AMINOTRANSFERASE INCREASED	11 (0.8)	0	5 (0.6)	21 (1.3)	26 (1.0)	
ABDOMINAL PAIN	12 (0.9)	2 (3.2)*	3 (0.3)	19 (1.2)	24 (0.9)	
ALANINE AMINOTRANSFERASE INCREASED	10 (0.7)	0	3 (0.3)	21 (1.3)	24 (0.9)	

Reference: ISS, Table A.2.5.1, Page 997.

The frequency of the most common treatment-related TEAEs in the POI population was similar in the alvimopan and placebo groups.

6.6 Laboratory Findings

For all the POI studies, the following laboratory studies were performed during the Screening Period: a complete blood count (CBC), a basic metabolic panel (BMP), a hepatic panel, direct bilirubin, and total protein. Additionally, a urine pregnancy test for female patients of child bearing potential and biochemical liver tests for all patients were performed on POD -1 or POD 0. In Studies 302, 308, 313, and 001, a CBC with differential, LDH, and calcium blood tests and a urinalysis were performed during the Screening visit.

In all the POI trials, prior to discharge from the hospital or at study termination, BMPs, hepatic panels, and CBCs were collected. In Studies 302, 308, 313, and 001, a CBC with differential and a urinalysis were also performed prior to discharge from the hospital or at study termination. In Study 306, the phase 3 safety study, these laboratory tests were repeated during the follow-up clinical visit (7-10 days after the last dose of study medication). In the eight other phase 2 and 3 POI studies (i.e., Studies 206, 213, 214, 302, 308, 313, 314, and 001), follow-up laboratory testing was not performed.

The percentage of patients with elevated liver tests (≥ 3 times normal) at the end of the study was comparable among the placebo and alvimopan groups (considering baseline

abnormalities) in the pooled U.S. POI studies. There were no significant differences in elevated liver tests (≥ 3 times normal) among the alvimopan and placebo treatment groups in the U.S. POI studies.

6.7 Vital Signs

In all of the POI studies, vital signs (including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) were obtained during the Screening Period, twice daily during POD 1 to POD 10 (while the patients were hospitalized), and at hospital discharge or study termination. Additionally, in Study 306 vital signs were performed 7-10 days after the last dose of study medication.

There is no evidence that alvimopan increases blood pressure, compared to the placebo group, in the POI studies.

6.8 Electrocardiograms (ECGs)

The two *in vitro* assays (cloned hERG channels expressed in mammalian cells and isolated dog Purkinje fibers) for CV effects of alvimopan and its primary degradant (ADL 08-0011) were completely negative for any significant cardiovascular pharmacologic effect. In addition, the *in vivo* safety studies of alvimopan and ADL 08-0011 in conscious dogs and anesthetized dogs were completely negative for any significant cardiovascular effect (e.g., there were no significant changes in blood pressure or heart rate and there were no significant changes in the ECG including the QTc interval).

In eight of the nine POI studies, ECGs were performed at baseline. Study 314 did not perform baseline or follow-up ECGs.

In Studies 302, 308, 313, and 001, ECGs were performed at hospital discharge/study termination. In Study 206, ECGs were performed 1-14 days after the last dose of study medication. In the Study 306, ECGs were performed 7-10 days after the last dose of study medication. In Study 214, ECGs were performed on PODs 1, 2, 3, and 4 (after the administration of the morning study medication) and at hospital discharge/study termination. In Study 213, ECGs were performed on POD 3, POD 5, and hospital discharge/study termination. In Study 001, four additional ECGs (i.e., before Day 3 dose, before Day 7 dose, and 1.5 hours after the morning dose on Day 3 and Day 7) were performed in a subset of study patients. In Study 214, QTc evaluations were performed.

In the U.S. POI studies that conducted ECGs, there were no significant differences in shifts from normal to abnormal ECGs among the alvimopan and placebo groups.

Study SB-767905/016 was a randomized, single-center, placebo-controlled, moxifloxacin-controlled, parallel thorough QT/QTc study of alvimopan in healthy subjects. Subjects were randomized to one of the following four study treatments:

- 1) Alvimopan 6 mg BID for 6.5 days;
- 2) Alvimopan 24 mg BID for 6.5 days;

- 3) Placebo BID for 6.5 days; and
- 4) Moxifloxacin 400 mg for one single dose.

Both alvimopan doses and placebo were administered under double-blind conditions; however, moxifloxacin was given open-label. ECGs were performed for QT analysis on Day 1 (prior to the first dose and 1, 2, 3, 6, and 12 hours after the first dose) and on Day 7 (prior to the AM dose on Day 7 and 1, 2, 3, 6, 12, 18, 23, 48, and 168 hours after the dose). Three ECGs were taken about one minute apart at each time point. Pharmacokinetics of alvimopan and its primary degradant (ADL 08-0011) were performed throughout the study period.

In this study, 162 patients were part of the efficacy analysis (they had one QTc measurement). There were no SAEs or arrhythmias in any of the treatment groups.

In a thorough QT study in healthy subjects, there appeared to be a dose-response relationship in QTc prolongation following multiple dose administration of alvimopan. However, the QT prolongation effect of alvimopan even at 24 mg BID is considered to be less than that of moxifloxacin 400 mg.

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

Meeting of the Gastrointestinal Drugs Advisory Committee (GIDAC)
January 23, 2007

**BACKGROUND MATERIALS
Clinical Evaluation Part 2: Special Safety Section
Prepared by Marjorie Dannis, M.D.**

- I. Cardiovascular Safety of Alvimopan in the POI Program**
- II. Cardiovascular Safety of Alvimopan in the OBD Program**
- III. Neoplasms in the Alvimopan OBD and POI Programs**
- IV. Fractures in the Alvimopan OBD Program**

I. Cardiovascular Safety of Alvimopan in the Postoperative Ileus (POI) Program

Note: this is a preliminary FDA evaluation of cardiovascular safety; the review is currently ongoing.

Background

A total of 3975 patients were included in the worldwide POI safety database, 1365 patients received placebo and 2610 patients received alvimopan at doses of 1 mg, 3 mg, 6 mg, or 12 mg. The patients were enrolled in 9 double blind, placebo-controlled, parallel-group studies. The dosing regimen for all studies was: 1 dose of study medication preoperatively followed by BID dosing on postoperative day 1 until discharge or up to a maximum of 7 days. Postoperative ileus patients in the worldwide safety database received a median of 9 to 10 doses of study drug over a median duration of 6 days. The pivotal registrational studies used a dose of 12 mg.

Patients received investigator follow up visits per study protocol while hospitalized; discharged patients received follow up only by telephone. The majority of POI patients were followed for a maximum of 2 weeks post study medication. Many patients received no follow up after hospital discharge.

Overall, the frequency of serious CV events in the POI population was similar in the alvimopan and placebo groups. The serious CV events analyzed included myocardial infarction (MI), unstable angina, congestive heart failure (CHF), serious arrhythmia, cerebrovascular accident (CVA) and cardiac arrest. Although there were minor differences in the interpretation of individual events, the end result was the same; the percent of serious CV events appeared balanced between treatment groups.

Baseline Demographics

In the overall POI population, baseline demographics were well balanced between treatment groups as seen in Table 1. Furthermore, the risk factors for cardiovascular disease were also represented equally between treatment groups as seen in Table 2.

Table 1: Demographic and Baseline Characteristics

Demographic Baseline Characteristic	Worldwide POI Population	
	Alvimopan Group (N=2610)	Placebo (N=1365)
Age (years)		
N	2610	1365
Mean (SD)	57.0 (14.78)	58.0 (14.39)
Median (min - max)	57.0 (19.0 – 97.0)	58.0 (20.0 – 95.0)
≥ 65 Years, n (%)	898 (34.4)	491 (36.0)
Race		
Black	238 (9.1)	132 (9.7)
Caucasian	2207 (84.6)	1156 (84.7)
Other	157 (6.0)	73 (5.3)
Gender		
Female	1680 (64.4)	850 (62.3)
Male	930 (35.6)	515 (37.7)
BMI (kg/m²)		
N	2575	1351
Mean (SD)	28.0 (6.18)	28.3 (6.20)
Median (min - max)	27.0 (13.8 – 70.8)	27.3 (15.4 – 67.0)

Reference: Cardiovascular Safety of Alvimopan in the Postoperative Ileus Program, adapted from Table 2, page 19

Table 2: CV Risk Factors in Worldwide POI Population

CV risk factor	Alvimopan (N=2610)	Placebo(N=1365)
Mean (SD) age	57 (15)	58 (14)
% BMI ≥ 30	29	32
% Diabetes	12	10
% Hypertension	39	43
% Smoking	8	10

Reference: Adolor's Response to Information Request on Sept 21, 2006

Results

The initial safety review for the short term indication of POI did not reveal any specific cardiovascular safety concerns. Due to a potential imbalance observed in CV events between treatment groups in a long term safety study (SB-767905/014) of alvimopan used for opioid induced bowel dysfunction (OBD), additional evaluations of the CV safety of alvimopan for the short term indication of POI were performed. In addition,

independent analyses by the sponsor, multiple FDA medical reviewers and a blinded adjudication (by the Duke Clinical Research Institute Clinical Events Committee (DCRI)) were completed. Table 3 is a summary of all the serious CV events as per the sponsor and the independent adjudication committee.

Table 3: Sponsor's Table of Cardiovascular Events in the Postoperative Ileus Population (Worldwide Postoperative Ileus Safety Database and DCRI Adjudication Results)

Event	Worldwide POI Safety Database			DCRI Adjudication Results		
	Alvimopan (N=2610)	Placebo (N=1365)	Relative Risk Alv vs Pbo (95% CI)	Alvimopan (N=2610)	Placebo (N=1365)	Relative Risk Alv vs Pbo (95% CI)
	n (%)	n (%)		n (%)	n (%)	
All cause death	13 (0.50)	9 (0.66)	0.76 (0.32, 1.76)	13 (0.50)	9 (0.66)	0.76 (0.32, 1.76)
Death from cardiovascular events	4 (0.15)	2 (0.15)	1.05 (0.19, 5.7)	5 (0.19)	2 (0.15)	1.31 (0.25, 6.73)
MI: Overall	13 (0.50)	7 (0.51)	0.97 (0.39, 2.43)	14 (0.54)	7 (0.51)	1.05 (0.42, 2.59)
- Fatal	1 (0.04)	0	--	1 (0.04)	0	--
- Non-fatal	12 (0.46)	7 (0.51)	--	13 (0.50)	7 (0.51)	--
Unstable angina	0	4 (0.29)	0.06 (0, 1.08)	1 (0.04)	2 (0.15)	0.26 (0.02, 2.88)
CVA: Overall	4 (0.15)	4 (0.29)	0.52 (0.13, 2.09)	4 (0.15)	3 (0.22)	0.7 (0.16, 3.11)
- Fatal	1 (0.04)	0	--	0	0	--
- Non-fatal	3 (0.11)	4 (0.29)	--	4 (0.15)	3 (0.22)	--
CHF: Overall	17 (0.65)	12 (0.88)	0.74 (0.35, 1.55)	16 (0.61)	9 (0.66)	0.93 (0.41, 2.1)
- Fatal	1 (0.04)	0	--	1 (0.04)	0	--
- Non-fatal	16 (0.61)	12 (0.88)	--	15 (0.57)	9 (0.66)	--
Serious arrhythmia: overall	16 (0.61)	11 (0.81)	0.76 (0.35, 1.63)	12 (0.46)	5 (0.37)	1.26 (0.44, 3.56)
- Fatal	0	0	--	0	0	--
- Non-fatal	16 (0.61)	11 (0.81)	--	12 (0.46)	5 (0.37)	--
Cardiac arrest: Overall	5 (0.19)	6 (0.44)	0.44 (0.13, 1.43)	8 (0.31)	7 (0.51)	0.6 (0.22, 1.64)
- Fatal	0	2 (0.15)	--	1 (0.04)	1 (0.07)	--
- Non-fatal	5 (0.19)	4 (0.29)	--	7 (0.27)	6 (0.44)	--

Data Source: [Tables 1.1.1 and 1.1.3](#)

Studies 13C206, 13C213, 13C214, 14CL302, 14CL306, 14CL308, 14CL313, 14CL314, and SB-767905/001

Note: Alvimopan group included the following alvimopan doses: 1 mg (N=27), 3 mg (N=35), 6 mg (N=898), and 12 mg (N=1650).

Tables 4A and 4B show FDA analyses that are based on the sponsor's data except for the situation wherein a patient had more than one serious CV event. In this case, a patient was assigned to the category of most clinical significance. *Ischemic events* included the following fatal and non-fatal events: MI, unstable angina, and cerebrovascular accident. *Other serious cardiovascular events* included the following fatal and non-fatal events: congestive heart failure, serious arrhythmia, cardiac arrest and non-ischemic cardiovascular death. Note that the total number of patients experiencing cardiovascular events in each group is less than the sum of events in each major category due to the following subjects with more than one event:

Alvimopan subject 14CL314-25-00025 had a non-fatal MI and non-fatal CHF
Alvimopan subject 14CL314-36-00240 had a non-fatal MI and non-fatal CHF
Alvimopan subject 14CL302-61-01173 had a non-fatal cerebrovascular accident and non-fatal CHF
Alvimopan subject 14CL308-03-01041 had non-fatal cardiac arrest and a non-fatal serious arrhythmia
Alvimopan subject 14CL314-26-00260 had non-fatal CHF and a non-fatal serious arrhythmia
Placebo subject 14CL308-13-01235 had a non-fatal MI, unstable angina, and non-fatal CHF
Placebo subject 14CL313-38-38001 had non-fatal CHF and a non-fatal serious arrhythmia
Placebo subject GSK001-62-01289 had a non-fatal serious arrhythmia and non-fatal cardiac arrest

See Table A, in the Appendix for this medical reviewer's analysis and summary of specific CV events in the total POI population.

These various assessments revealed minor differences in the interpretation of specific cardiovascular events, thus the tables created by the sponsor, the DCRI adjudication and by this medical reviewer are different. These were retrospective analyses of cardiovascular events without pre-specified criteria defining CV events; therefore, minor differences in classification are not unexpected. Some patients had multiple events which were medically related, and in others, necessary information to confirm a diagnosis was missing. Despite the individual interpretations, there do not appear to be differences in the number of serious cardiovascular events in the alvimopan group relative to the placebo group. As seen in Tables 4A and 4B, the alvimopan and placebo group are balanced for these events as well as for all cause death.

Table 4A: Number (%) of Patients Experiencing Death or Serious Cardiovascular Events by Treatment Group in the Total POI Population

	Alvimopan N=2610 n (%)	Placebo N=1365 n (%)	Relative Risk (asymptotic 95% CI)
All cause death (total)	13 (0.50)	9 (0.66)	0.76 (0.33, 1.72)
• Death from cardiovascular events	4 (0.15)	2 (0.15)	1.05 (0.22, 4.88)
Subjects with cardiovascular events (total)	51 (1.95)	39 (2.86)	0.68 (0.45, 1.03)

Source: Statistical Reviewer's calculation using sponsor Table 9 on pages 41 to 44 of the Cardiovascular Safety of Alvimopan in the Postoperative Ileus Program.

Includes studies 13C206, 13C213, 13C214, 14CL302, 14CL306, 14CL308, 14CL313, 14CL314, and SB-767905/001

Note: Alvimopan group includes the following alvimopan doses: 1 mg (N=27), 3 mg (N=35), 6 mg (N=898), and 12 mg (N=1650).

Table 4B: Number (%) of Cardiovascular Events by Treatment Group in the Total POI Population

	Alvimopan N=2610 n (%)	Placebo N=1365 n (%)	Relative Risk (asymptotic 95% CI)
Ischemic events	17 (0.65)	14 (1.03)	0.64 (0.32, 1.27)
• Fatal	2 (0.08)	0 (0.0)	- (0.27, -)
Other serious cardiovascular events	39 (1.49)	29 (2.12)	0.70 (0.44, 1.13)
• Fatal	2 (0.08)	2 (0.15)	0.52 (0.09, 2.96)

Source: Statistical Reviewer's calculation using sponsor Table 9 on pages 41 to 44 of the Cardiovascular Safety of Alvimopan in the Postoperative Ileus Program.

Includes studies 13C206, 13C213, 13C214, 14CL302, 14CL306, 14CL308, 14CL313, 14CL314, and SB-767905/001

Note: Alvimopan group includes the following alvimopan doses: 1 mg (N=27), 3 mg (N=35), 6 mg (N=898), and 12 mg (N=1650).

Limitations of Study Design

All of the POI studies had limited post-treatment follow-up visits. Most of the studies relied upon a telephone call shortly after hospital discharge to gather potential adverse event data. Very few patients were followed beyond a 2 week period, with the majority of telephone follow up calls occurring between 6 and 14 days post discharge. Hospitalized patients in the POI clinical trials could achieve the primary efficacy endpoint in the morning and be discharged later that day. In this example, the discharge procedures would have been conducted within several hours of the last study medication dose. Since the alvimopan metabolite can last in the body for several days after the last alvimopan dose (95% of alvimopan and its metabolite are out of the body in 5 days after the last dose), these patients may have had sub optimal post-treatment follow-up.

Follow-up telephone calls occurring 5-7 days post discharge may not elicit all adverse events. In addition, if a patient is unreachable, no follow up data for that patient is obtained. The study design for most of the POI studies defined patients who completed the study as: “if all protocol specified in-hospital assessments were performed as captured on the CRF”. Patients who completed the inpatient part of the study, yet had NO follow-up after discharge were counted as patients who completed the entire study. Table 5 clarifies the post hospital discharge surveillance.

According to the sponsor, 580 patients did not complete the study for any reason and an additional 257 patients received **NO** follow up after discharge from the hospital. These numbers were reasonably well balanced between treatment groups; the alvimopan group had a total of 20% of patients discontinuing the study or receiving no follow up and the placebo group had 23%. (Reference: Sponsor’s Response to IR dated October 18, 2007)

Table 5: Post-discharge safety surveillance of patients in POI population

	Time after last study dose	Alvimopan (N=2610)	Placebo (N=1365)
Had a follow-up telephone call, n (%)	Anytime	1874 (72)	1052 (77)
	1-5 days after	332 (13)	164 (12)
	6-14 days after	1453 (56)	835 (61)
	> 15 days after	89 (3)	53 (4)
Had investigator follow-up visit, n (%)	Anytime	416 (16)	110 (8)
	1-5 days after	22 (<1)	11 (<1)
	6-14 days after	374 (14)	94 (7)
	> 15 days after	19 (<1)	5 (<1)

Reference: September 21, 2006 submission (response to our September 6, 2006 information request), Table 3, Page 122.

Statistical Reviewer Comments on Sponsor's POI Kaplan-Meier Curves (Figure 1)

The Kaplan-Meier curves for time to cardiovascular event reproduced below were generated using:

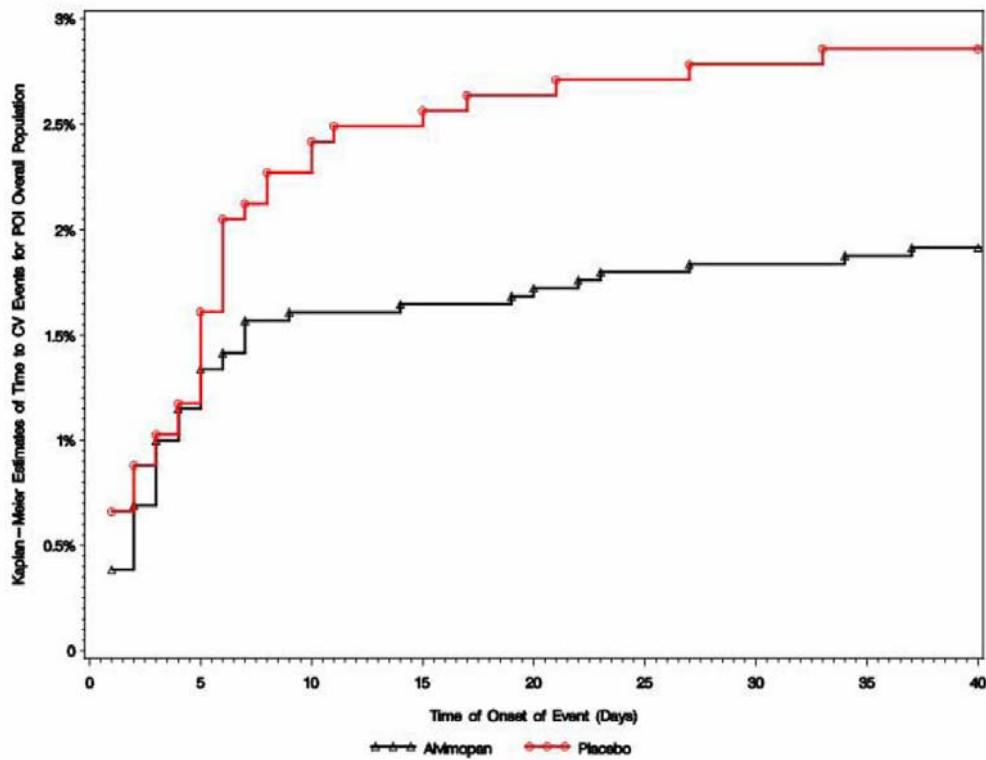
- The day of the CV event for subjects who had a CV event and the remaining subjects were censored at day 40
- The CV events ascertained while the subject was in the study, in hospital, or at the 2-week phone post-study follow-up.

By using the day of the CV event for those subjects with CV events and assigning day 40 as the last day for inclusion in the risk set for the non-CV subjects, the risk set is reduced only by subjects with a CV event over the entire 40-day period. If the last observed time was used for the non-CV subjects, the risk set would be reduced by both the CV and non-CV subjects over the 40-day time period.

The lack of follow-up beyond two weeks post-study does not justify assuming that those subjects with no CV events ascertained from time of first study drug dose to follow-up phone call did not have a CV event during the remainder of the 40-day time period or after.

Thus, the time to cardiovascular event as represented in these Kaplan-Meier curves cannot be reliably estimated. An analysis using the last known follow-up time for each subject will be done to better estimate the Kaplan-Meier curves.

Figure 1: Kaplan-Meier Estimate of Time to Cardiovascular Event for the Overall Postoperative Ileus Population



Reference: Sponsor's Figure 2 from POI CV Safety Report

Studies 13C206, 13C213, 13C214, 14CL302, 14CL306, 14CL308, 14CL313, 14CL314, and SB-767905/001

Note: Cardiovascular events in the above figure include cardiovascular death, fatal and nonfatal MI, CHF, stroke, unstable angina, serious arrhythmia, and cardiac arrest

Conclusion

In summary, with the available safety data, where multiple approaches were undertaken, the occurrence of serious cardiovascular events appears to be balanced between the alvimopan and placebo treatment groups. However, given the limited patient follow up, complete information is not be available, thus no definite conclusions about cardiovascular safety in the POI population can be drawn.

Appendix: Medical Reviewer's Listings

Table A: Medical Reviewer's Summary of MI, Cardiac Arrest and CV Deaths in All POI Studies By Patient Number

	Alvimopan (N=2610)	Placebo (N=1365)	
MI	14CL313.13.13015*	13C213.05.00006	
	14CL313.03.03014	14CL308.13.01235	
	14CL314.01.00702	13C213.05.00006	
	14CL314.25.00025	14CL302.06.01056	
	14CL314.32.00586	14CL308.13.01235	
	14CL314.36.00240	14CL313.18.18016	
	GSK001-02-00022	14CL314.01.00068	
	GSK001.15.00970	14CL314.08.00733	
	GSK-001-19-00257		
	GSK001-27-00404		
	GSK001.29.00432		
	GSK001-34-00520		
	14CL308.31.01182#		
Cardiac arrest	14CL308-03-01041	14CL313.02.02006	
	14CL308.25.01126	GSK001-03-00042	
	GSK001-15-00964	GSK001-15-00977	
	GSK001.38.01221	14CL308.15.02143	
	GSK001.39.01284		
CV deaths	14CL308.31.01182#	GSK00119263	
	14CL313.13.13015*	14CL31440191	
	GSK001.56.00273		
	14CL302.22.01118		

*, #: These two patients were categorized as MI and CV death

Reference: Adolor's Clinical Perspective: Cardiovascular Safety of Alvimopan in the Postoperative Ileus Program, Table 9 and individual narrative summaries

II. Cardiovascular Safety of Alvimopan in the Opioid Induced Bowel Dysfunction (OBD) Program

Note: this is a preliminary FDA evaluation of cardiovascular safety; the review is currently ongoing.

Background

Another source of safety data for alvimopan comes from the OBD development program. This clinical program includes studies of cancer patients with OBD (N=295: 210 alvimopan and 85 placebo) and non-cancer patients with OBD (N=2518: 1728 alvimopan and 790 placebo). The pooled analyses include randomized, double blind placebo controlled studies of these populations. The majority of the alvimopan studies performed for this indication were from 3-12 weeks in duration. In general, this population was exposed to a lower dose of alvimopan (0.5mg QD- 1.0 mg BID).

In the only long-term safety study SB-767905/014 (Study 014), of 1 year duration, a greater incidence of serious cardiovascular adverse (CV) events was noted in the alvimopan treatment group as compared to the placebo group. Study 014 was a placebo-controlled, safety study of alvimopan 0.5mg BID in the non-cancer pain population. The study used a blinded 2:1 (alvimopan/placebo) treatment allocation.

Safety Analyses

Due to the potential imbalance observed in study 014, a thorough review of serious cardiovascular events in the world-wide OBD program was performed. Several analyses were done to calculate the incidence of serious cardiovascular events in pooled OBD studies as well as in study 014 alone. These analyses included the following cardiovascular events: myocardial infarction (MI), unstable angina, congestive heart failure (CHF), serious arrhythmia and cerebrovascular accident (CVA).

As seen in Tables 1A and 1B, there was an imbalance of serious CV events and CV deaths between treatment groups in the non-cancer OBD population. The percent of patients having any CV event was 1.22% in the alvimopan group and 0.51% in the placebo group. This imbalance was largely driven by an imbalance of CV ischemic events with 0.81% occurring in the alvimopan group vs. 0.38% occurring in the placebo group. In addition, there were 2 CV deaths in the alvimopan group and no CV deaths in the placebo group.

Tables 1A and 1B were slightly different from the sponsor's tables; patients who had more than 1 CV event were placed in the category of most severity, thus each patient was counted only once. *Ischemic events* included the following fatal and non-fatal events: MI, unstable angina, and cerebrovascular accident. *Other serious cardiovascular events* included the following fatal and non-fatal events: congestive heart failure, serious arrhythmia, and sudden death. Note that the total number of patients experiencing

cardiovascular events in each group is one less than the sum of events in each major category due to the following subjects with more than one event:

- ❖ **Alvimopan** subject 011 006513 1650 had unstable angina and non-fatal congestive heart failure
- ❖ **Placebo** subject 012 060006 6053 had a non-fatal MI and non-fatal congestive heart failure

See Table 2 for further details.

Table 1A: Number (%) of Patients Experiencing Death or Serious Cardiovascular Events by Treatment Group in the Non-Cancer OBD Population (FDA Analysis)

	Alvimopan N=1728 n (%)	Placebo N=790 n (%)	Relative Risk (asymptotic 95% CI)
All cause death (total)	4 (0.23)	2 (0.25)	0.91 (0.17, 4.98)
• Death from cardiovascular events	2 (0.12)	0 (0.0)	- (0.24, -)
Subjects with cardiovascular events (total)	21 (1.22)	4 (0.51)	2.40 (0.87, 6.67)

Source: Statistical Reviewer's calculation using sponsor Table 1 on page 9 of the OBD CV safety report.

Includes studies SB-767905/011, SB-767905/012, SB-767905/014, 13C217, and 13C304

Note: Alvimopan group includes the following alvimopan dose and regimens: 0.5 mg QD (N=401), 1 mg QD (N=197), 0.5 mg BID (N=1000), and 1 mg BID (N=130).

Table 1B: Number (%) of Cardiovascular Events by Treatment Group in the Non-Cancer OBD Population (FDA Analysis)

	Alvimopan N=1728 n (%)	Placebo N=790 n (%)	Relative Risk (asymptotic 95% CI)
Ischemic events	14 (0.81)	3 (0.38)	2.13 (0.66, 6.92)
• Fatal	1 (0.06)	0 (0.0)	- (0.12, -)
Other serious cardiovascular events	8 (0.46)	2 (0.25)	1.83 (0.44, 7.60)
• Fatal	1(0.06)	0 (0.0)	- (0.12, -)

Source: Statistical Reviewer's calculation using sponsor Table 1 on page 9 of the OBD CV safety report.

Includes studies SB-767905/011, SB-767905/012, SB-767905/014, 13C217, and 13C304

Note: Alvimopan group includes the following alvimopan dose and regimens: 0.5 mg QD (N=401), 1 mg QD (N=197), 0.5 mg BID (N=1000), and 1 mg BID (N=130).

Table 2: Duplicate Patients in Sponsor's Analysis

Subject ID	Brief History	Diagnosis/category	Treatment Group
*GSK012-020300-010087	Pt was" diagnosed with pulmonary embolus due to the lack of cardiac history and the abruptness of the onset of death"; had sudden death	CV death	Alvimopan
GSK011-006513-001650	Reported as having unstable angina and CHF, could only find some documentation of USA	Unstable angina	Alvimopan
GSK008-000505-001347	History of metastatic prostate cancer, extremely limited information, presumed CHF, renal failure, had serious arrhythmia, question of cardiac arrest	Serious arrhythmia	Alvimopan
GSK012-019618-006053	Had MI and CHF	MI	Placebo
*GSK008-022436-002077	Sudden death	CV death	Placebo

*These 2 patients were in the CV death category but not in any other category in sponsor's tables
Reference: OBD CV safety report page 11 and individual narratives.

Tables 3A and 3B list the serious CV events which occurred in study 014 alone. There was a large imbalance of CV events between treatment groups with 14 patients (2.60%) having a serious CV event (including one CV death) in the alvimopan group and not one patient having a serious CV event in the placebo group. Of note, 7 patients (1.3%) in the alvimopan group had a myocardial infarction. There was no difference between treatment groups in "all cause death"; however, only 2 patients died in each group. Of significance is that the lower bound of the 95% confidence interval for the percent of subjects with cardiovascular events is 1.83 (Table 3A); the relative risk for ischemic events in the alvimopan group vs. the placebo group is 1.44 (Table 3B).

Table 3A: Number (%) of Patients Experiencing Death or Serious Cardiovascular Events by Treatment Group in the Non-Cancer OBD Study SB-767905/014 (FDA Analysis)

	Alvimopan N=538 n (%)	Placebo N=267 n (%)	Relative Risk (asymptotic 95% CI)
All cause death (total)	2 (0.37)	2 (0.75)	0.50 (0.09, 2.80)
• Death from cardiovascular events	1 (0.19)	0 (0.0)	- (0.13, -)
Subjects with cardiovascular events (total)	14 (2.60)	0 (0.0)	- (1.83, -)

Source: Statistical Reviewer's calculation using sponsor Table 2 on page 10 of the OBD CV safety report.
Ischemic events include the following fatal and non-fatal events: MI, Unstable angina, and cerebrovascular accident.
Other serious cardiovascular events include the following fatal and non-fatal events: congestive heart failure and serious arrhythmia.
Note: Alvimopan group includes the following alvimopan dose and regimens: 0.5 mg BID (N=538),

Table 3B: Number (%) of Cardiovascular Events by Treatment Group in the Non-Cancer OBD Study SB-767905/014 (FDA Analysis)

	Alvimopan N=538 n (%)	Placebo N=267 n (%)	Relative Risk (asymptotic 95% CI)
Ischemic events	11 (2.05)	0 (0.0)	- (1.44, -)
• Fatal	1 (0.19)	0 (0.0)	- (0.13, -)
Other serious cardiovascular events	3 (0.56)	0 (0.0)	- (0.39, -)

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

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

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

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

The entire safety population, both cancer and non-cancer patients with OBD is displayed in Tables 4A and 4B. Once again there is an imbalance between treatment groups in total CV events; 1.38% of patients in the alvimopan group had serious CV events vs. 0.70% in the placebo group. In addition, the alvimopan treatment group has a much higher percentage of CV deaths than the placebo group, 0.26% and 0.12% respectively. The “all cause death” rates are also imbalanced with 1.27% in the alvimopan group and 0.58 % in the treatment group.

The slight difference in total number of CV events per patient as compared to the sponsor's analyses can be explained by duplicate events. *Ischemic events* included the following fatal and non-fatal events: MI, unstable angina, and CVA. *Other serious cardiovascular events* include the following fatal and non-fatal events: CHF, serious arrhythmia, and sudden death. The total number of patients experiencing cardiovascular events in each group is less than the sum of events in each major category due to the following subjects with more than one event:

- ❖ **Alvimopan** subject 008 0246881347 had death from serious arrhythmia and non-fatal CHF
- ❖ **Alvimopan** subject 011 006513 1650 had unstable angina and non-fatal CHF
- ❖ **Placebo** subject 012 060006 6053 had a non-fatal MI and non-fatal CHF

Table 4A: Number (%) of Patients Experiencing Death or Serious Cardiovascular Events by Treatment Group in the Long-Term (>14days) OBD Population (FDA Analysis)

	Alvimopan N=1888 n (%)	Placebo N=860 n (%)	Relative Risk (asymptotic 95% CI)
All cause death (total)	24 (1.27)	5 (0.58)	2.19 (0.87, 5.53)
• Death from cardiovascular events	5 (0.26)	1 (0.12)	2.28 (0.35, 14.70)
Subjects with cardiovascular events (total)	26 (1.38)	6 (0.70)	1.97 (0.84, 4.66)

Source: Statistical Reviewer's calculation using sponsor Table 3 on pages 11 and 12 of the OBD CV safety report.

Includes studies SB-767905/008, SB-767905/011, SB-767905/012, SB-767905/013, SB-767905/014, 13C217, 13C304, and ABD101684

Note: Alvimopan group includes the following alvimopan dose and regimens: 0.5 mg QD (N=401), 1 mg QD (N=224), 0.5 mg BID (N=1068), 1 mg BID (N=195).

Table 4B: Number (%) of Cardiovascular Events by Treatment Group in the Long-Term (>14days) OBD Population (FDA Analysis)

	Alvimopan N=1888 n (%)	Placebo N=860 n (%)	Relative Risk (asymptotic 95% CI)
Ischemic events	14 (0.74)	4 (0.46)	1.59 (0.55, 4.60)
• Fatal	1 (0.05)	0 (0.0)	- (0.12, -)
Other serious cardiovascular events	14 (0.74)	3 (0.35)	2.13 (0.66, 6.89)
• Fatal	4 (0.21)	1 (0.12)	1.82 (0.27, 11.12)

Source: Statistical Reviewer's calculation using sponsor Table 3 on pages 11 and 12 of the OBD CV safety report.

Includes studies SB-767905/008, SB-767905/011, SB-767905/012, SB-767905/013, SB-767905/014, 13C217, 13C304, and ABD101684

Note: Alvimopan group includes the following alvimopan dose and regimens: 0.5 mg QD (N=401), 1 mg QD (N=224), 0.5 mg BID (N=1068), 1 mg BID (N=195).

The sponsor's analyses of deaths and cardiovascular events in the long-term (>14days) OBD population included one additional study, SB-767905/007. This was a double blind-placebo controlled study of patients with Chronic Idiopathic Constipation (CIC). See Tables A1 and A2 in the Appendix for the FDA analysis of Number (%) of Patients Experiencing Death or Serious Cardiovascular Events by Treatment Group in the Long-Term (>14days) OBD Population including one CIC study, SB-767905/007, and the Number (%) of Cardiovascular Events by Treatment Group in the Long-Term (>14days) OBD Population (including one CIC study, SB-767905/007).

When the CV events in the non-cancer OBD population were categorized separately (Table 5) MI, unstable angina, as well as serious arrhythmias were imbalanced between treatment groups with the alvimopan treatment arm having a higher percentage of each such event; the relative risks for each were 1.83, 4.12 and 5.03 respectively.

Table 5: Summary of Specific CV Events in Non-Cancer OBD Population
(Studies: SB-767905/011, SB-767905/012, SB-767905/013, SB-767905/014, 13C217, and 13C304)

CV event category	Alvimopan (N=1728) n (%)	Placebo (N=790) n (%)	Relative Risk Alvimopan/ Placebo (95% CI)
MI	8 (0.46)	2 (0.25)	1.83 (0.39,8.59)
Unstable Angina	4 (0.23)	0	4.12 (0.22,76.4)
CVA	2 (0.12)	1 (0.13)	0.91 (0.08,10.1)
CHF: Overall	2 (0.12)	2 (0.25)	0.46 (0.06,3.24)
Serious Arrhythmia	5 (0.29)	0	5.03 (0.28,90.9)

Reference: Adapted from Adolor's OBD CV safety summary page 9

When the CV events in study 014 were examined separately, the differences were particularly apparent as seen in Table 6. The imbalances between treatment groups were most pronounced in the rates of MI and unstable angina. The incidences of MI and unstable angina for alvimopan were 1.3% and 0.56% respectively; the placebo group did not have any events. According to the sponsor, the treatment groups in study 014 were well matched overall with respect to pre-existing CV disease and concomitant risk factors.

Table 6: Summary of Specific CV Events in Study SB-767905/014

CV event category	Alvimopan N=538	Placebo N=267 (%)	Relative Risk Alvimopan/ Placebo (95% CI)
	n (%)	n (%)	
MI	7 (1.30)	0	7.46 (0.43,130.1)
Unstable Angina	3 (0.56)	0	3.48 (0.18,67.1)
CVA	1 (0.19)	0	1.49 (0.06,36.5)
CHF: Overall	1(0.19)	0	1.49 (0.06,36.5)
Serious Arrhythmia	2 (0.37)	0	2.49 (0.12,51.6)

Reference: Adapted from Adolor's OBD CV safety summary page 10

When the CV events of the entire OBD population (Table 7) were examined separately, there was a striking imbalance in the number of serious arrhythmias, two of which were fatal. Patients in the alvimopan treatment arm had a 0.44% incidence of serious arrhythmia, as compared to the placebo arm, where there were no events.

Table 7: Summary of Specific CV Events in Long-Term (>14 days) OBD Population
(Studies: SB-767905/007, SB-767905/008, SB-767905/011, SB-767905/012, SB-767905/013, SB-767905/014, 13C21713C304, and ABD101684)

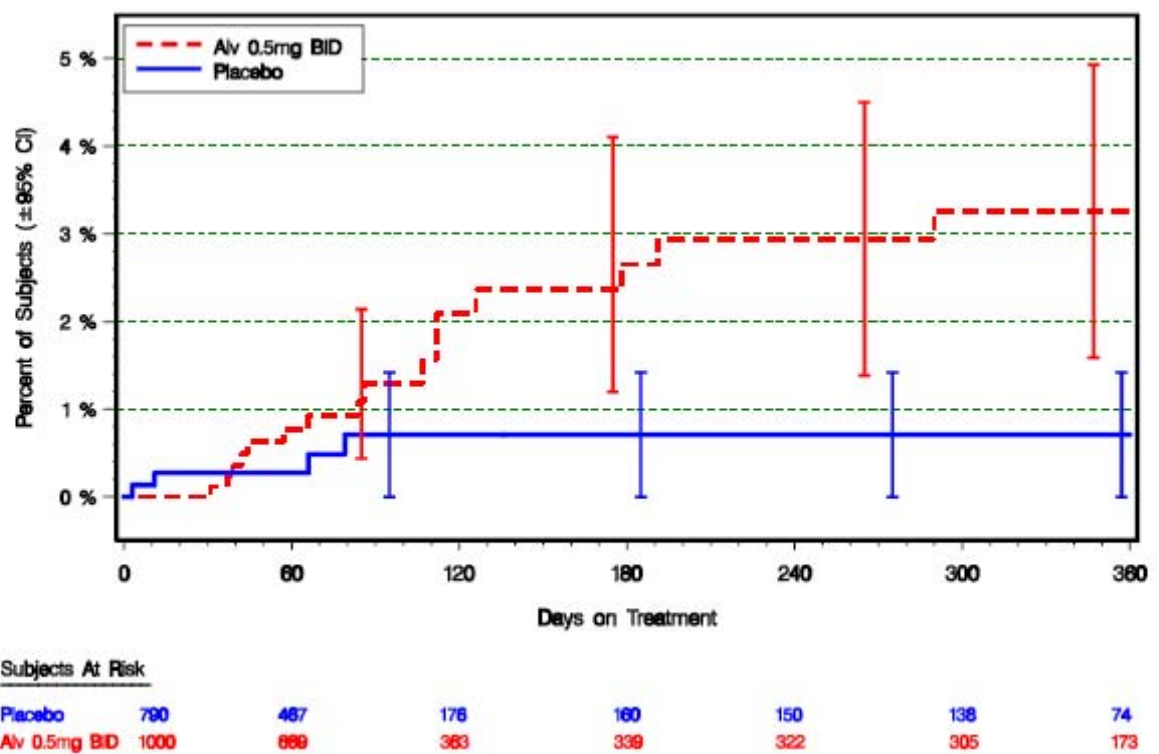
CV event category	Alvimopan N=538	Placebo N=267	Relative Risk Alvimopan/ Placebo (95% CI)
	n (%)	n (%)	
MI	8 (0.39)	3 (0.33)	1.19 (0.32,4.46)
Unstable Angina	4 (0.20)	1 (0.11)	1.78 (0.20,15.9)
CVA	2 (0.10)	1 (0.11)	0.89 (0.08,9.79)
CHF: Overall	4 (0.20)	2 (0.22)	0.89 (0.16,4.85)
Serious Arrhythmia	9 (0.44)	0	8.45 (0.49,145.1)

Reference: Adapted from Adolor's OBD CV safety summary page 11-12

Time to event analysis

The sponsor's time to cardiovascular event analysis (Figure 1) suggests that prior to approximately 30 days of exposure, the placebo group has a higher percentage of serious CV events than the alvimopan group; however, after about 30 days of exposure, the alvimopan treatment group has a higher percentage of serious CV events than the placebo group. Additionally, after approximately 85 days of treatment, there are no more placebo serious events reported but, the events in the alvimopan group continued to accrue. Of note, this analysis done by the sponsor included only the 0.5mg BID dose of alvimopan.

Figure 1: Kaplan-Meier Estimates of Time to CV [1] Events: Non-cancer OBD Studies [2]



[1] CV events include cardiovascular death, nonfatal MI, CHF, stroke, unstable angina, serious arrhythmia

[2] Data are from studies 217, 304, 011, 012, 013, and 014.

Reference: Adolor's OBD CV safety summary page 18

Statistical Reviewer Comments on non-Cancer OBD Kaplan-Meier Curves

The Kaplan-Meier curves for time to cardiovascular event represented here were generated using:

- The day of the CV event for subjects who had a CV event and the time-on-treatment for those subjects without a CV event
- All placebo subjects and all 0.5 mg BID subjects were used to generate the Kaplan-Meier curves. None of the other alvimopan doses were used
- A combination of five short-term studies (3 to 12 weeks) and a one long-term (1 year) study

For the non-CV subjects in the short-term studies, a reliable assessment of CV-events between the last day of study drug dose and day 360 was not done. Since these curves used the time-on-treatment for the non-CV subjects and combined the short-term with long-term studies, the Kaplan-Meier estimates after day 84 are not reliable.

For those non-CV subjects in the long-term studies, a reliable assessment of CV events between days 84 and 360 was not done.

By combining the short-term and long-term studies in a single Kaplan-Meier curve, the drop-out rates for the short-term and long-term studies during the first 84 days (12 weeks) are not distinguishable.

Thus, separate Kaplan-Meier analyses for the long-term and short-term studies will be performed.

Conclusion

There is a numeric imbalance of several serious CV events in the pooled analyses of OBD studies and in study 014 alone; the alvimopan treatment group has a higher rate of such events than the placebo group. These imbalances seem to be driven by an overwhelming imbalance in study 014. This was the largest as well as the longest trial. A detailed examination of the data from study 014 failed to identify any differences in patient demographics relative to the other alvimopan OBD studies which would explain the difference in the incidence of CV events observed in Study 014. It does not appear that the study 014 population was at a substantially higher risk for cardiovascular disease than other previously studied OBD populations.

In addition, study 014 was a placebo controlled study and there was no evidence of a failed randomization process. Generally, the baseline demographics were similar between treatment groups; there were no other aspects of study design or study population in study 014 which could accurately explain the large imbalance observed between treatment groups. However, the analysis, follow-up and reporting of events may influence the calculation of the risk estimates. Statistical significance is difficult to achieve in the evaluation of rare events; however, these imbalances suggest a clinical safety issue. There is no clear etiology to explain the differences presented in the aforementioned analyses. Final analysis by the FDA is ongoing.

Appendix

The slight difference in total number of CV events per patient as compared to the sponsor's tables can be explained by duplicate events. *Ischemic events* included the following fatal and non-fatal events: MI, unstable angina, and CVA. *Other serious cardiovascular events* include the following fatal and non-fatal events: CHF, serious arrhythmia, and sudden death. The total number of patients experiencing cardiovascular events in each group is less than the sum of events in each major category due to the following subjects with more than one event:

- ❖ **Alvimopan** subject 008 0246881347 had death from serious arrhythmia and non-fatal CHF
- ❖ **Alvimopan** subject 011 006513 1650 had unstable angina and non-fatal CHF
- ❖ **Placebo** subject 012 060006 6053 had a non-fatal MI and non-fatal CHF

Table A1: Number (%) of Patients Experiencing Death or Serious Cardiovascular Events by Treatment Group in the Long-Term (>14days) OBD Population (including one CIC study, SB-767905/007) (FDA Analysis)

	Alvimopan N=2049 n (%)	Placebo N=911 n (%)	Relative Risk (asymptotic 95% CI)
All cause death (total)	24 (1.17)	5 (0.55)	2.13 (0.85, 5.40)
• Death from cardiovascular events	5 (0.24)	1 (0.11)	2.22 (0.34, 14.35)
Subjects with cardiovascular events (total)	26 (1.27)	7 (0.77)	1.65 (0.74, 3.71)

Source: Statistical Reviewer's calculation using sponsor Table 3 on pages 11 and 12 of the OBD CV safety report. Includes studies SB-767905/007, SB-767905/008, SB-767905/011, SB-767905/012, SB-767905/013, SB-767905/014, 13C217, 13C304, and ABD101684

Note: Alvimopan group includes the following alvimopan dose and regimens: 0.5 mg QD (N=401), 1 mg QD (N=224), 0.5 mg BID (N=1068), 1 mg BID (N=248), 3 mg BID (N=55), and 8 mg BID (N=53).

Table A2: Number (%) of Cardiovascular Events by Treatment Group in the Long-Term (>14days) OBD Population (including one CIC study, SB-767905/007) (FDA Analysis)

	Alvimopan N=2049 n (%)	Placebo N=911 n (%)	Relative Risk (asymptotic 95% CI)
Ischemic events	14 (0.68)	5 (0.55)	1.24 (0.47, 3.32)
• Fatal	1 (0.05)	0 (0.0)	- (0.12, -)
Other serious cardiovascular events	14 (0.68)	3 (0.33)	2.08 (0.64, 6.73)
• Fatal	4 (0.20)	1 (0.11)	1.78 (0.27, 11.83)

Source: Statistical Reviewer's calculation using sponsor Table 3 on pages 11 and 12 of the OBD CV safety report. Includes studies SB-767905/007, SB-767905/008, SB-767905/011, SB-767905/012, SB-767905/013, SB-767905/014, 13C217, 13C304, and ABD101684

Note: Alvimopan group includes the following alvimopan dose and regimens: 0.5 mg QD (N=401), 1 mg QD (N=224), 0.5 mg BID (N=1068), 1 mg BID (N=248), 3 mg BID (N=55), and 8 mg BID (N=53).

III. Neoplasms in the Alvimopan OBD and POI Programs

Background

Alvimopan is a μ -opioid receptor antagonist under development for the treatment of post-operative ileus (POI) and opioid induced bowel dysfunction (OBD). A long term (1 year) safety study SB-767905/014 (Study 014) of alvimopan for the treatment of OBD in non-cancer pain showed a numerical imbalance in the incidence of neoplasms.

Patients in the alvimopan treatment group reported a higher number of neoplasms, as compared to patients in the placebo group in trials involving non-cancer OBD. Study 014 was a randomized, double-blind, placebo-controlled, parallel group study in which 538 subjects were randomized to alvimopan 0.5mg BID and 267 subjects to placebo. This was the only 12 month study planned and completed.

In addition, there was an imbalance in the number of deaths in two of the OBD trials in cancer patients (008 and ABD101684). Patients in the alvimopan treatment group had a higher incidence of death as compared to those in the placebo group.

With the apparent imbalance in neoplasms, all of the studies of alvimopan for any indication were examined. Studies for the POI indication were separately examined as these studies were of a much shorter duration, evaluated higher doses of alvimopan (6 and/or 12 mg twice daily) and had limited follow up (mostly 1-2 weeks)

All randomized, double blind, placebo controlled, multi-center studies of OBD in either non-cancer or cancer pain patients on chronic opiates were pooled and subsequently analyzed below.

Neoplasms in the OBD population

A total of 2330 subjects with chronic non-cancer pain were evaluated in 4 studies (1598 treated with alvimopan and 732 subjects treated with placebo). A total of 230 subjects with cancer-related pain were evaluated in Study 008 (160 treated with alvimopan, 70 treated with placebo). The patients in study ABD 101684 were already included in study 008, as this was an extension study. Table 1 shows the specifics of each of these studies.

Table 1: Primary OBD Safety Population: Subjects Who Took at Least One Dose of Study Drug

Study (Trt)	Placebo	Alvimopan	Total
011 (6 wks)	129 (13.6 pt-y)	393 (41.3 pt-y)	522 (54.9 pt-y)
012 (12 wks)	172 (33.2 pt-y)	346 (71.6 pt-y)	518 (104.8 pt-y)
013 (12 wks)	164 (34.5 pt-y)	321 (64.1 pt-y)	485 (98.6 pt-y)
014 (12 mos)	267 (165.5 pt-y)	538 (350.9 pt-y)	805 (516.4 pt-y)
008 (3-6 wks)	70 (4.5 pt-y)	160 (10.9 pt-y)	230 (15.4 pt-y)
101684* (<2 yrs)	15 (6.7 pt-y)	50 (32.4 pt-y)	65 (39.1 pt-y)
Total†	802 (258 pt-y)	1758 (571.2 pt-y)	2560 (829.2 pt-y)

*Subjects enrolled in 101684 represent a continuation of exposure from 008.

†The total is the sum of subjects from 011, 012, 013, 014, and 008; 101684 subjects are included among the 008 population.

Reference: Adolor's Comprehensive Summary of Alvimopan Safety Data: Neoplasms and Related Events, page 12

OBD Studies in Non-Cancer Pain

In general, the incidence of neoplasia was low across all OBD studies in non-cancer pain. Numeric imbalances were observed between treatment groups in the number of all neoplasms reported by patients; alvimopan treated patients had a higher proportion of neoplasms than those patients who received placebo. As seen in Table 2, the incidence of all neoplasms was 1.4% in the alvimopan treated subjects and 0.5% in placebo treated subjects.

Table 2: All Neoplasms in Non-Cancer Pain Studies*

	Placebo	Alvimopan	Relative Risk (Alv/Pla) (asymptotic 95% C.I.)
All Neoplasms	4 / 732 (0.5%)	22 / 1598 (1.4%)	2.5 (0.91, 6.98)
Malignant Neoplasms	3 / 732 (0.4%)	13 / 1598 (0.8%)	1.98 (0.61, 6.48)
Benign Neoplasms	1/732 (0.1%)	9/1598 (0.6%)	4.12 (0.67, 25.16)

* Non-Cancer pain studies: 011, 012, 013, 014

Reference: Adolor's Comprehensive Summary of Alvimopan Safety Data: Neoplasms and Related Events, Derived from Clinical Narratives, Appendix 1

(Numerical differences from sponsor's tables are secondary to minor differences in interpretation of narratives, see Tables 1 and 2 in Appendix)

The MedDRA term “neoplasm” contains both benign and malignant neoplasms, so the two terms were also analyzed separately in Table 2. Numeric imbalances in the number of benign neoplasia events reported by subjects who received alvimopan resulted in a higher proportion of events than in those who received placebo, 0.6% and 0.1% respectively. The same imbalance is observed in malignant neoplasms; there is an incidence of 0.8% in the alvimopan group vs. 0.4% in the placebo group. Since there was a recent addition of a new case of malignant neoplasm to the placebo group, the imbalance in malignant neoplasms was less prominent than originally observed.

Given that the original neoplasm imbalance was reported from the results of study 014, this study was analyzed separately in Table 3. Even with the additional placebo case, the relative risk of all neoplasms was 2.5 in alvimopan treated subjects compared to in placebo treated subjects.

Table 3: Neoplasms in Study 014

	Placebo	Alvimopan	Relative Risk (Alv/Pla) (asymptotic 95% C.I.)
All Neoplasms	3 / 267 (1.1%)	15 / 538 (2.8%)	2.5 (0.77, 7.98)
Malignant Neoplasms	2 / 267 (0.7%)	7 / 538 (1.3%)	1.7 (0.41, 7.34)
Benign Neoplasms	1/.267 (0.4%)	8/538 (1.5%)	4.0 (0.65, 24.43)

Reference: Adolor’s Comprehensive Summary of Alvimopan Safety Data: Neoplasms and Related Events, Derived from Clinical Narratives, Appendix 1
(Numerical differences from sponsor’s tables are secondary to minor differences in interpretation of narratives, see Tables 1 and 2 in Appendix)

The time to neoplasm analyses are illustrated in Figures 1 and 2. If differences do exist between the time to event in the alvimopan group and the time to event in the placebo group, these differences may not be apparent until after many months of treatment.

Figure 1: Time to Any Neoplasm: Non-Cancer Pain Studies

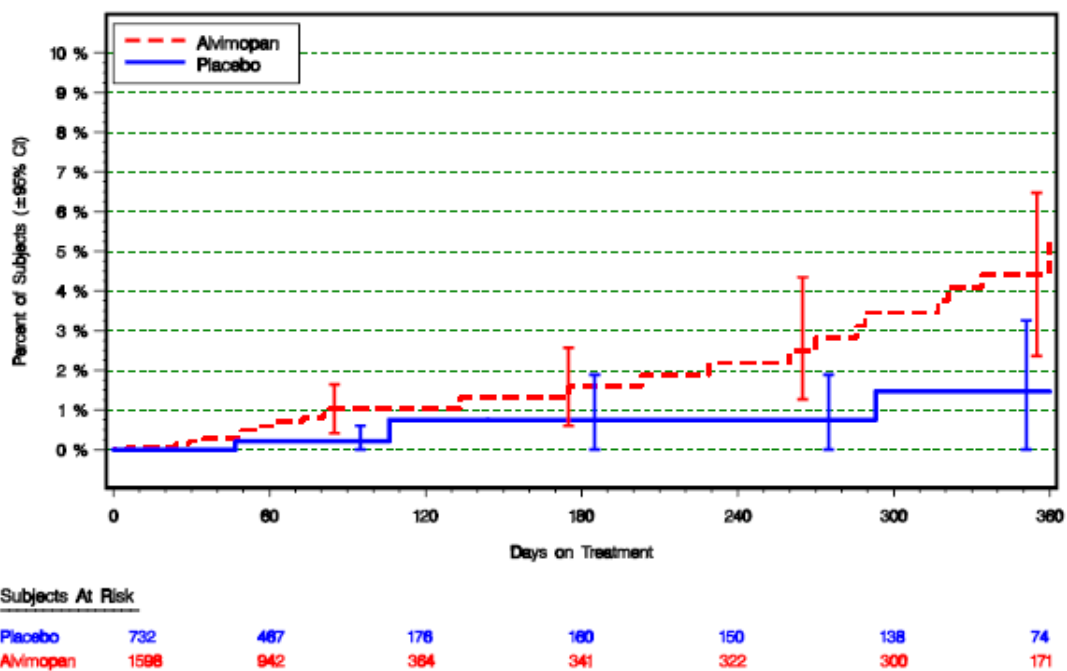
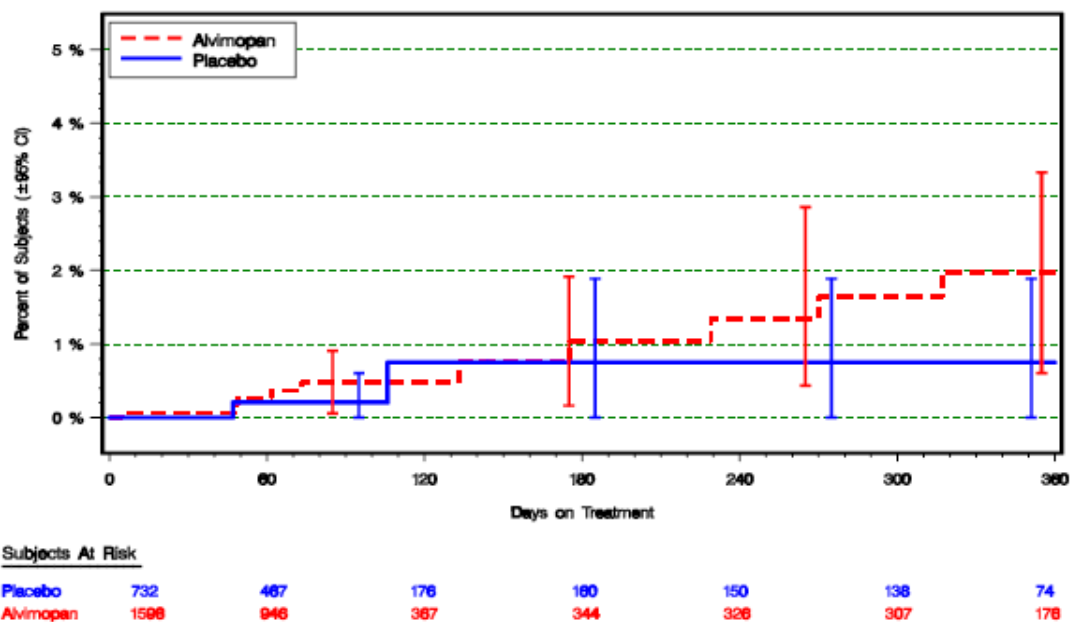


Figure 2: Time to Malignant Neoplasm: Non-Cancer Pain Studies



Reference: Adolor's Comprehensive Summary of Alvimopan Safety Data: Neoplasms and Related Events, page 28

Demographics of Non-Cancer Studies

Overall, review of studies 011, 012, 013, and 014 does not reveal any apparent differences between these studies with respect to age, gender, race, Body Mass Index (BMI), or tobacco use as seen in Table 4a.

For study 014 alone, except for a slight imbalance in the percentage of subjects who were ≥ 65 years of age (15% for placebo vs. 21% for alvimopan), other demographic factors were evenly distributed across treatment groups (Table 4b)

Table 4a: Demographics of Non- Cancer studies

Protocol	N	Age mean	Race (% white)	BMI (% >30)	Tobacco (%)	% WD (all)	% WD (due to AEs)	Duration of Study (wks)
011	522	50	92	29 (39%)	42	17	9	6
012	518	52	91	29 (36%)	45	21	7	12
013	485	52	91	30 (42%)	37	22	8	12
014	805	53	90	30 (40%)	39	48	15	52

Reference: Adolor's Comprehensive Summary of Alvimopan Safety Data: Neoplasms and Related Events, page 21

Table 4b: Demographic Summary of All Subjects (Study 014)

	Placebo (N = 267)	Alvimopan (N = 538)
Mean age (years)	51.9	53.8
Range (years)	22 - 88	24 - 93
≥ 65 years	41 (15%)	113 (21%)
Female	167 (63%)	350 (65%)
White	233 (87%)	492 (91%)
Mean BMI (kg/m ²)	29.5	29.9
Tobacco history	107 (40%)	203 (38%)
Mean METDD (mg)	209.6	183.5

Reference: Adolor's Summary of Fracture Data from OBD Development Program, page 10

OBD Studies in Cancer Pain

An analysis of the ongoing extension study in cancer pain (ABD101684) revealed more neoplasms reported as adverse events (AEs) and more deaths occurring in subjects who received alvimopan. Pre-existing conditions are by definition not reported as AEs unless the time course or severity of the condition changes beyond what would reasonably be expected for a particular case.

While the total number of deaths reported in the non-cancer pain studies was low (*approximately 0.24% in both treatment groups), by comparison there were several deaths reported during the two randomized, double blind, placebo controlled studies in cancer-related pain: study 008 (N=10, 4%), and its extension study ABD101684 (N=13, 20%). Overall, a total of 230 persons received investigational product during study 008 and 65 subjects continued in the extension study. There were 10 patients who died during the course of study 008, nine of them received alvimopan. Similarly, 13 patients died during study ABD101684, 11 of them received alvimopan. Pooling of the 2 studies in Table 5 shows a 4% death rate in the placebo group as compared to a 13% death rate in the alvimopan group.

Table 5: Deaths Reported During GSK OBD Studies in Cancer-Related Pain (Studies 008 and ABD101684 Combined)

Vital Status at Study Withdrawal	Placebo N (%)	Alvimopan N (%)
Alive	67 (96%)	140 (87%)
Deceased	3 (4%)	20 (13%)
Total	70 (100%)	160 (100%)

Reference: Adolor's Comprehensive Summary of Alvimopan Safety Data: Neoplasms and Related Events, page 17

All of the patients enrolled in studies 008 and ABD101684 carried a diagnosis of cancer. The exact diagnoses of Index Cancer at enrollment of the patients who died are listed in Table 6. The general cause of each death in study 008 is listed in Table 7. Thorough review of the patient deaths in study ABD101684 revealed that they were all secondary to progression of the patient's underlying malignancy. A time to death analysis for subjects in the cancer studies is represented in Figure 3.

* Reference: Adolor's OBD CV Safety Summary; page 9

Table 6: List of Deaths Reported in Study 008 and ABD101684

STUDYID	Subject ID	Treatment	Index cancer
008	1346	Alvimopan	Breast
	1347	Alvimopan	Genitourinary
	1349	Alvimopan	Breast
	1676	Alvimopan	Breast
	1747	Alvimopan	Breast
	1756	Alvimopan	Genitourinary
	1758	Alvimopan	Gynecologic
	1888	Alvimopan	Breast
	2065	Alvimopan	Non-Small Cell Lung cancer
	2077	Placebo	Gynecologic
ABD101684	116	Alvimopan	Non-Small Cell Lung cancer
	119	Alvimopan	Non-Small Cell Lung cancer
	125	Alvimopan	Non-Small Cell Lung cancer
	145	Alvimopan	Breast
	200	Alvimopan	Genitourinary
	801	Alvimopan	Non-Small Cell Lung cancer
	803	Alvimopan	Non-Small Cell Lung cancer
	806	Alvimopan	Non-Small Cell Lung cancer
	2006	Alvimopan	Non-Small Cell Lung cancer
	2203	Placebo	Non-Small Cell Lung cancer
	2225	Placebo	Small Cell Lung cancer
	2226	Alvimopan	Non-Small Cell Lung cancer
	2047	Alvimopan	Prostate

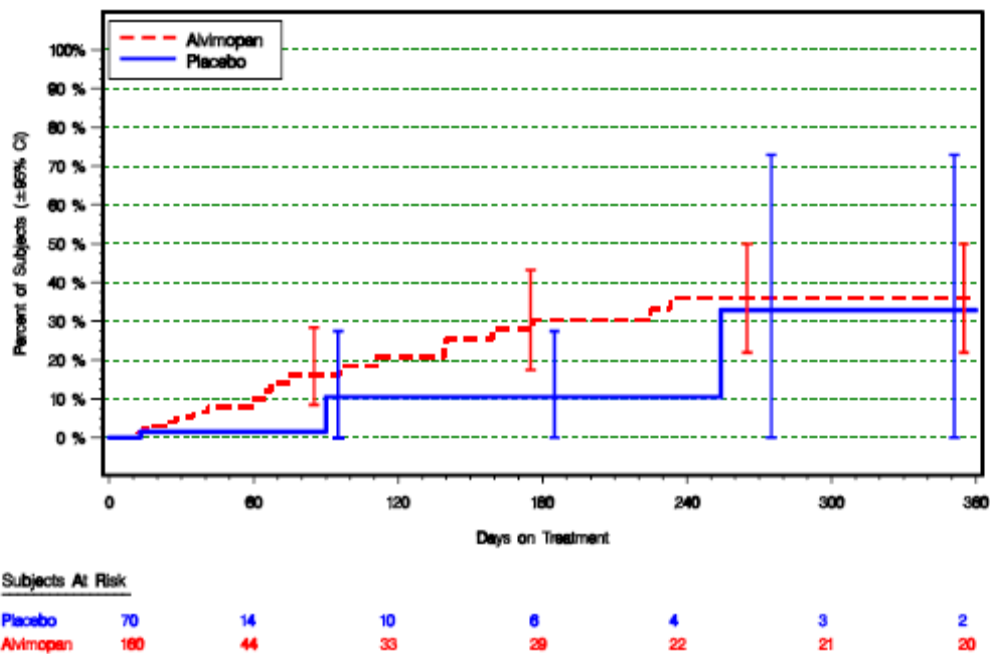
Reference: Adolor's Comprehensive Summary of Alvimopan Safety Data: Neoplasms and Related Events, page 18

Table 7: Summary of Deaths in Study SB-767905/008

System organ class - preferred term	Placebo (N=70) n (%)	Alvimopan			Total (N=160) n (%)
		1.0 mg QD (N=27) n (%)	0.5 mg BID (N=68) n (%)	1.0 mg BID (N=65) n (%)	
Number of subjects with at least one AE	1 (1.4)	2 (7.4)	3 (4.4)	4 (6.2)	9 (5.6)
Cardiac disorders	0	0	1 (1.5)	1 (1.5)	2 (1.3)
- Cardiac arrest	0	0	1 (1.5)	1 (1.5)	2 (1.3)
Gastrointestinal disorders	0	0	0	1 (1.5)	1 (0.6)
- Haematemesis	0	0	0	1 (1.5)	1 (0.6)
General disorders and administration site conditions	1 (1.4)	0	0	0	0
- Sudden death	1 (1.4)	0	0	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	1 (3.7)	0	2 (3.1)	3 (1.9)
- Breast cancer	0	0	0	1 (1.5)	1 (0.6)
- Malignant neoplasm progression	0	0	0	1 (1.5)	1 (0.6)
- Prostate cancer	0	1 (3.7)	0	0	1 (0.6)
Respiratory, thoracic and mediastinal disorders	0	1 (3.7)	2 (2.9)	0	3 (1.9)
- Acute pulmonary oedema	0	1 (3.7)	0	0	1 (0.6)
- Pleural effusion	0	0	1 (1.5)	0	1 (0.6)
- Pneumothorax	0	0	1 (1.5)	0	1 (0.6)
- Respiratory failure	0	0	1 (1.5)	0	1 (0.6)

Reference: Adolor's Safety Update page 15

Figure 3: Time to All Cause Death: Studies 008 and ABD10168



Reference: Adolor's Comprehensive Summary of Alvimopan Safety Data: Neoplasms and Related Events, page 20

Demographics of Cancer Studies (Study 008 and ABD101684)

Overall, the main demographic characteristics appear similar between the study 008 population and the subjects enrolled in study ABD101684. As seen in Table 8, there appears to be equal distribution overall between placebo and alvimopan groups within each study with the exception of tobacco use. Interpreting the available information, the percentage of tobacco use in study ABD101684 is over 3 times higher in the placebo group than in the alvimopan group.

Table 8: Mean Demographic Characteristics in Study 008 and ABD101684

	Study 008		ABD101684	
	Placebo N=70	Alvimopan N=160	Placebo N=15	Alvimopan N=50
Age (years)	59	59	56	57.3
> 65 y (%)	35%	31%	27%	24%
% Female/ Male	61/39	59/41	67/33	62/38
% White/Other	74/26	86/14	80/20	86/14
Body Mass Index	26	26	28	26
Current tobacco use (% = yes)	6%	4%	7%	2%
# with tobacco use information	N=13	N=42	N=1	N=6

Reference: Adolor's Comprehensive Summary of Alvimopan Safety Data: Neoplasms and Related Events, page 20

There was a wide range of index cancer sites in these study populations overall as seen in Table 9. The most common cancer types in both studies were breast, lung, and genitourinary. Two imbalances were noted between the placebo and active treatment arms within the studies. In study 008, more subjects with head and neck cancers received alvimopan (N= 14, 9%) than placebo (N=1, 1%). In addition, there were more subjects with non-small cell lung cancer in study ABD101684 who received alvimopan (N=16, 31%) than placebo (N=1, 7%).

Table 9: Index Cancer Site Reported in > 1 ABD101684 Subject or > 3 Subjects in Study 008

	Study 008		ABD101684	
	Placebo N=60 (85%)	Alvimopan N=145 (90%)	Placebo N=13 (87%)	Alvimopan N=46 (90%)
Breast	19 (27%)	43 (26%)	7 (47%)	12 (24%)
Non-Small Cell Lung	14 (20%)	36 (22%)	1 (7%)	16 (31%)
Genitourinary	8 (11%)	22 (14%)	2 (13%)	4 (8%)
CNS	0	4 (2%)	0	4 (8%)
Head & Neck	1 (1%)	14 (9%)	0	3 (6%)
Gynecologic	5 (7%)	5 (3%)	0	2 (4%)
Soft tissue sarcoma	1 (1%)	4 (2%)	0	2 (4%)
Myeloma	0	0	0	2 (4%)
Lymphoma	3 (4%)	2 (1%)	1 (7%)	1 (2%)
Small cell Lung	2 (3%)	5 (3%)	1 (7%)	0
Mesothelioma	4 (6%)	2 (1%)	1 (7%)	0
Colorectal	2 (3%)	5 (3%)	0	0
Pancreas	1 (1%)	3 (2%)	0	0

Reference: Adolor's Comprehensive Summary of Alvimopan Safety Data: Neoplasms and Related Events, page 23

The baseline functional status of patients, as measured by the Karnofsky Performance Score, appeared balanced between treatment groups in study 008. In study ABD101684, there was a higher percentage of patients with lower Karnofsky Performance scores in the alvimopan group as compared to the placebo group, 42% vs. 13% respectively.

(Reference Adolor's Comprehensive Summary of Alvimopan Safety Data: Neoplasms and Related Events, page 24- 25)

Neoplasms in the POI Population

The POI clinical trial program included nine randomized, double-blind, placebo-controlled, multi-center studies. These studies evaluated higher doses of alvimopan (mainly 6 and/or 12 mg twice daily) than the OBD studies but for a shorter duration (maximum of 7 days). Follow up care was by telephone call and for most patients did not exceed 1-2 weeks. Table 10 lists the neoplasia events. Treatment groups appear to be balanced; however, reported events were few.

Table 10: Summary of Neoplasia Events Reported in the POI Studies		
	Placebo N=1365	Alvimopan (All Doses) N=2610
Burkitt's lymphoma	1	0
Bladder neoplasm	1	0
Carcinoma	1	0
Chronic myelogenous leukaemia	0	1
Colon cancer metastatic	0	1
Hepatic neoplasm	0	1
Lymphoma	0	1
Thyroid neoplasm	0	1
Total	3 (0.2%)	5 (0.2%)

Reference: Adolor's Integrated Safety Summary

Conclusion

With the available information, there appears to be an imbalance in neoplasia events between treatment groups in the OBD non-cancer studies; the alvimopan group has a higher incidence of such events as compared to the placebo group. This imbalance seems to be driven by the imbalance in neoplasia events observed in the only long term safety study for OBD in patients without cancer, study 014. Except for a slight imbalance within study 014 in the percentage of subjects who were ≥ 65 years of age (15% for placebo vs. 21% for alvimopan), other demographic factors were evenly distributed across treatment groups (Table 4b). There is no obvious reason for the observed imbalance between treatment groups in this placebo controlled study.

There is also an imbalance in deaths between treatment groups in the OBD studies in cancer patients. Differences in index cancer etiology and patient performance status were noted; these differences may explain, in part, the large discrepancy seen in the death rates.

In the POI studies, the number of neoplasms in each treatment group appears to be balanced: however, the study design used in these trials does not allow for any significant conclusions to be drawn. Long term effects of a drug used for a short indication, with limited follow up, may not reliably assess risk.

In summary, the true incidence of neoplasm may be difficult to quantify in retrospective analyses. When study entry criteria are not pre-specified and information is incomplete, it may be difficult to assess potential neoplastic findings. For studies including patients with pre-existing neoplasms, evaluating additional neoplastic events or progression of underlying malignancies can be especially challenging.

Appendix: Medical Reviewer's Listings

Table 1: Individual Cases in Non-Cancer Studies Cases

Study	Subject	Treatment group	Neoplasm/Other	Days on treatment	Category
011	64 yo f w/ RA (21 cigs/week)	alvimopan	Inoperable pancreatic CA	4	Malignant
011	63 yo m former smoker (70 cigs/week) w/ neuralgia	alvimopan	Metastatic non small cell ca lung- had ca operated 1994—study drug in 2004	229	Malignant
011	48 yo m chronic back pain x 17 years non smoker	alvimopan	*Mass in pancreas- no f/u info-- presented to ER w/ abdominal pain	5 Subject withdrawn from study	Unclear
012	55 yo m rx'ed for visceral pain non smoker	placebo	Cancer of caecum h/o colon ca 1998 got new metastatic colon CA	106	Malignant
012	51 f rx'ed peripheral neuropathy non smoker	alvimopan	New CLL	88	Malignant
012	72yo f back pain non smoker	alvimopan	Metastatic breast cancer	48	Malignant
012	47yo f non smoker fibromyalgia	alvimopan	left ductal carcinoma <i>in situ</i>	29	Malignant
012	74 yo m non smoker	alvimopan	*Scrotal mass c/w increased fluid	62	Not neoplasm
013	46 yo w/ back pain non smoker	alvimopan	Breast cancer	62	Malignant
013	58 yo f w/ back pain nonsmoker	alvimopan	Lipoma	81	Benign
013	42 yo f w/ fibromyalgia 8 cig/day	alvimopan	*Breast implant lump	83	Not neoplasm
014	57 yo m w/ back pain,	new placebo	Non small cell lung cancer	50 days after	Malignant

	smoker	case		stopping drug (took for 364 days)	
014	68 yo w/ back pain, former smoker	placebo	Metastatic prostate cancer -died	45	Malignant
014	44 yo f nonsmoker w/ back pain	placebo	Tubular adenoma (colon polyp)	293	Benign
014	58 yo f smoker w/ RA	placebo	*5 cm adrenal mass surgically removed “incidentaloma”– No pathology	129	Unclear
014	81yo m w/ neuralgia, smoker	alvimopan	Lung cancer— “nontuberculosis mycobacterium with lung cavitations and rib involvement.” 6 months ago(sponsor said 2 years ago)	133	Malignant
014	61 yo m smoker arthritis pain	alvimopan	Squamous cell carcinoma	270	Malignant
014	74 yo f smoker, w/ back pain	alvimopan	Squamous cell cancer of larynx	316	Malignant
014	63 yo m nonsmoker w/ back pain	alvimopan	Squamous cell cancer of lung	49	Malignant
014	77 yo f nonsmoker w/ back pain	alvimopan	1. R ear melanoma 2. *Breast lump	175 364	Malignant *Unclear
014	66 yo f nonsmoker w/ back pain	alvimopan	Benign tubular adenoma with low grade dysplasia	286	Benign
014	47 yo f (unknown smoking) neuralgia	alvimopan	Breast mass--benign	198	Benign
014	45 yo f smoker	alvimopan	Lipoma	55	Benign
014	39 yo f	alvimopan	Probable uterine	260	Benign

	nonsmoker w/ back pain		fibroid		
014	49 yo f smoker w/ arthritis pain	alvimopan	Trichoepithelioma right lateral nasal fold (reported as growing)	203	Benign
014	45 yo f smoker w/ fibromyalgia	alvimopan	Uterine fibroids	321	Benign
014	66 yo f nonsmoker w/ arthritis	alvimopan	Hyperpigmented lentigo with clear margins (right foot)	365	Benign
014	68 yo m nonsmoker w/ back pain	alvimopan	Invasive moderately differentiated squamous cell carcinoma with acantholytic features and deep surgical margin involved by tumor (of scalp)- <i>Skin cancer</i>	289	Malignant
014	51 yo m smoker w/ DDD of spine	alvimopan	Ulcerated basal cell carcinoma, circumscribed type, involving deep margins of nose- <i>Skin cancer</i>	24	Malignant
014	30 yo f smoker w/ cervical dystonia pain	alvimopan	Dermoid cyst of the left adnexa measuring 5.2 cm.	110	Benign
014	43 yo f smoker w/ DDD back pain	alvimopan	*Left ovarian cysts (had two of them)	74 354	Not neoplasm
014	40 yo f nonsmoker	alvimopan	*Neuroma left thumb "The neuroma was trauma-induced"	334	Not neoplasm.

014	56 yo f smoker	alvimopan	*Skin papilloma – wart on scalp- Not neoplasm	35	Not neoplasm
014	44 yo f smoker w/ limb pain	alvimopan	*Right axillary mass-abscess- Not neoplasm	53	Not neoplasm

Table 2: Medical Reviewer's Non-Cancer OBD Neoplasm Summary by Study Number

Study	Malignant		Benign		Unspecified		
	alvimopan	placebo	alvimopan	placebo	alvimopan	placebo	
011	2				1		
012	3	1			1		
013	1		1		1		
014	7	2	8	1	5	1	
Total	13	3	9	1	8	1	

IV. Fractures in the Alvimopan OBD Program

Background

A review of the study 014 results also found an apparent increase in the incidence of bone fractures in subjects receiving alvimopan as compared to subjects receiving placebo. The incidence of bone fractures was 3.7% (20/538) in patients in the alvimopan group compared with 1.1% (3/267) in patients in the placebo group. The hazard ratio estimate was 3.16 (95% CI 0.94, 10.62). Due to this imbalance, an in depth analysis of bone fractures was done for all similar OBD studies as well as for study 014.

Fracture Events

Study 014

As seen in Table 1, with the exception of age 65 years or older, the alvimopan and placebo groups were reasonably balanced for demographic factors including mean age (approximately 52-54 years) and mean opioid daily dose, expressed in morphine equivalents (METDD).

Table 1 Demographic Summary of All Subjects in Study 014

	Placebo (N = 267)	Alvimopan (N = 538)
Mean age (years)	51.9	53.8
Range (years)	22 - 88	24 - 93
≥ 65 years	41 (15%)	113 (21%)
Female	167 (63%)	350 (65%)
White	233 (87%)	492 (91%)
Mean BMI (kg/m ²)	29.5	29.9
Tobacco history	107 (40%)	203 (38%)
Mean METDD (mg)	209.6	183.5

Reference: Adolor's Summary of Fracture Data from OBD Development Program, page 10

The demographic information for the fracture subjects in study 014 is displayed in Table 2. It may be difficult to make comparisons between patients with fractures reported in the alvimopan group, and those in the placebo group as there were only 3 fractures in the placebo group vs. 20 in the alvimopan group.

Table 2: Demographic Summary of Fracture Subjects in Study 014

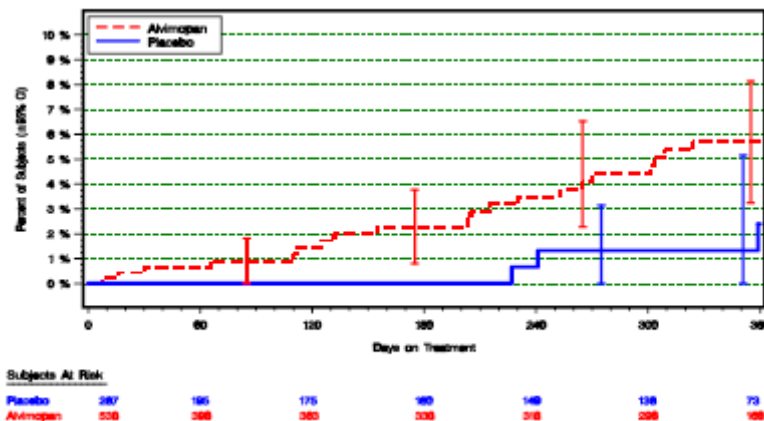
	Placebo (N = 3)	Alvimopan (N = 20)
Mean age (years)	55.7	56.8
Range (years)	60 - 71	37 - 84
≥ 65 years	1 (33%)	6 (30%)
Female	1 (33%)	15 (75%)
White	2 (67%)	20 (100%)
Mean BMI (kg/m ²)	23.8	28.6
Tobacco history	0	6 (30%)
Mean METDD (mg)	100	203

Reference: Adolor's Summary of Fracture Data from OBD Development Program, page 10

The average time on treatment prior to bone fracture was 182 days, ranging from 8 to 324 days, for alvimopan-treated subjects. The corresponding time for placebo-treated subjects was 276 days, ranging from 227 to 359 days. The time to fracture occurrence in the alvimopan and placebo groups is graphically displayed in Figure 1. The majority of fractures were reported after 120 days of treatment. In the alvimopan group, there appears to be a relationship between duration of treatment and risk of bone fracture.

There was a limited amount of documentation of fractures, risk factors for fractures as well as inadequate information on the etiology of the fractures. Fracture causes were only identified in 12 patients. The overwhelming reason for fracture was falls: 11 falls (9 alvimopan: 2 placebo) and 1 motorcycle accident (placebo). Further fracture information was obtained retrospectively by investigators; this information had a varying degree of completeness and reliability. Confirmatory data such as: x- ray reports, documentation of fracture, ER visits, diagnoses, etc. were often missing.

Figure 1: Time to Bone Fracture in Study 014



Reference: Adolor's Summary of Fracture Data from OBD Development Program, page 11

The more typical osteoporotic-type fractures to the hip or vertebrae were rare as seen in Table 3. The bones most often reported as broken were the ribs and those in the extremities. For subjects treated with alvimopan, the bones more commonly affected were the ribs, humerus, ankle and foot.

Table 3: Location of Bone Fractures in Study 014

Fracture location	Total placebo N=267	Total Alvimopan N=538
Vertebra	0	2
Rib*	1	4
Clavicle*	0	1
humerus	0	3
hip	1	0
femur	0	1
Patella/fibula/tibia	1	2
ankle	0	3
foot	0	4
Total	3	20

Reference: Adapted from Adolor's Summary of Fracture Data from OBD Development Program, page 11

There was a question as to whether the patients with the starred fractures in Table 3 actually had fractures, so table 4 has the questionable cases removed. A significant imbalance in fracture cases still exists.

Table 4: Location of Bone Fractures in Study 014 Amended

Fracture location	Total placebo N=267	Total Alvimopan N=538
Vertebra	0	2
Rib	1	3
humerus	0	3
hip	1	0
femur	0	1
Patella/fibula/tibia	1	2
ankle	0	3
foot	0	4
Total	3	18

Reference: Adapted from Adolor's Summary of Fracture Data from OBD Development Program, page 11

Additional Analyses of the Study 014 Population

Multiple distinct statistical analyses performed by the sponsor (Tables 5 and 6) continue to show an increased relative risk for fracture in alvimopan treated patients as well as increased hazard ratio for alvimopan/placebo.

Table 5: Sensitivity Analysis Excluding Two Questionable Fracture Cases

	Placebo	Alvimopan	Relative Risk (Alv/Pla)	Hazard Ratio (Alv/Pla)
Study 014	3/267 (1.1%)	18/538 (3.4%)	3.0 (0.88, 10.02)	2.8 (0.83, 9.58)

Reference: Adolor's Summary of Fracture Data from OBD Development Program, page 19

Table 6: Sensitivity Analysis Using Cases with Confirmed Fracture Diagnosis

	Placebo	Alvimopan	Relative Risk (Alv/Pla)	Hazard Ratio (Alv/Pla)
Study 014	1/267 (0.4%)	8/538 (1.5%)	4.0 (0.50, 31.58)	3.8 (0.47, 30.08)

Reference: Adolor's Summary of Fracture Data from OBD Development Program, page 19

Other OBD Studies: Non-Cancer (011, 012, 013) and Cancer (008, ABD101684)

The incidence of fractures in all OBD studies excluding Study 014 was 0.4% (5/1220) in subjects treated with alvimopan compared with 1.3% (7/535) in subjects assigned to placebo. The hazard ratio estimate was 0.3 (95% CI 0.10 and 0.97). Baseline demographics were reasonably well balanced between treatment groups. Demographics of the fracture subjects are listed in Table 7.

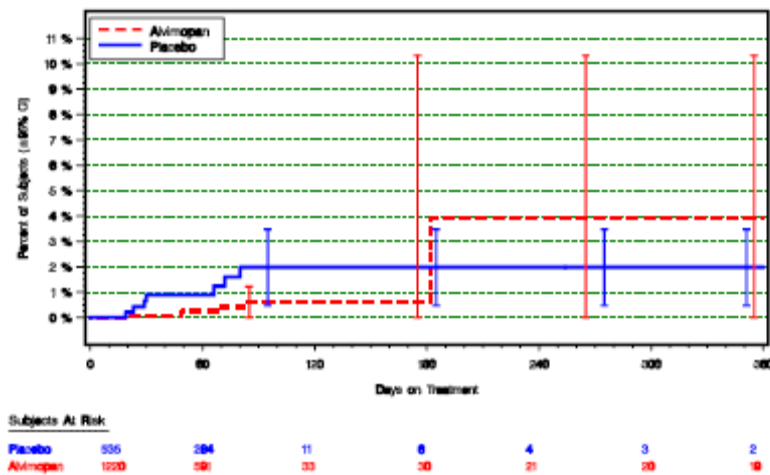
Table 7: Demographic Summary of Fracture Subjects (Studies 011, 012, 013, 008, ABD101684)

	Placebo (N = 7)	Alvimopan (N = 5)
Mean age (years)	51.7	59
Range (years)	41 - 61	34 - 72
≥ 65 years	0	3 (60%)
Female	4 (57%)	3 (60%)
White	6 (86%)	5 (100%)

Reference: Adolor's Summary of Fracture Data from OBD Development Program, page 13

With the exception of study ABD101684, the treatment periods ranged from 3 to 12 weeks in these studies. The average time on treatment prior to bone fracture was 81 days, ranging from 22 to 182 days, for alvimopan-treated subjects. The corresponding time for placebo treated subjects was 46 days, ranging from 19 to 80 days. The time of fracture occurrence in the alvimopan and placebo groups are graphically displayed in Figure 2.

Figure 2: Time to Bone Fracture (Studies 011, 012, 013, 008, ABD101684)



Reference: Adolor's Summary of Fracture Data from OBD Development Program, page 14

Similar to findings from Study 014, osteoporotic-type fractures to the hip or vertebrae were uncommon. The bones most often reported as broken were those in the extremities. Broken bones in the alvimopan group involved humerus, wrist, fibula, ankle, and foot. Fractures occurring in the placebo group included rib, vertebra, wrist, patella, ankle, and foot (Table 8).

Table 8: Location of Bone Fractures (Studies 011, 012, 013, 008, and ABD101684)

Fracture Location	Placebo		Alvimopan		Total	
	Female (N = 4)	Male (N = 3)	Female (N = 3)	Male (N = 2)	Female (N = 7)	Male (N = 5)
Vertebra	1	0	0	0	1	0
Rib	0	1	0	0	0	1
Humerus	0	0	0	1	0	1
Wrist	1	0	1	0	2	0
Femur	0	0	1	0	1	0
Patella/fibula/tibia	0	1	0	1	0	2
Ankle	1	0	1	0	2	0
Foot	1	1	1	0	2	1

Reference: Adolor's Summary of Fracture Data from OBD Development Program, page 14

Table 9 lists some of the factors potentially associated with an increase fracture risk. Information regarding fracture cause and outcome, relevant medical history, and risk factors for fractures was limited. From the available data, a comparison of alvimopan and placebo fracture cases would also be limited secondary to the small number of cases, and the lack of prospective information which may be predictive of an increased fracture risk. Generally, both fracture groups were balanced with the exception of obesity.

Table 9: Comparison of Alvimopan and Placebo Fracture Cases

	Placebo (N = 7) (total N=535)	Alvimopan (N =5) (Total N=1220)
Female Gender	4	3
Obese (BMI \geq 30)	1	4
Fracture due to a fall	4	4
Post-menopausal	2	3
Bone or joint disease	3	2
Prior fracture	2	5

Reference: Adapted from Adolor's Summary of Fracture Data from OBD Development Program, page 15

Total GSK-Sponsored OBD Studies

Combining all the data, the incidence of fractures was 1.4% (25/1758) in the alvimopan group compared with 1.2% (10/802) in the placebo group. The hazard ratio estimate was 1.15 (95% CI 0.55 and 2.39). Table 10 lists the demographics of patients with reported fractures; the alvimopan group had a higher percentage of women, more individuals 65 years or older, and a higher average BMI. However, these baseline demographics were reasonably well balanced between treatment groups in the overall OBD population.

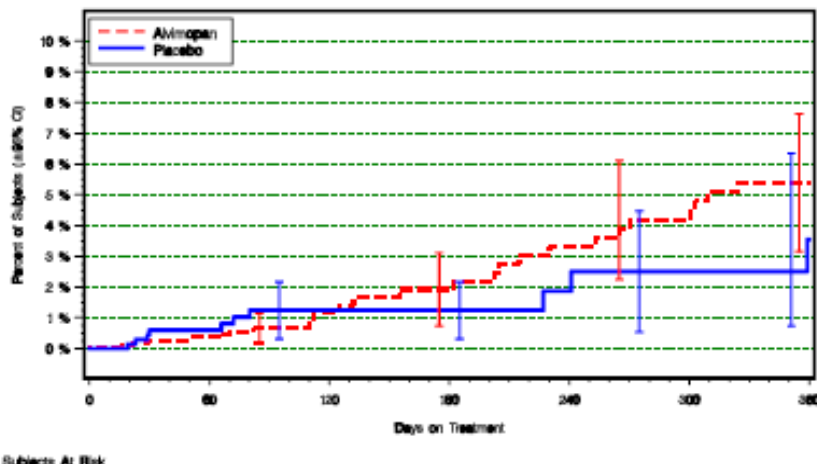
Table 10: Demographic Summary of Fracture Subjects (All OBD Studies)

	Placebo (N = 10)	Alvimopan (N = 25)
Mean age (years)	55	57
Range (years)	41 - 71	34 - 84
\geq 65 years	1 (10%)	9 (36%)
Female	5 (50%)	18 (72%)
White	8 (80%)	25 (100%)
Mean BMI (kg/m ²)	25.3	29.1
Tobacco history	6 (60%)	6 (25%)

Reference: Adolor's Summary of Fracture Data from OBD Development Program, page 16

The time to fracture occurrence in the alvimopan and placebo groups is graphically displayed in Figure 3. The incidence of fractures for the alvimopan group was similar to the placebo group through 120 days of treatment; however, the percentage of patients with fractures in the alvimopan group was higher relative to the placebo group following 120 days of exposure. This difference could be represented by fractures which occurred in subjects randomized to alvimopan in Study 014. Of note, study 014 was the only long term (1 year) safety study. It appears that after 120 days of treatment with alvimopan, the risk of fractures increases with time.

Figure 3: Time to Bone Fracture (All OBD Studies)



Reference: Adolor's Summary of Fracture Data from OBD Development Program, page 17

The database was examined for concomitant medications that are associated with an increased risk of fracture or serve as a marker for bone disease. The effects of systemic corticosteroid therapy on bone are well-known; however, there was no difference between the alvimopan and placebo fracture groups in corticosteroid use. The role of other medications (proton pump inhibitors, laxatives, antiepileptics, and psychoanalptics) as possible risk factors for bone disease and fracture risk is not clear at this time. Patients on chronic treatment for osteoporosis may not be considered at higher risk for fractures if their bone density has increased to within normal limits. In addition, patients who are diagnosed and treated for osteoporosis may actually have a higher bone density than those undiagnosed and untreated.

Summary of Specific Clinical Findings

The patient population in the GSK-sponsored OBD non-cancer studies have typically been white (90%), female (65%), and in their early fifties. For the cancer studies, subjects were typically white (82%), female (60%), and in their late fifties. The non-cancer population was also characterized by a high prevalence of tobacco use (40%). While advanced age, female sex and Caucasian race are risk factors for osteoporosis, these factors were generally balanced across alvimopan and placebo treatment arms during the non-cancer and cancer studies.

Review of bone fractures in shorter-term OBD studies completed prior to Study 014 failed to find an increased fracture incidence. The fracture incidence in subjects treated with alvimopan was less than that in the placebo group; 0.4% versus 1.3%, respectively. These subjects were generally in their sixth decade and predominantly white; fractures typically involved bones in the extremities and were balanced between men and women. A time-to-event analysis showed the occurrence of fracture over time was similar in the alvimopan and placebo groups.

Retrospective analyses of the patients with fractures offered limited information. The major risk factors for fractures were generally balanced between the treatment groups in the OBD program. According to the sponsor, the alvimopan fracture group included a higher percentage of female, elderly, and obese subjects, as well as more subjects prescribed bisphosphonates for osteoporosis. It is possible that these subgroups of patients have a higher fracture risk; however, in general, both the total alvimopan group and the total placebo group were well matched on these variables.

In the only long term study, 014, there exists an imbalance in the number of fractures experienced by the treatment group vs. the placebo group; it is unclear why this imbalance exists. The sponsor described several potential explanations as listed in Table 11. It is important to note that all of these findings were also present in the placebo population; however, the placebo group had fewer fractures.

Table 11: Sponsor’s Findings in 20 Women Reporting Fractures in Study 014:

- ❖ Fifteen women
- ❖ All white women
- ❖ Seven between ages 50-64; five greater than 64
- ❖ Twelve were postmenopausal
- ❖ Five with osteoporosis, treated with bisphosphonates
- ❖ Three with history of prior fracture (unknown time frame and etiology)
- ❖ Seven with nonspecific impairments predisposing to falls (included here was “poor vision”)
- ❖ Ten were former/current smokers (unknown cigarette years)

Reference: Adapted from Adolor’s Summary of Fracture Data from OBD Development Program, page22-23

Epidemiologic Factors Related to Fractures

A reference from the literature was provided by the sponsor as depicted in Table 12; the sponsor claims that the risk factors in Table 12 are relevant; however, the table is entitled “Risk ratio for hip fracture...” . Most of the fractures discussed in the OBD program are of the extremities; there was only one hip fracture and it was in the placebo group. Furthermore, the sponsor states, “the spine, hip, and wrist are regarded as the typical osteoporotic fractures” and “most hip fractures take place after a fall; 80% occur in women and 90% in individuals older than 50 years”. The fact that most of the fractures present did not represent typical osteoporotic fractures suggests that the increased

fractures observed in the alvimopan treatment group may be secondary to another mechanism.

Table 12: Risk ratio for hip fracture associated with risk factors adjusted for age, with and without adjustment for bone mineral density

Risk indicator	Without BMD		With BMD	
	RR	95% CI	RR	95% CI
Body mass index (20 vs 25 kg/m ²)	1.95	1.71–2.22	1.42	1.23–1.65
(30 vs 25 kg/m ²)	0.83	0.69–0.99	1.00	0.82–1.21
Prior fracture after 50 years	1.85	1.58–2.17	1.62	1.30–2.01
Parental history of hip fracture	2.27	1.47–3.49	2.28	1.48–3.51
Current smoking	1.84	1.52–2.22	1.60	1.27–2.02
Ever use of systemic corticosteroids	2.31	1.67–3.20	2.25	1.60–3.15
Alcohol intake > 2 units daily	1.68	1.19–2.36	1.70	1.20–2.42
Rheumatoid arthritis	1.95	1.11–3.42	1.73	0.94–3.20

Reference: Adolor's Summary of Fracture Data from OBD Development Program, page 25

Decreased bone density is a known risk factor for increased fracture; however, there was no data available on bone density measurements. One could assume that since the main demographic factors (age, sex, and race) were balanced, the bone density measurements would also be balanced. There is no substantial convincing argument that this measurement would not be similar for the treatment groups.

Etiology of Fractures

Although, the causality for many of the fracture cases was not determined, the overwhelming majority of cases were secondary to a fall. Table 13 lists some of the possible conditions which could contribute to a fall. Adverse event data within the sponsor's Safety Update for the OBD studies were reviewed looking for an imbalance in the fall risk between treatment groups. There did not appear to be any imbalance between treatment groups for any of these adverse events reported.

Table 13: Potential Etiologies for Increased Fall Risk

- ❖ Dizziness
- ❖ Hypotension
- ❖ Ataxia
- ❖ Gait instability
- ❖ Syncope
- ❖ Bradycardia
- ❖ Meniere's disease
- ❖ Nystagmus
- ❖ Hypoglycemia

Similarly, if there is an underlying increased risk of fracture in patients who take opioids, this fracture risk would be expected to be balanced between treatment groups as both groups in study 014 involved similar opiate amounts as depicted in Table 1. The mean opioid daily dose expressed in morphine equivalents (METDD) was actually higher in the placebo group as compared to the alvimopan group, 209.6 mg vs. 183.5 mg respectively.

Conclusion

The available data suggest that in the only long term OBD study, there is a significant imbalance in the number of fractures occurring in the alvimopan group as compared to the placebo group. At this time, there is no clear explanation for this imbalance.



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

**MEETING OF THE GASTROINTESTINAL DRUG ADVISORY COMMITTEE
(GIDAC)
JANUARY 23, 2007**

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

BACKGROUND MATERIALS

NDA NUMBER:	21-775
DRUG NAME:	Alvimopan (EnteregTM Capsules)
INDICATION:	To accelerate time to upper and lower GI recovery following partial large or small bowel resection surgery with primary anastomosis
SPONSOR:	Adolor Corporation
REVIEW DIVISION:	Division of Gastroenterology Products
PHARM/TOX REVIEWER:	Tamal K. Chakraborti, Ph.D.
PHARM/TOX ACTING TEAM LEADER:	Sushanta K. Chakder, Ph.D.

Safety Pharmacology:

Cardiovascular Effects

Effect of Alvimopan and ADL 08-0011 on Cloned hERG Channels Expressed in Mammalian Cells

In this study, *in vitro* effects of alvimopan and its metabolite, ADL 08-0011, on ionic currents was tested using voltage-clamped human embryonic kidney 293 (HEK-293) cells that stably expressed the human ether-a-go-go-related gene (hERG). Terfenadine was used as a concurrent positive control. Alvimopan and ADL 08-0011 were tested at 5, 15, and 50 μM concentrations. Alvimopan inhibited hERG current by 1.0% (n = 4), 0.7% (n = 3), and 1.8% (n = 3) at 5, 15, and 50 μM , respectively. ADL 08-0011 inhibited hERG current by 0.4% (n = 3), 0.5% (n = 4), and 0.5% (n = 3) at 5, 15, and 50 μM , respectively. The IC_{50} for the inhibition of hERG current was not determined for either compound since neither produced greater than 50% inhibition of hERG current. Under identical experimental conditions, 60 nM terfenadine inhibited [76.5% (n = 2)] hERG current as expected indicating the validity of the experiment.

Effect of Alvimopan and ADL 08-0011-0 on Action Potential Parameters in Dog Isolated Purkinje Fibers

This study was conducted to examine the effects of alvimopan and ADL 08-0011-0 on the dog isolated Purkinje fiber action potential. Purkinje fibers were perfused with Tyrode's solution for baseline control and 10, 50 and 100 μM concentrations of alvimopan or ADL 08-0011-0. The following action potential parameters were measured: resting membrane potential (RMP), maximum rate of depolarization of the action potential upstroke (V_{max}), overshoot (OS) action potential amplitude (APA) and action potential duration at 30, 50 and 90% (APD_{30} , APD_{50} and APD_{90}) repolarization. Alvimopan or ADL 08-0011-0 did not show any significant effects on RMP, V_{max} , OS, APA, APD, APD_{30} , APD_{50} and APD_{90} . However, dl-sotalol (50 μM) used as a positive control, significantly prolonged APD_{50} and APD_{90} indicating the validity of the experiment. Alvimopan or its metabolite ADL08-0011-0 did not prolong action potential duration at any of the tested concentrations.

Cardiovascular Effects of Alvimopan Administered Orally to Conscious Male Sprague Dawley Rats

Alvimopan was examined for potential cardiovascular effects in conscious male Sprague Dawley rats (n = 4/group) at oral doses of 50, 100, and 200 mg/kg (5 ml/kg). Control animals received 10% acacia suspension by gavage (5 ml/kg). Blood pressure and heart rate were measured prior to dosing (time point 0) and at 10, 20, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, and 240 minutes post-dose. Administration of alvimopan produced no biologically significant changes in any parameters tested (mean arterial pressure, systolic pressure, diastolic pressure, pulse pressure, or heart rate). Overall, alvimopan did not produce any biologically significant cardiovascular effects at the tested doses.

Cardiovascular Effects of Alvimopan in Conscious Dogs (Are these conscious or anesthetized dogs?)

In this study, six Beagle dogs (n = 3/sex) were administered a slow bolus intravenous injection (over a two-minute period) of alvimopan at 2 mg/kg. Blood pressure, heart rate, electrocardiogram (ECG) was recorded at 15, 30, 60, 120, and 240 minutes post dose. Blood samples were also collected immediately following recording of cardiovascular parameters. Alvimopan did not significantly alter blood pressure, heart rate and electrocardiograms recorded at any of the five-time points when compared to the base line values.

Cardiovascular (Hemodynamic) and QTc Prolongation Evaluation of Alvimopan in Anesthetized Dogs

This study was conducted to examine the potential effects of intravenous infusion of alvimopan on blood pressure, heart rate and QT interval in anesthetized dogs. Four Beagle dogs (n = 2/sex) received alvimopan at 0.05, 0.2 and 2.5 mg/kg, i.v. dose (bolus). The following cardiovascular parameters were recorded: arterial blood pressure (systolic, diastolic and mean), heart rate, and electrocardiogram (ECG). Alvimopan had no effect on systolic, diastolic and mean arterial blood pressures or heart rate, ECG and QT at any of the tested doses.

In summary, in the *in vitro* and *in vivo* cardiovascular safety pharmacology studies, alvimopan did not show any adverse effect. Alvimopan and ADL 08-0011, the active metabolite of alvimopan, did not inhibit the cloned human cardiac potassium channel (hERG) at concentrations up to approximately 46 and 35 μ M, respectively. Neither alvimopan nor ADL 08-0011 produced any effect on action potential duration (APD) in the dog Purkinje fiber assay at concentrations up to 100 μ M. Alvimopan at intravenous doses of 0.05, 0.2 and 2.5 mg/kg showed no significant effect on the ECG or QTc in dogs.

Toxicology Studies:

Nonclinical toxicity of alvimopan and its metabolite, ADL 8-0011, has been studied in several single and repeated dose (up to 6 months) toxicity studies in mice, rats and dogs using oral and intravenous routes of administration. Overall, alvimopan showed a very low order of toxicity in mice, rats and dogs. Generally, the highest tested dose did not produce any significant organ toxicity, which could be partly attributed to its poor systemic absorption following oral administration. As a result, the target organ of toxicity could not be identified from these studies. It is to be noted here that in animal toxicity studies, alvimopan had no treatment-related effect on bones, including the bone marrow.

After repeated oral administration of alvimopan to rats for 1 (200, 500 and 1000 mg/kg/day) or 6 months (50, 100 and 200 mg/kg/day), the no-observed-adverse-effect-levels (NOAELs) were 1000 and 200 mg/kg/day, respectively, the highest tested doses.

After repeated oral doses of alvimopan to dogs for 1 (100, 250, 500 and 1000 mg/kg/day) or 6 months (10, 30 and 100 mg/kg/day), the NOAELs were 1000 and 100 mg/kg/day, respectively, the highest tested doses. In repeat dose i.v. toxicity studies in rats (1, 5 and 10 mg/kg/day) and dogs (0.05, 0.2 and 2.0 mg/kg/day), the NOAELs were 10 and 2 mg/kg/day, respectively. The highest tested doses in rats (200 mg/kg/day) and dogs (100 mg/kg/day) in 6-month oral toxicity studies were approximately 67.4 and 112.3 times the proposed human dose (12 mg b.i.d. or 24 mg/day or 0.48 mg/kg), respectively, based on the body surface area.

Genotoxicity

Alvimopan was not genotoxic in the Ames test, the mouse lymphoma cell (L5178Y/TK⁺) forward mutation test, the Chinese Hamster Ovary (CHO) cell chromosome aberration test or the mouse micronucleus test. The pharmacologically active metabolite, ADL 08-0011 was negative in both the Ames test and chromosome aberration test in CHO cells.

Carcinogenicity:

Mice

In a 104-week oral (gavage) carcinogenicity study in CD-1 mice, animals (60/sex/group) were administered 0 (purified water), 0 (vehicle), 100, 1000 or 4000 mg/kg/day alvimopan in 10% (w/v) aqueous acacia (10 mL/kg). Survival in the female group at 100 mg/kg/day fell below 15 animals in Week 101, and all surviving females in this group were sacrificed in Week 101. Survival in the vehicle control female group fell below 15 in Week 102, and all remaining females from all groups were killed in Weeks 102/103. For male mice, survival at 1000 mg/kg/day and 4000 mg/kg/day was higher than the vehicle control group. In males, the water control demonstrated significantly lower mortality than the vehicle control. Alvimopan caused significant increase in the incidences of fibroma, fibrosarcoma and sarcoma in the skin/subcutis, and osteoma/osteosarcomas in bones of female mice.

The following Table shows significant tumor findings in female mice.

Organ	Tumor Type	Vehicle	100 mg/kg/day	1000 mg/kg/day	4000 mg/kg/day	P-Value (Trend Test)
BONE	OSTEOGENIC TUMOR	0	0	1	4	0.0063
SKIN/APPENDAGES	FIBROBLASTIC TUMOR	0	0	0	5	0.0003
SKIN + SUBCUTIS	SARCOMA	0	0	0	3	0.0063

Rat

In a 104-week oral (gavage) carcinogenicity study in SD rats, animals (60/sex/group) were administered 0 (water), 0 (vehicle), 100, 200 or 500 mg/kg/day alvimopan in 10% (w/v) aqueous acacia (5 mL/kg). Treatment with alvimopan had no effect on survival in either sex. There were no significant in-life findings associated with treatment with alvimopan. Macroscopic observations included statistically significant increased incidence of enlargement of the deep cervical lymph nodes in male decedent rats at 500 mg/kg/day. In males, a statistically significant increased incidence of enlargement of lumbar lymph nodes was observed at high dose. There were no significant tumor findings in either sex.

Overall, oral administration of alvimopan for 104 weeks caused significant increases in the incidences of fibroma, fibrosarcoma and sarcoma in the skin/subcutis, and osteoma/osteosarcoma in bones of female mice at 4000 mg/kg/day (about 675 times the recommended human dose of 12 mg bid based on the body surface area). Alvimopan was not tumorigenic in rats up to 500 mg/kg/day (about 169 times the recommended human dose based on the body surface area).



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: December 18, 2007

To: FDA Gastrointestinal Drugs Advisory Committee

Thru: Gerald Dal Pan, MD, MHS, Director
Office of Surveillance and Epidemiology (OSE)

From: OSE Entereg Risk Management Review Team:
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Ann Corken Mackey, RPh, MPH, Safety Evaluator, DDRE
Mary Dempsey, Risk Management Program Coordinator
Lanh Green, PharmD, MPH, Safety Evaluator Team Leader, DDRE
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Cheryle Milburn, Regulatory Health Project Manager, DSRCS
Kellie Taylor, PharmD, MPH, Team Leader, DMETS
Joyce Weaver, PharmD, Senior Risk Management Analyst
Mary Willy, PhD, Senior Risk Management Analyst
Kendra Worthy, PharmD, Drug Utilization Data Specialist, DSRCS

Subject: Review of RiskMAP Proposal

Drug Name(s): Entereg (alvimopan)

Application Type/Number: 21-775

Applicant/sponsor: Adolor Corporation

OSE RCM #: 2007-2232

1 INTRODUCTION

Entereg (alvimopan) is an opioid receptor antagonist being evaluated for the proposed indication of accelerating the time to recovery following partial large or small bowel resection surgery with primary anastomosis. The proposed dosage regimen for Entereg is one 12mg capsule 30 minutes to 5 hours before bowel resection surgery, followed by 12mg twice daily for up to 7 days after surgery for a maximum of 15 doses.

The sponsor submitted a Risk Minimization Action Plan (RiskMAP) addressing the risk of ischemic cardiovascular events observed with long-term use, by restricting its use to short term inpatient use. The primary method proposed to prevent outpatient use is to establish agreements with wholesalers to sell Entereg only to hospitals. While we agree that limiting use of Entereg to short-term use may be an acceptable approach to minimizing cardiovascular events, the Sponsor's proposal raises a number of important issues and challenges. We recommend the Advisory Committee members discuss the proposed RiskMAP and its implementation with regard to these issues. The details of this discussion will be considered in the final design of the RiskMAP program.

2 BACKGROUND

The Agency has taken two previous approvable actions on this application. The first approvable letter, issued July 21, 2005, cited a lack of sufficient proof of efficacy for accelerating recovery of gastrointestinal function following bowel resection surgery. The sponsor was requested to provide at least one additional adequate and well-controlled study establishing superiority over placebo. Additionally, the sponsor was requested to justify the conclusion that the median reduction in time to gastrointestinal recovery relative to placebo would be clinically meaningful.

The sponsor submitted a complete response to the approvable letter on May 9, 2006. The sponsor submitted data that indicates alvimopan achieves a one-day shorter hospital stay in gastrointestinal resection patients compared to placebo. However, before the Agency acted on the application, the sponsor notified the Agency of a cardiovascular toxicity signal noted in an interim analysis in an ongoing long-term study in the Opioid Bowel Dysfunction Clinical Development Program. A second approvable letter was issued November 3, 2006. This letter cited the need for the sponsor to submit the 12-month safety findings from this study, including analyses of myocardial infarction, unstable angina, and other serious cardiovascular events. Secondly, the approvable letter stated that the sponsor should develop a RiskMAP that includes elements to a) communicate the possible cardiovascular risk of longer-term alvimopan exposure, and b) minimize off-label use. The letter advised that the RiskMAP could include appropriate labeling for prescribers and patients, and restriction of alvimopan use to hospital settings.

Review of the Sponsor's safety data in response to the approvable letter has revealed that long-term use (6-12 months) results in an increased risk of cardiovascular ischemic events compared to placebo. Short-term use (defined as duration "not to exceed 7.5 days") has not been associated with increased cardiovascular ischemic events, although study patients were not followed to ascertain all cardiovascular events, especially events occurring after hospital discharge. The cardiovascular signal was observed in a long-term trial that used much lower doses (the most commonly used dose was 0.5mg BID) than the dose proposed for short-term use (12mg BID). Other safety issues noted in the safety review of alvimopan include an increased incidence of tumors in the treatment group, and increased incidence of bone fractures in the treatment group. The cardiovascular, neoplasia, and fracture safety signals all were observed in long-term study for opioid-induced bowel dysfunction.

3 SUMMARY OF PROPOSED RISKMAP FOR ENTEREG

Adolor Corporation submitted a proposed Risk Management Plan for Alvimopan in the Management of POI Following Bowel Resection Surgery on August 9, 2007. The proposed RiskMAP¹ comprises the following components:

1. agreements with wholesale distributors to sell Entereg only to hospitals;
2. targeted education, sales, and promotion (directed to hospitals and hospital-based practitioners);
3. product packaging that states “Hospital Use Only”;
4. reimbursement for Entereg only via diagnosis-related group (DRG) payment for bowel resection surgery; and
5. an alert system to alert outpatient pharmacists via the outpatient dispensing software not to dispense Entereg on an outpatient basis (if implemented, this is projected to be available in 50% of outpatient pharmacies).

The sponsor did not propose any plan to evaluate the performance of the RiskMAP in minimizing the risk of ischemic cardiovascular events.

The sponsor proposes routine pharmacovigilance and data mining of their safety database to help detect safety signals.

4 DISCUSSION

We note that the sponsor has not yet submitted full details of the RiskMAP proposal. Nevertheless, we agree that limiting use of Entereg to short-term use may be an acceptable approach to minimizing the risk of cardiovascular events. However, the RiskMAP proposal raises the following issues that should be discussed during the January 23, 2008 meeting of the Gastrointestinal Drugs Advisory Committee.

Will cardiovascular risk be minimized sufficiently?

The cardiovascular risk emerged only in long-term (6-12 months) testing. However, the short-term trials were not designed to ascertain all cardiovascular events. Patients were not followed after hospital discharge in the short-term trials, so cardiovascular events occurring after hospital discharge might not have been captured. It is not clear if patients at high risk for ischemic cardiovascular events might be at risk for Entereg-related cardiovascular events even with short-term use.

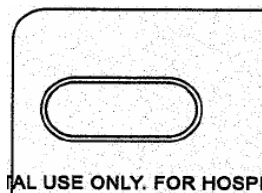
Can longer term use and outpatient use with Entereg be prevented by limiting sales by wholesalers to hospitals only?

Long-term use of alvimopan that could occur with outpatient use would be especially concerning, because the dose for short-term inpatient use is 24 times higher (12mg) than the most commonly used dose in long-term testing (0.5mg). Long-term outpatient use would expose patients to higher doses than the dose that yielded an ischemic cardiovascular toxicity signal. The approach of limiting sales to hospitals might require additional measures other than described in the RiskMAP

¹ Adolor Corporation Proposed Risk Management Plan for Alvimopan in the Management of POI Following Bowel Resection Surgery, submitted to the NDA August 9, 2007,

proposal to be sure that use really is confined to short-term use in hospitals. The challenges and possible approaches are discussed below.

1. The RiskMAP proposal indicates that the pharmaceutical wholesalers would carry a large part of the responsibility for the successful implementation of the RiskMAP because wholesalers must agree to sell the product only to hospitals. This would require the wholesalers to maintain a list of acute-care hospitals, and dispense only to these hospitals. We note that it may not be clear to the wholesalers whether a facility is an acceptable facility (e.g., free-standing surgical centers, nursing homes etc may be indistinguishable from acute-care hospitals to the wholesalers). Additionally, if additional elements are introduced to the RiskMAP, the wholesalers would need to manage these additional elements as well in determining whether a prospective purchaser meets the RiskMAP requirements for using the product. It may be more appropriate for the responsibility for who meets RiskMAP requirements and who purchases the product to rest with the sponsor.
2. The plan, as explained so far, might not be sufficient to prevent outpatient use.
 - a. Hospitals with outpatient pharmacies, as well as outpatient pharmacies attached to hospitals which have a hospital contract with wholesalers, will be able to obtain the product and dispense to outpatients.
 - b. Outpatients can obtain medications from inpatient pharmacies. The indication states Entereg is used for a maximum of 7 days post operatively or upon discharge from the hospital. However, patients discharged sooner than 7 days after surgery are likely to be receiving oral opioid pain medications at the time of discharge. The continued use of opioid pain relievers may lead prescribers to attempt to continue Entereg at home to complete a full 7 days or 15 doses of therapy. The inpatient pharmacy might be requested to provide the medication to the patient upon discharge or by providing Entereg to an outpatient pharmacy in the interest of discharging the patient sooner.
 - c. The proposed RiskMAP includes the use of the Rx Safety Advisor program to alert outpatient pharmacists of the “for hospital use only” indication. However, this type of alert system permits pharmacists to override the warning with an explanation. Retail pharmacists are likely to call the prescriber’s office to confirm the intention of the use of the product even with the current warnings. If the prescriber confirms the ordered medication is intended for outpatient therapy, the pharmacist would be able to override the warning and dispense the medication if they have it available.
 - d. The sponsor proposes inclusion of a warning, “For hospital use only” or “For use in hospitals only,” throughout the labels and labeling. We note that the printed warning is not highlighted to draw the health care provider’s attention when reading the label or labeling. In addition, the warning may not be legible between the rows of the blister cards once blisters are torn from the card. See the illustration below.



3. The RiskMAP proposal does not set out a role for the hospital in ensuring that Entereg is used only for short-term inpatient use. Hospital-based practitioners must understand the need to limit doses to 15 doses only, and they must understand that patients should not be discharged on alvimopan. It might be necessary to require that hospitals have systems in place to limit the use of the product to short-term inpatient use. To this end, the RiskMAP could register hospitals into the RiskMAP after meeting requirements for safe use (i.e., after receiving education and after attesting to having systems in place to limit the use of the product to short-term inpatient use).

Are process outcomes sufficient to measure the performance of the RiskMAP?

Although generally the evaluation of RiskMAPs through medical outcomes is preferred to process outcomes, the use of process outcomes might be acceptable in this case. We note that the RiskMAP as proposed will not collect data on the medical outcomes of interest, ischemic cardiovascular events. The RiskMAP uses a process outcome (limiting use to short-term only), and supposes that if the process is adhered to (and therefore use actually is limited to short-term use in hospital settings), the cardiovascular risk will be minimized. Although the clinical trial data are not conclusive on this matter, the data suggest that the cardiovascular risk probably would be minimized if use is restricted to short-term use. The direct collection of medical outcome data would greatly complicate the RiskMAP for all stakeholders. For these reasons, the use of process outcomes to measure the success of the RiskMAP should be considered.

5 CONCLUSION

The sponsor submitted a RiskMAP addressing the risk of ischemic cardiovascular events with long-term use. The primary method proposed to accomplish this is to establish agreements with wholesalers to sell Entereg only to hospitals. We agree with the Sponsor's overall approach; however, the proposal raises a number of important issues and challenges that we request the Advisory Committee discuss. The details of this discussion will be considered in the final design of the RiskMAP program.