CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-775

MEDICAL REVIEW(S)

MEMORANDUM

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

DATE: 5/1/2008

FROM: Ruyi He, MD
Medical Team Leader
Division of Gastroenterology Products/ODE III

TO: Donna Griebel, MD,
Director
Division of Gastroenterology Products/ODE III

SUBJECT: GI Team Leader AP Comments
NDA 21-775, Alvimopan (ENTEREG)

THERAPEUTIC CLASS: μ-opioid receptor antagonist

APPLICANT: Adolor Corporation

FORMULATION: Oral capsule

PROPOSED INDICATION: To accelerate the time to upper and lower GI recovery following partial large or small bowel resection surgery with primary anastomosis

RECOMMENDATION:

I concur with the conclusion of FDA Gastrointestinal Drugs Advisory Committee (GIDAC) Meeting held on January 23, 2008 that the overall benefits of treatment with alvimopan outweigh the potential risks for short term in-hospital use in patients following partial large or small bowel resection surgery with primary anastomosis.

I recommend that the new drug application (NDA) 21-775, Entereg (alvimopan) Capsules, be approved 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. The recommended dose is one 12 mg capsule given prior to surgery and then 12 mg twice daily for up to 7 days. To obtain approval, the sponsor should agree with Division's phase 4 requirements, establish an adequate risk manage plan, and incorporate the Division's labeling recommendations.

The sponsor is requesting deferral pediatric studies. I recommend that this request be granted until additional safety data in adult patients become available.

As Phase 4 commitments, the sponsor should conduct additional prospective, randomized, placebo controlled, double blind study to evaluate the safety of alvimopan for short term use in postoperative ileus (POI) population that is different from partial large or small bowel resection (BR) surgery patient population. The study should be designed to adequately assess adverse events with special attention to the possible cardiovascular events. The sponsor agrees to conduct a phase 4, multicenter, double-blind, placebo-controlled, parallel study of alvimopan for the management of postoperative ileus in subjects undergoing radical cystectomy. The sponsor has committed to enhanced monitoring for cardiovascular safety in this study.

BACKGROUND:

Alvimopan is a μ-opioid receptor antagonist that is being investigated for the management of postoperative ileus. 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 "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, in this second-cycle the sponsor submitted the results of one additional adequate and well controlled POI study in partial small and partial large bowel resection surgery patients.

During review of the second-cycle submission, in May 2006, 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 14). This study was a one-year long, 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 the 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.

The GI advisory committee meeting took place on January 23, 2008 to discuss efficacy and safety for the POI indication, specific safety issues which were identified in the long term OBD study (serious cardiovascular events, neoplasms and fractures), pre-clinical findings and risk management strategies.

The AC members unanimously agreed that the efficacy results of hospital discharge occurring approximately 1 day earlier were clinically meaningful. The majority of AC members (9 to 6) agreed that the benefits outweighed the risks for short term in- hospital use in patients following partial large or small bowel resection surgery with primary anastomosis.

DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

This is the 3rd review cycle for NDA 21-775. There is no issue related to DDMAC, DMETS, Chemistry and Manufacturing, Pre-Clinical Pharmacology/Toxicology and Biopharmaceutics in this submission.

Clinical/Statistical:

Efficacy:

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 and placebo, respectively].

Table 1 delineates the efficacy results of **GI2** (toleration of solid food and first bowel movement) 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. In all five POI trials, 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. 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: Summary of GI2 in days in BR patients in the POI studies

Study	Treatment Group	N[2]	50th Percentile in days	Change from placebo in days	75th 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			

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 discharge order written **(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. In the four U.S. trials, 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.

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

Study	Treatment Group	N*	50th Percentile in days	Change from placebo in days	75th 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:

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., ≥ 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].

POI Trials
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.

In the POI studies, the number of neoplasms in each treatment group appeared to be balanced.

Chronic Opioid-Induced Bowel Dysfunction (OBD)
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.

Serious CV adverse events in GSK014 and in OBD population are summarized Table 3 and 4 below.

Table 3: Summary of CV Events of Interest in Study 014

CV Event Category	Placebo Group N=267 n (%)	Alvimopan Group N=538 n (%)	Relative Risk Alvimopan/Placebo (95% CI)
All causes of death	2 (0.75)	2 (0.37)	0.50 (0.07, 3.50)
Death from CV events	0	1 (0.19)	1.49 (0.06, 36.5)
Myocardial infarction	0	7 (1.3)	7.46 (0.43, 130.1)
Unstable angina	0	3 (0.56)	3.48 (0.18, 67.1)
Non-fatal cerebrovascular accident	0	1 (0.19)	1.49 (0.06, 36.5)
Congestive heart failure	0	1 (0.19)	1.49 (0.06, 36.5)
Serious arrhythmia	0	2 (0.37)	2.49 (0.12, 51.6)

Table 4: Summary of CV Events of Interest in OBD population

CV Event Category	Placebo N=790 n (%)	Alvimopan N=1728 n (%)	Relative Risk Alvimopan/Placebo (95% CI)
All-cause death	2 (0.25)	4 (0.23)	0.91 (0.17,4.98)
Death from CV events	0	2 (0.12)	2.29 (0.11,47.6)
MI: Overall	2 (0.25)	8 (0.46)	1.83 (0.39,8.59)
Fatal	0	1 (0.06)	--
Non-fatal	2 (0.25)	7 (0.41)	--
Unstable angina	0	4 (0.23)	4.12 (0.22,76.4)
Non-fatal CVA	1 (0.13)	2 (0.12)	0.91 (0.08,10.1)
CHF: Overall	2 (0.25)	2 (0.12)	0.46 (0.06,3.24)
Fatal	0	0	--
Non-fatal	2 (0.25)	2 (0.12)	--
Serious arrhythmia	0	5 (0.29)	5.03 (0.28,90.9)
Fatal	0	0	--
Non-fatal	0	5 (0.29)	--

Studies: GSK011, GSK012, GSK013, GSK014, 13C217 and 13C304.

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 that 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. There is no clear etiology to explain the differences.

Neoplasm events in non-cancer pain studies are summarized in Table 5.

Table 5: Summary of 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)

With the available information, there appears to be an imbalance in neoplasm 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. In the POI studies, the number of neoplasms in each treatment group appears to be balanced. When study entry criteria are not pre-specified and information is incomplete, it may be difficult to assess potential neoplastic findings.

Combining all the data revealed that the incidence of fractures was 1.4% (25/1758) in the alvimopan group compared with 1.2% (10/802) in the placebo. The HR estimate was 1.15 (95%CI = 0.55, 2.39).

Patients studied in the OBD program have typically been white (82% - 90%), female (60% - 65%), and in their fifties. The non-cancer population is also characterized by a high prevalence of tobacco use (40%). While these demographic characteristics are known risk factors for bone fractures, 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 GSK014 failed to find an increased fracture incidence. In fact, the fracture incidence in patients treated

with alvimopan was less than that in the placebo group; 0.4% vs. 1.3%, respectively. These patients 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.

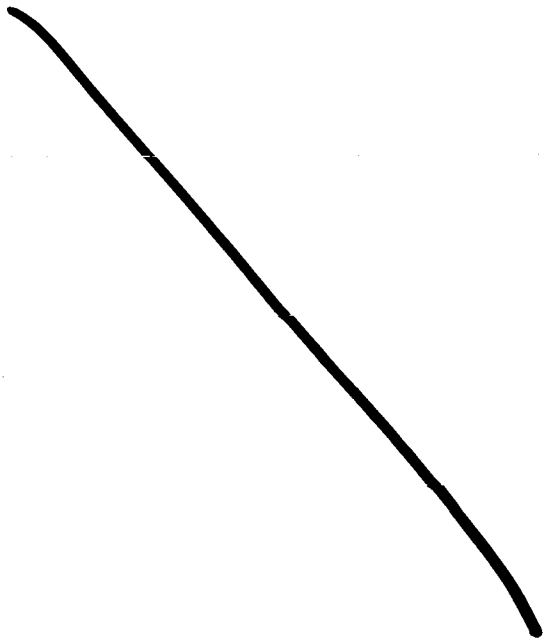
Given these findings, the higher fracture incidence observed in the alvimopan group in GSK014 was unexpected and not readily explained by data available in the dataset.

For detailed evaluations of MIs, neoplasms and bone fractures in OBD population, please see Dr. Marjorie Dannis's review dated February 27, 2008.

Pediatric Use:

The sponsor is requesting a deferral for pediatric studies. I recommend that this request be granted for the indication until additional safety data in adult patients become available. The sponsor agrees to conduct a phase 4, multicenter, double-blind, placebo-controlled, parallel study of alvimopan for the management of postoperative ileus in subjects undergoing radical cystectomy. The sponsor has committed to enhanced monitoring for cardiovascular safety in this study.

RISK EVALUATION AND MITIGATION STRATEGY (REMS)



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/s/

Ruyi He
5/1/2008 05:53:42 PM
MEDICAL OFFICER

Alvimopan (ENTEREG®) Special Safety Review

Established Name	Alvimopan
(Proposed) Trade Name	ENTEREG®
Therapeutic Class	μ-opioid receptor antagonist
Applicant	Adolor Corporation
Formulation	Oral capsule
Application Type	NDA (third cycle)
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".
Reviewer Name	Marjorie Dannis, M.D.
PDUGA Goal Date	May 10, 2008
Review Completion Date	Feb 22, 2008

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

V. Summary

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

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:

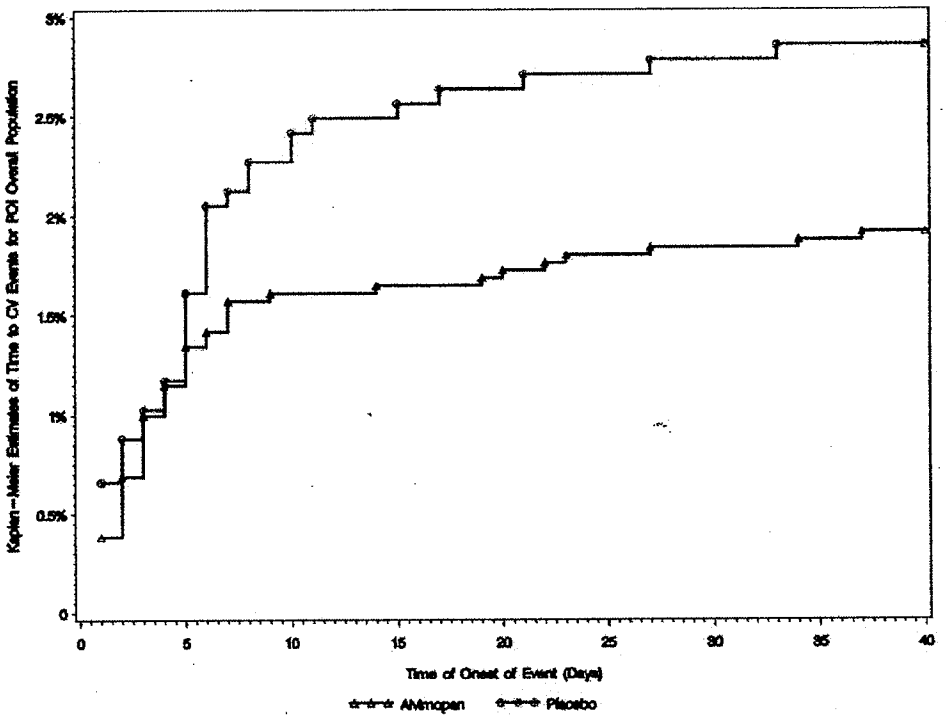
- The day of the CV event for subjects who had a CV event and the remaining subjects were censored at day 40
- The CV events ascertained while the subject was in the study, in hospital, or at the 2-week phone post-study follow-up.

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.

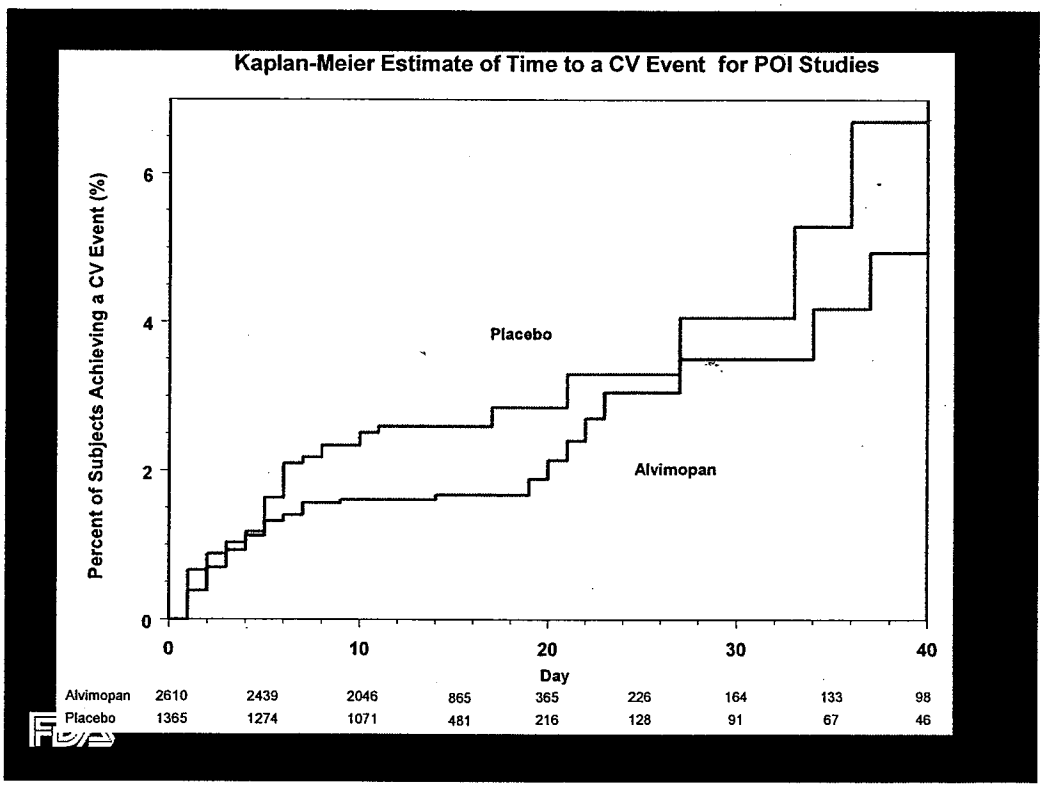
Thus, the time to cardiovascular event as represented in these Kaplan-Meier curves cannot be reliably estimated. The FDA analysis using the last known follow-up time for each subject is shown below in Figure 2.

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

Figure 2: Kaplan-Meier Estimate of Time to Cardiovascular Event for the Overall Postoperative Ileus Population (FDA analysis)



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

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** n (%)	**Placebo N=267 (%)** n (%)	**Relative Risk Alvimopan/ Placebo (95% CI)**
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)

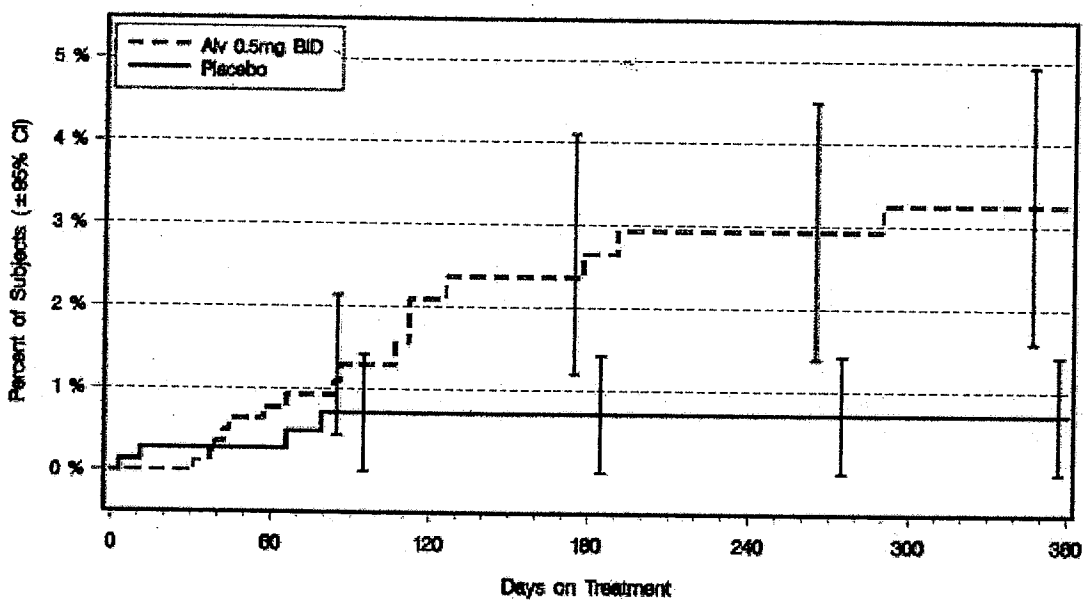
CV event category	**Alvimopan N=538** n (%)	**Placebo N=267** n (%)	**Relative Risk** Alvimopan/ Placebo (95% CI)
MI	8 (0.39)	3 (0.33)	1.19 (0.32,4.46)
Unstable Angina	4 (0.20)	1 (0.11)	1.78 (0.20,15.9
CVA	2 (0.10)	1 (0.11)	0.89 (0.08,9.79)
CHF: Overall	4 (0.20)	2 (0.22)	0.89 (0.16,4.85)
Serious Arrhythmia	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 (Figure1) 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:

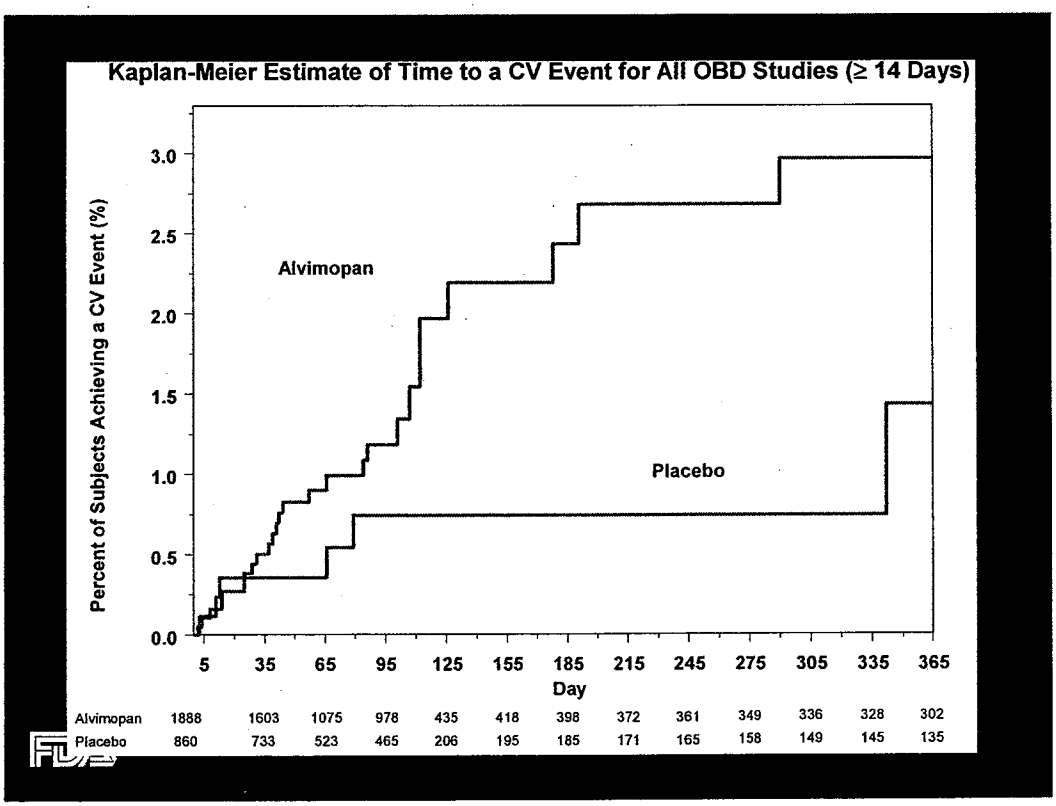
- The day of the CV event for subjects who had a CV event and the time-on-treatment for those subjects without a CV event
- All placebo subjects and all 0.5 mg BID subjects were used to generate the Kaplan-Meier curves. None of the other alvimopan doses were used
- A combination of five short-term studies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

The FDA's Kaplan-Meier analyses for the long-term and short-term studies are presented below in Figure 2.



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.

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.

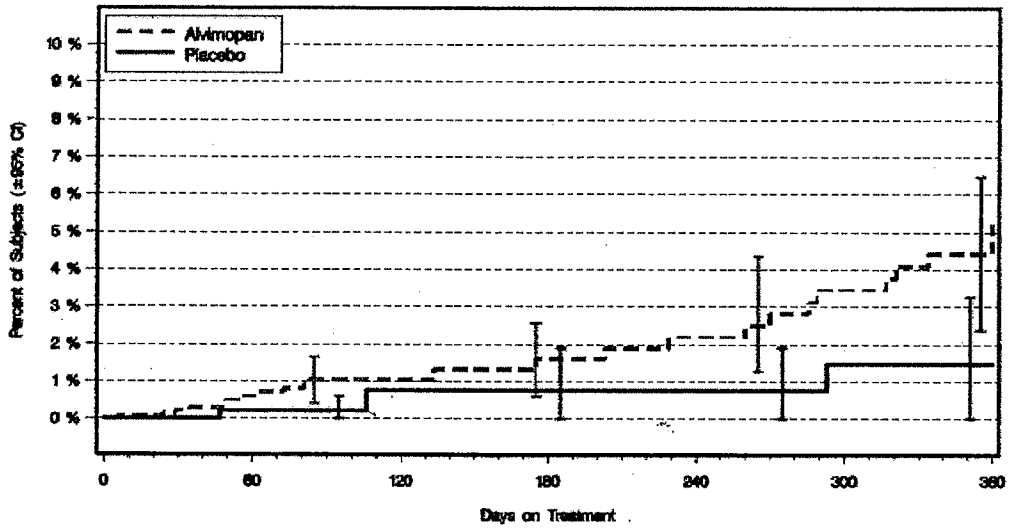
Table 3: Neoplasms in Study 014

	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.

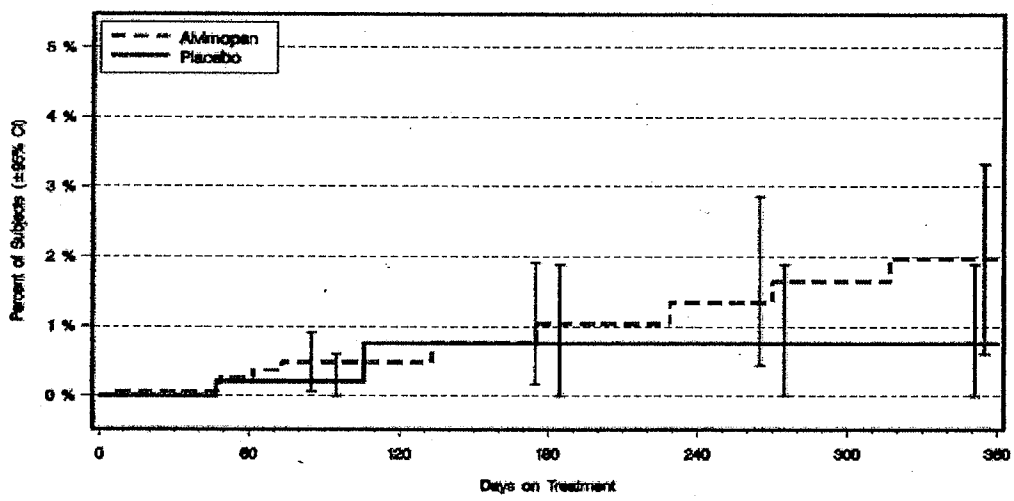
Figure 1: Time to Any Neoplasm: Non-Cancer Pain Studies



Subjects At Risk

Placebo	732	467	176	160	150	138	74
Alvimopan	1598	942	364	341	322	300	171

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



Subjects At Risk

Placebo	732	467	176	160	150	138	74
Alvimopan	1598	946	367	344	328	307	176

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

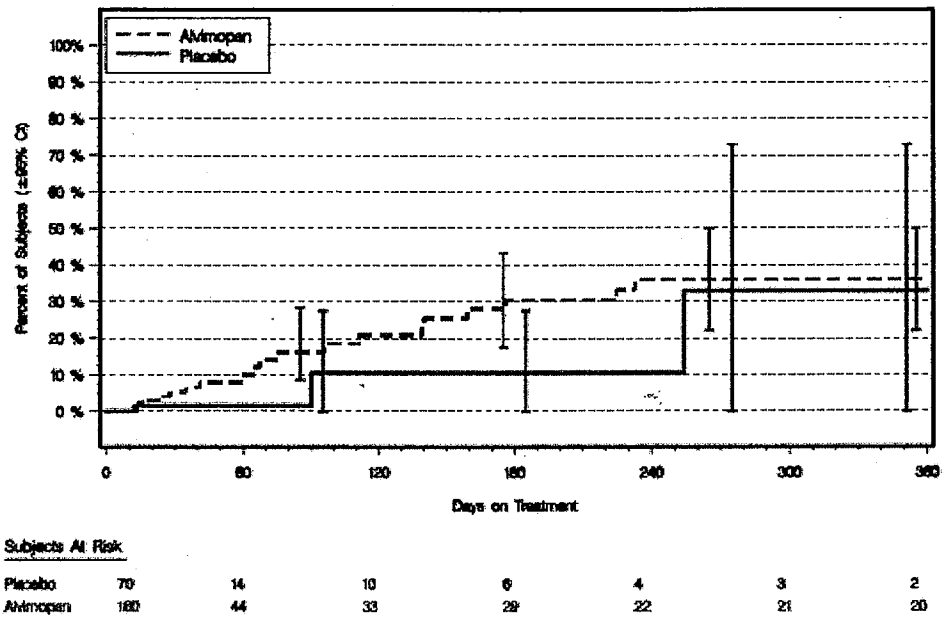
Reference: Adolor's Comprehensive Summary of Alvimopan Safety Data: Neoplasms and Related Events, page 18

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

System organ class - preferred term	Placebo (N=70) n (%)	Alvimopan 1.0 mg QD (N=27) n (%)	Alvimopan 0.5 mg BID (N=68) n (%)	Alvimopan 1.0 mg BID (N=65) n (%)	Alvimopan Total (N=160) 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	3 (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	Alvimopan	Placebo	Alvimopan
	N=70	N=160	N=15	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 *in situ*	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)- *Skin cancer*	289	Malignant
014	51 yo m smoker w/ DDD of spine	alvimopan	Ulcerated basal cell carcinoma, circumscribed type, involving deep margins of nose- *Skin cancer*	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	53.6
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/m²)	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

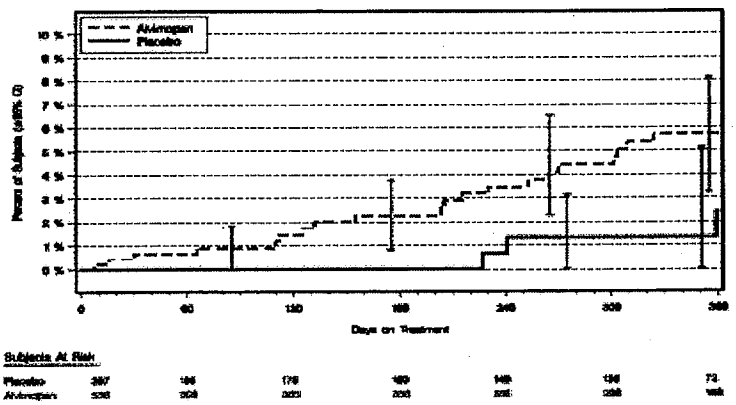
	Placebo (N = 3)	Alvimopan (N = 20)
Mean age (years)	55.7	56.6
Range (years)	60 - 71	37 - 84
≥ 65 years	1 (33%)	6 (30%)
Female	1 (33%)	15 (75%)
White	2 (67%)	20 (100%)
Mean BMI (kg/m²)	23.8	28.6
Tobacco history	0	6 (30%)
Mean METDD (mg)	100	203

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, 30.06)

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.

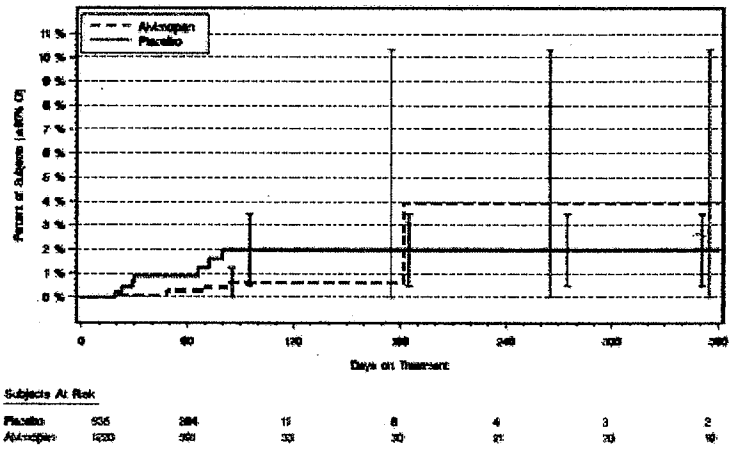
Table 7: Demographic Summary of Fracture Subjects (Studies 011, 012, 013, 008, ABD101684)

	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 ≥ 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.

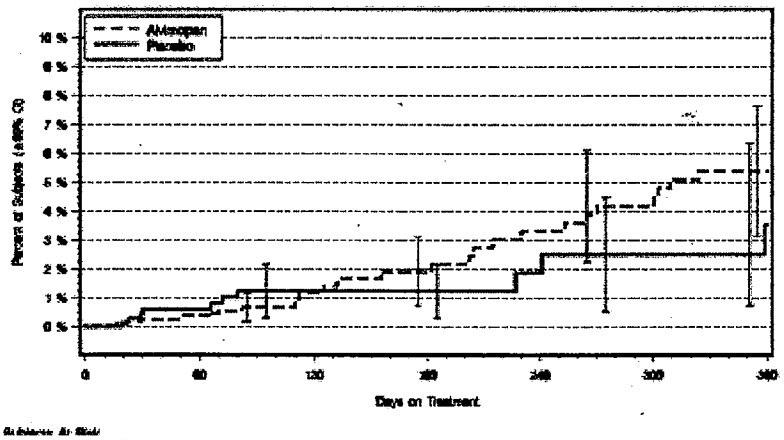
Table 10: Demographic Summary of Fracture Subjects (All OBD Studies)

	Placebo (N = 10)	**Alvimopan (N = 25)**
Mean age (years)	55	57
Range (years)	41 - 71	34 - 84
≥ 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 psychoanaleptics) 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.

Additional Tables

CV Safety in the POI Population

Table AA: Medical reviewer's analysis of MI's and cardiac arrests in POI population
(Studies 13C206, 13C213, 13C214, 14CL302, 14CL306, 14CL308, 14CL313, 14CL314, and SB-767905/001)

Subject Number	Comments	Primary event/ outcome	Treatment group
14CL302.22.01118	Prominent first serious event	CHF death	alvimopan
14CL308.31.01182	h/ o PE rx'd	Cardiac arrest death	alvimopan
14CL313.13.13015	Clear MI	MI death	alvimopan
13C213.05.00006	Clear MI	MI	placebo
14CL302.06.01056	Very questionable Small MI, CHF, RAF ,hypotension (could be any of these CV events)	CHF	placebo
14CL313-18-18016	RAF	Serious arrhythmia	placebo
14CL308.13.01235	Unstable angina/small mi	MI	placebo
14CL314-01-00068	Unstable angina No mi	Unstable angina	placebo
14CL308-03-01041	72 yo V tach/ Cardiac arrest In casino got alvimopan for 7 days. 20 days later had event	Cardiac arrest Survived. Well documented	alvimopan
14CL308.25.01126	39 yo healthy had 1 preop dose of A, had asystole and cardiac arrest intraop "athletic heart syndrome" ?	Cardiac arrest Survived Well documented	alvimopan
GSK001-15-00964	76 alvimopan for 7 days, but 2 hours after first dose has asystole in OR, precordial thump	Cardiac arrest Survived Well documented	alvimopan
GSK001.38.01221	63 yo m, had MI 1.5 month ago, had cardiac arrest x2 after 1 dose of	cardiac arrest Survived, seems translated well	alvimopan

	alvimopan, 3 hours after 1dose (? pre op clearance w/ recent mi)		
GSK001.39.01284	75 yo m,had alvimopan x 7 day, suture dehiscence and peritonitis, then cardiac arrest	Cardiac arrest Survived,	alvimopan
13C213.05.00009,	82 had pharyngeal trauma related to the placement of his endotracheal tube, pneumonia, sepsis multiorgan failure then cardiac arrest	All cause death (not Cardiac arrest died because other factors, not primary cardiac, CV was secondary)	placebo
14CL314.04.00191	68 lactic acidosis, SMA thrombosis, PEA secondary to above	All cause death, (not cardiac arrest PEA secondary to underlying cause, not primary cardiac)	placebo
14CL313.02.02006	77 yo m placebo x 6 days, but episode of asystole occurred shortly after induction and intubation after one dose placebo. Treatment for the asystole included atropine	cardiac arrest (Survived, asystole, ? beta blocker)	placebo
GSK001-03-00042	57 yo f had asystole 2 hours after placebo 30 min after induction of anaesthesia. "likely to be due to exaggerated vasovagal response"	Cardiac arrest Survived	placebo
GSK001-15-00977	74 yo m had asystole 7 hours after placebo, had CPR"EKG revealed supraventricular tachyarrhythmia without	Cardiac arrest Survived	placebo

	conduction to the ventricles" Sketchy history,translated, but had asystole, unclear what else—primary cardiac, had permanent neuron sequalae ?		
GSK001-62-01289	82 yo m had placebo for 5 days, 2 days later had sepsis, afib, GIB	All cause death Died, not primary cardiac	placebo
14CL308.15.02143	53 yo f had 4 doses of placebo, last at home had abd pain at home, sudden death witnessed- Reported to have toxic levels of oxycodone and flexeril Unclear etiology of death-if sudden death/cardiac arrest in same category? O	cardiac arrest	placebo
14CL313.13.13015,	64 yo m had MI 2 days after alvimopan stopped, Vfib, died	MI death	alvimopan
14CL313.03.03014	69 yo 28 days after last dose of alvimopan, had MI m	MI	alvimopan
14CL308.24.1224	76 yo m had 1 dose alvimopan preop (case cancelled) then had SVT with high trop. 4 days after only dose	Serious arrhythmia	alvimopan
14CL314.01.00702	75 yo f had MI, then multiorgan failure, long hospitalization	MI	alvimopan
14CL314.25.00025	70 yo m had MI	MI	alvimopan

14CL314.32.00586	73yo m got alvimopan, 2 doses, etoh withdrawal, respiratory failure, MI x2	MI	alvimopan
14CL314.36.00240	78 yo f, had MI, CHF, respiratory failure, drug for 4 days	MI (then multiorgan failure) death	Alvimopan
GSK001-02-00022	83 yo f had one preop dose of alvimopan x 1 dose then 2 days later had RAF and MI, Had both, which event should she be in? (sponsor has both)	MI	alvimopan
GSK001.15.00970	75 yo m got alvimopan for 7 days then had MI first, then Afib	MI	Alvimopan
GSK-001-19-00257	68 yo m Femoral artery occlusion, Myocardial infarction. Drug for 4/5 days (had fem/pop bypass and coronary artery stenosis in past)	MI (and femoral artery occlusion)	Alvimopan
GSK001-27-00404	67 yo m had arterial GI bleed then MI after 4 days alvimopan for 6 days	MI (Had GIB first)	Alvimopan
GSK001.29.00432	69 yo m got alvimopan for 3 days; Had AF with mildly elevated trop., also MI,	MI	Alvimopan
GSK001-34-00520	58 yo f, no cardiac history had 1 dose alvimopan; tachyarythmia "because of 1 cc adrenaline" and had MI and CHF; Unclear what tachy was, but all seems because of mistake,	MI	alvimopan

GSK001.56.00273	70 yo f h/o TIA, had alvimopan for 3 days, then had PRIND, then another , then CVA then peritonitis, small MI, had alvimopan for 6 days	CVA (death) Had neuro events first then anastomotic leak, MI_	Alvimopan
13C213.05.00006	67 yo m had placebo for 2 days had MI then wound dehiscence and intestinal perforation creating an anastomotic leak on study day 12	MI	placebo
14CL302.06.01056	75 yo f had hypotension,,CHF, MI, afib, pneumonia Could be any of these but something cardiac	MI	placebo
14CL308.13.01235	71 yo f with AF, small MI, unstable angina, placebo x 6 days' Could be any	MI	Placebo
14CL313.18.18016	64 yo f had afib with tiny increase in trop;placebo x 7 days(Could be afib),	MI	Placebo
14CL314.01.00068	63 yo m with six days of placebo uneventful surgery; Unclear, readmitted with unstable angina, got bypass, had CHF, increased trop, but maybe after surgery, could be man	MI	Placebo
14CL314.08.00733	50 yo m 5.5 hours after placebo x 1 dose, had MI	MI	Placebo
14CL314.68.00716	81 yo m readmitted with CHF ; Not clear MI,	CHF	placebo

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

Table BB: Medical Reviewer's Interpretation of POI Cardiovascular Deaths

Study number/Study ID	Treatment group	history	Hospital course	Possible CV death etiology	differences
14CL302 01118	Alvimopan	71 yo male had BR , one preop dose of alvimopan only (secondary to colostomy); positive risk factors for CV disease.	POD 5 had CHF, died on POD12 of CHF	CHF	
14CL313 13015	Alvimopan	64 yo male BR discharged POD 6 (got last dose POD 6). Readmitted POD 8 with CP and acute MI; positive CV risk factors	POD 8 acute MI, died POD 10.	Acute MI	
GSK 001 273	Alvimopan	70 yo female BR, had CVA with left hemiparesis on POD 2, stopped study med. POD5, POD 9 had anastomosis leak/peritonitis, exploratory lap; positive CV risk factors	POD 2 had CVA; POD 16 died	CVA	
GSK 001 448	Alvimopan	63 yo male BR, stopped study drug POD 7; discharged POD 13; expired POD 16 in sleep; unclear CV risk factors	POD 16 died in sleep	Sudden death in sleep	
14CL314 360240	Alvimopan	78 yo female , POD 3 had MI, CHF, renal failure, respiratory failure; study med stopped POD3; POD 4 had liver failure; positive CV risk factors;	POD 6 discharged to hospice; died POD 9	MI, CHF, respiratory failure	* Sponsor does not count as CV death.

14CL308 01182	Alvimopan	57 yo male BR, discharged POD 7; readmitted POD 13 with recurrent PE; positive CV risk factors	Readmitted POD 13 with recurrent PE; had cardiac arrest and died POD 13	Pulmonary embolism	
GSK 00119 263	Placebo	61 yo male discharged POD 7; died POD 9; unclear CV risk factors	discharged POD 7; died POD 9	? sudden death	
14CL314 40191	Placebo	68 yo male BR, last study med on POD 6 then discharged; readmitted POD 9 with lactic acidosis and PEA; died POD 9; autopsy with arterial thrombus in thoracic aortaand superior mesenteric artery; unclear CV risk factors	Died POD 9 with arterial thrombi	arterial thrombi	

Reference: Adolor's original study reports and information requests

Neoplasms in the OBD Population

Table CC: Medical Reviewer's Non-Cancer OBD Neoplasm Summary

	Alvimopan	Placebo
Malignant	13	3
Benign	9	1
Total Neoplasms	22	4

V. Summary

Brief Overview of Clinical Program

Adolor originally submitted NDA 21-775 on June 25, 2004 for the treatment of post-operative ileus (POI). The Division of Gastroenterology Products (DGP) took an approvable action on this NDA on July 7, 2005 because of "insufficient proof of efficacy" to support the POI indication. They recommended that Adolor provide at least one additional adequate and well-controlled study (in patients scheduled to have partial small or partial large bowel resection) that demonstrated statistically significant superiority and clinical meaningful results for the alvimopan group compared to the placebo group.

To satisfy the deficiencies in the original submission, Adolor submitted a **second-cycle** NDA on May 2006 as a Complete Response to the Approvable Letter (July 7, 2005). This **second-cycle** submission contained the results of an additional POI study in partial small and large bowel resection surgery patients. During the 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 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.

Thus, a **second** approvable action was taken by the FDA on November 3, 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, also in Study 014, a numeric imbalance in reports of neoplasms and bone fractures was noted, with a higher incidence in the alvimopan treatment groups than in the placebo groups. The identification of the imbalance in neoplasms in Study 014 led to an interim analysis of an 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 during this review cycle.

It was further decided by the DGP to bring alvimopan's use for the POI indication before an advisory committee. In this forum, the division hoped to gather expert advice on the clinical interpretation of the product's efficacy, the impact on the POI indication of the

potential safety issues identified in the long-term safety study 14, and the appropriate risk management strategy.

The advisory committee meeting took place on January 23, 2008. Presentations by the sponsor and FDA included: a surgical perspective of POI, overviews of efficacy and safety for the POI indication, discussions of specific safety issues (serious cardiovascular events, neoplasms, fractures), pre-clinical findings and risk management strategies. Several questions were asked of the committee. The **questions** and answers as best captured by this reviewer are presented below. (The advisory committee transcript was not available at the time of this review)

- **Do you consider the efficacy results from the submitted POI studies to be clinically meaningful?**

  Unanimously, the members felt the efficacy results of hospital discharge occurring approximately 1 day earlier were clinically meaningful.

- **Based on currently available data, do you have concerns for the use of alvimopan 12mg capsules in the short-term (i.e., 7 days or 15 doses) for patient following partial large or small bowel resection surgery with primary anastomosis with regard to the cardiovascular events?**

  The majority of AC members (8 to 6, 1 abstain) felt that there were concerns for the use of alvimopan 12mg capsules in the short-term with regard to cardiovascular events.

- **Do you believe the overall benefits of treatment with alvimopan outweigh the potential risks for short term in-hospital use in patients following partial large or small bowel resection surgery with primary anastomosis?**

  The majority of AC members (9 to 6) felt that the benefits outweighed the risks for short term in- hospital use in patients following partial large or small bowel resection surgery with primary anastomosis.

- **If alvimopan is approved for the POI indication, do you believe Adolor Corporation's proposed risk management plan is adequate to address the potential risks?**

  The AC committee unanimously agreed that Adolor's proposed risk management plan was not adequate.

- **Based on currently available data, how should safety monitoring be enhanced for patients enrolled in future short term and long term clinical studies of alvimopan?**

  At least one committee member (a cardiologist) recommended longer patient f/u (at least 30 days) with investigator visits as opposed to telephone calls. There was consensus by the committee that a prospective study would be the best way to assess specific adverse events (cardiovascular, neoplastic and fractures). They recommended that this study could be part of a phase-4 commitment.

Medical Reviewers Discussion:

This medical reviewer believes that the proper review of a new drug involves a thorough risk/benefit analysis. Although, this reviewer did not independently evaluate the efficacy of alvimopan, there is consensus that the efficacy of alvimopan was demonstrated. As presented in the previous sections of this review, this medical reviewer has some concerns about the safety of alvimopan for both the short-term indication (POI) as well as for the long-term indication (OBD).

The use of alvimopan did accelerate the time to upper and lower GI recovery in patients undergoing partial bowel resection surgery with primary anastomosis; alvimopan treated patients were discharged from the hospital an average of 24 hours earlier than placebo treated patients. There does appear to be a clinical benefit to treating post-operative ileus ; decreasing patient discomfort and beginning PO intake earlier seem to be beneficial to recovery .The expedition of hospital discharge by 1 day also seems to be beneficial to patient care. There clearly is a financial benefit to decreasing length of stay for hospitals, insurance companies, etc; however, it is unclear what the longer term consequences of an earlier discharge are. Did the patients who were hospitalized for one day longer have a higher incidence of nosocomial infections (pneumonia, Clostridium difficile), deep vein thrombosis, pulmonary emboli etc? Was there a difference in morbidity/mortality at 30 days, at 60 days? Did the patients who were discharged earlier actually do better at home? These questions remain unanswered.

Another important aspect to consider is the natural history of POI. Most post-operative bowel surgery patients do recover bowel function on their own within a few days. A small percentage (approximately 10-15%) of patients require intervention or change in hospital management due to unresolving POI. Since alvimopan is given pre-operatively to everyone , a large percentage of patients may be unnecessarily exposed to the medication.

This medical reviewer believes that a prophylactic treatment for a non-life threatening condition should be proven to be effective and safe. This reviewer further believes that since follow-up of the patients after hospital discharge was not adequate, there may be some question about the drugs safety. With the information that was ***collected****, there does not appear to be a safety issue for alvimopan's use for POI; however, missing*

information does not imply that no events took place. Missing information means incomplete data which means the safety of alvimopan is indeterminate. Furthermore, the only long-term safety study showed some potential safety signals in serious cardiovascular events, neoplasms and fractures. The higher incidence of these events in alvimopan treated patients as compared to placebo can not be explained.

This medical reviewer recommends that an additional pre-approval, prospective, randomized, placebo controlled, double blind study be conducted to ensure the safety of alvimopan's use for POI. This study should be designed to accurately assess adverse events with special attention to the possible signals present in Study 14. All patients should have protocol defined investigator visits following discharge with appropriate safety monitoring in place (i.e. EKG's, vital signs etc). Patients should be assessed at 30 days (and possibly 60 days) to try to determine the ultimate clinical outcome (morbidity/mortality) that an earlier hospital discharge would bring.

This reviewer also recommends that patients ***without*** *post-operative PCA pumps be included in the study. It is unclear if alvimopan would have efficacy in patients without constant opiate infusion. (Sponsor's surgical expert claimed there would be no efficacy.)*

In conclusion, this medical reviewer believes that, at this time, the potential risks of alvimopan outweigh the potential benefits. Information gained from a properly designed prospective trial in POI as outlined above could possibly diminish the potential risks and thus offer the public a novel, safe and effective treatment for post-operative ileus in patients undergoing bowel resection surgery.

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/s/

Marjorie F. Dannis
2/27/2008 05:37:30 PM
MEDICAL OFFICER

Ruyi He
2/27/2008 05:50:17 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE:	November 3, 2006
FROM:	Brian E. Harvey, M.D., Ph.D. Division Director, DGP/ODE III/OND
TO:	Julie G. Beitz, M.D. Director, ODE III/OND
SUBJECT:	Division Director Concurrence Memo NDA 21-775
APPLICANT:	Adolor Corporation
DRUG:	ENTEREG® (Alvimopan)
DATE SUBMITTED:	May 9, 2006, as a complete response to Approvable Letter of July 21, 2005

DIVISION RECOMMENDATION

The primary Medical Officer and Medical Team Leader recommend that NDA 21-775, ENTEREG® (Alvimopan) be approvable for the proposed indication to accelerate the time to upper and lower GI recovery following partial large or small bowel resection surgery with primary anastomosis. I am in agreement with this recommendation.

I. BACKGROUND:

Alvimopan is an opioid-receptor antagonist. It is a new molecular entity and is not currently marketed in the United States or any other country in the world.

In February 2004, the forerunner to the Division of Gastroenterology Products (DGP) granted the alvimopan development program for the treatment of Post-Operative Ileus (POI) fast tract status because POI "is a serious condition for which no drugs have been approved" and alvimopan "appears to be a safe and effective treatment for this medical need". In May 2004, the division accepted alvimopan for the treatment of POI into the Pilot 1 Continuous Marketing Application program.

The sponsor originally submitted the complete NDA 21-775 on June 25, 2004 for POI. The division took an approvable action on this NDA on July 21, 2005 due to "insufficient proof of

efficacy" in support the of POI indication. The recommendation was for the sponsor to provide at least one additional adequate and well-controlled study (in patients scheduled to have partial small or partial large BR) that demonstrates statistically significant and clinical meaningfulness for the proposed dosing regimen of Alvimopan.

The sponsor submitted their complete response on May 9, 2006. To satisfy the deficiencies in their original submission, the sponsor submitted the results of one additional adequate and well-controlled POI study in partial small and partial large BR surgery patients (i.e., Study 14CL314) in this second-cycle submission. The sponsor modified their original POI indication in the first-cycle ("to accelerate time to recovery of GI function following abdominal or pelvic surgery") to the following proposed POI indication: alvimopan is indicated "to accelerate the time to upper and lower GI recovery following partial large or small bowel resection (BR) surgery with primary anastomosis".

On May 15, 2006, GlaxoSmithKline (GSK), a partner of the sponsor Adolor in the development of alvimopan, informed the DGP of a numerically higher incidence of serious CV events in the alvimopan treatment group, compared to the placebo group, in one of their ongoing, long-term alvimopan trials (SB-767905/014) in opioid-induced constipation (OIC).

On September 29, 2006, the safety issues regarding this drug were presented to a CDER Regulatory Briefing. The stated purpose of this briefing was to seek advice regarding the approval of ENTEREG® (alvimopan), for the treatment of post-operative ileus (POI). The major safety concern was the possible CV signal observed in one of the long-term opioid-induced constipation (OIC) alvimopan studies, which was 52 weeks in duration. There was an increased incidence of myocardial infarctions (MI) in the alvimopan treatment group, compared to the placebo group. In this briefing, the following was discussed:

1) The adequacy of the POI safety database;
2) The potential of a long-term alvimopan-associated CV signal;
3) The approval of alvimopan for the short-term POI indication;
4) If approved, the need for CV WARNINGS and/or a RiskMAP; and
5) If not approved, the required additional safety studies.

After a detailed presentation by the primary medical officer, there was active discussion by the attendees on these important safety issues. Although there were no final conclusions at the end of this briefing, these discussions have been incorporated into the reviews of the primary medical officer and medical team leader.

II. SUMMARY

I concur with the conclusions of the primary medical officer and medical team leader regarding the use of alvimopan for the short-term POI indication, that efficacy was demonstrated, and there was no evidence of a significant safety signal with short-term use.

I also agree that there may be CV signal associated with the long-term use of alvimopan. Therefore, I concur with the recommendations of the primary medical officer and medical team leader that the sponsor should submit the CV data from ongoing Study 14 prior to approval of alvimopan for the short-term POI indication, in order to fully inform the labeling, such as th need for CV WARNINGS and to determine the nature of the drug's risk management plan.

III. RECOMMENDATIONS FOR REGULATORY ACTIONS

I concur with the primary medical officer and medical team leader recommendation for an approvable action for the 12 mg dose of ENTEREG® (alvimopan) Capsules, for the indication to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis. In order to obtain approval of the 12 mg dose of alvimopan for this post-operative ileus (POI) indication, the sponsor must provide the results of their one-year, ongoing, alvimopan phase 3 trial in opioid-induced constipation patients (SB-767905/014), including detailed analyses of myocardial infarction, unstable angina, and other serious cardiovascular events.

The following information should be included in the approvable letter to the sponsor:

> "We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to:
>
> - Submit the 12 month safety findings (including analyses of myocardial infarction, unstable angina, and other serious cardiovascular events) from Study SB767905/014 for review when they become available; and
> - Develop a risk management plan that includes elements to a) communicate the possible cardiovascular risk of longer-term alvimopan exposure and b) minimize off-label use. This plan could include appropriate labeling for prescribers and patients, and restriction of alvimopan use to hospital settings.
>
> In addition, we recommend you collect blood samples to assess levels of alvimopan and its active degradant (i.e., ADL 08-0011) in patients experiencing cardiovascular adverse events enrolled in ongoing alvimopan studies, if this is not already being done.
>
> Product labeling remains unresolved at this time. Please include revised draft product labeling with submission of your NDA amendment."

At the time of our regulatory action, we plan to have a telephone conference with the sponsor in order to inform them of our action and answer clarifying questions regarding this action.

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/s/

Brian Harvey
11/3/2006 09:08:17 AM
MEDICAL OFFICER

MEMORANDUM

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

DATE: November 3, 2006

FROM: Julie Beitz, MD

SUBJECT: Office Director Memo

TO: NDA 21-775 Alvimopan Capsules; Adolor Corporation

Alvimopan is a μ-opioid receptor antagonist that has been evaluated in the postoperative setting for the management of ileus, a common cause of prolonged hospitalization. It received Fast Track designation and was selected for inclusion in the Continuous Marketing Application Pilot 1. Currently there are no products approved for the treatment of post-operative ileus. This memo documents my concurrence with the Division of Gastroenterology Product's (DGP's) approvable action for alvimopan capsules to accelerate time to recovery of gastrointestinal function following bowel resection surgery.

On August 24, 2004, Adolor Corporation submitted NDA 21-775 containing three randomized, double-blind, placebo-controlled studies in support of an indication to *accelerate time to recovery of gastrointestinal function following abdominal or pelvic surgery*. In February 2005, post hoc subgroup analyses in 346 complex hysterectomy patients were performed by the sponsor and lead to a modification of the proposed indication to *accelerate time to recovery of gastrointestinal function following major abdominal or complex pelvic surgery*. At a March 16, 2005, meeting, the DGP advised Adolor that their submitted studies did not support an indication in pelvic surgery and that their post hoc analysis in a select group of complex hysterectomy patients, a population not previously specified, was exploratory and would need to be further evaluated in prospective clinical studies. At a teleconference on July 14, 2005, Adolor proposed to revise its indication yet again to *accelerate time to recovery of gastrointestinal function following bowel resection surgery*. The proposed regimen was alvimopan 12 mg administered orally within 30 minutes and no more than 5 hours prior to surgery, then 12 mg bid daily beginning the day after surgery for up to 7 days.

In January 2005, results of a fourth randomized, double-blind, placebo-controlled study in bowel resection patients conducted in Europe, Australia and New Zealand (sponsored by Adolor's partner, GlaxoSmithKline) became available. DGP requested a full study report which was submitted in April 2005. The magnitude of this submission necessitated extension of the review clock.

All four studies randomized patients 1:1:1 to receive 6 mg, 12 mg or placebo orally prior to surgery, then bid daily beginning the day after surgery for up to 7 days. The primary efficacy endpoint was GI^3 or the time (in hours) to recovery of both upper gastrointestinal tract motility (defined as the time from the end of surgery to the time of first tolerated solid food) and lower gastrointestinal tract motility (defined as the time from the end of surgery to the first flatus or the first bowel movement). FDA statistical reviewers re-calculated the median time to recovery of gastrointestinal tract motility derived from Kaplan-Meyer survival curves as described in the *Draft Guidance for Industry: Clinical Studies Section of Labeling for Prescription Drugs and Biologics – Content and Format*. Hazard ratios of alvimopan to placebo were calculated by the sponsor and FDA from a Cox proportional hazards model that included treatment.

In FDA's analysis of the bowel surgery patient subgroup, Study 14CL302 demonstrated a significant hazard ratio of 1.48 (95% CI: 1.10, 1.98) for the 6 mg dose of alvimopan compared to placebo (p=0.009). Study 14CL313 demonstrated a significant hazard ratio of 1.49 (95% CI: 1.17, 1.91) for the 12 mg dose of alvimopan compared to placebo (p=0.002). In addition, there were positive trends favoring the 6 mg dose compared to placebo in Study SB767905/001 (hazard ratio 1.22), and favoring the 12 mg dose compared to placebo in Study 14CL308 (hazard ratio 1.32). In both instances, the lower bound of the 95% CI of the

hazard ratio excluded 1.0 but the p value was too large (> 0.025). When both doses are considered together, time to gastrointestinal recovery, when assessed at 108 hours post-surgery, ranged from one hour longer to 17 hours shorter relative to placebo suggesting that an earlier hospital discharge would be possible for some alvimopan-treated patients. The Division concluded, and I agreed, that these results do not show substantial evidence of efficacy for either the 6 mg or the 12 mg dose of alvimopan, and that a statistically significant positive finding for the 12 mg dose in the ongoing US bowel surgery study (14CL314) would be needed for approval.

In FDA's analysis of the pelvic surgery patient subgroup, [redacted]

DGP concluded, and I agreed, that both the 6 mg and 12 mg dose of alvimopan were not effective in this patient subgroup.

At the time of the first regulatory action, a randomized, double-blind controlled study in bowel resection patients in the US was ongoing (Study 14CL314) and was expected to complete in 2006. This study compared 12 mg alvimopan to placebo using a similar composite endpoint representing recovery of upper and lower gastrointestinal tract motility. The approvable letter of July 21, 2005, stated that Study 14CL314, if positive, could serve to replicate the efficacy findings for alvimopan 12 mg in bowel resection patients that have been observed to date.

The sponsor submitted the results of Study 14CL314 in its complete response to the approvable letter on May 9, 2006. This additional study brought the number of randomized controlled studies evaluating alvimopan 12 mg versus placebo in bowel resection patients for the endpoint of time to recovery of upper (toleration of solid food) and lower (first bowel movement) gastrointestinal motility to five. The hazard ratio for the comparison of the 12 mg dose of alvimopan versus placebo on this endpoint favored alvimopan in all five studies. Time to recovery of gastrointestinal motility averaged one day shorter on alvimopan 12 mg compared to placebo treatment. In addition, alvimopan-treated patients had a reduced length of hospital stay of about one day compared to placebo-treated patients. DGP has concluded, and I agree, that these shortened recovery times would be clinically meaningful to bowel resection patients.

Safety

The alvimopan safety database that was submitted in the complete response on May 9, 2006, included a total of nine phase 2/3 post-operative ileus studies enrolling 2610 patients on alvimopan and 1365 on placebo. The median duration of alvimopan exposure in these studies was 6 days. At the time of the first regulatory action in July 2005, DGP concluded, and I agreed, that the safety profile of alvimopan 6 mg and 12 mg administered up to 7 days post-operatively was acceptable. The most common treatment-emergent side effects reported were gastrointestinal in nature, including nausea and vomiting, abdominal distention, flatulence, diarrhea, and dyspepsia. These events occurred with similar frequency in the alvimopan and placebo treatment arms. As might be expected, the frequency of postoperative ileus (reported as a non-fatal serious adverse event) was lower on alvimopan (1.2% on 6 mg, 0.8% on 12 mg) as compared to placebo treatment (4.4%). The frequency of opioid withdrawal symptoms in alvimopan-treated patients was similar to that of placebo-treated patients, although patients who had taken opioids in the two weeks prior to study enrollment were excluded.

In the nine post-operative ileus studies, myocardial infarction was reported in 20 patients (13 on alvimopan and 7 on placebo), corresponding to an event rate of 0.5% in each group. The relative risk of having a myocardial infarction on alvimopan compared to placebo treatment was 0.97 (0.39, 2.43). Infarctions typically occurred within a week of the initiation of dosing. A blinded adjudication of case narratives by a Division of Cardiology Drugs consultant confirmed that the proportion of possible or likely myocardial infarctions in the two treatment groups was similar. There were no differences in baseline cardiovascular risk factors between alvimopan- and placebo-treated patients in these studies. DGP and the Division of Cardiology Drugs have concluded, and I agree, that there does not appear to be a cardiovascular safety signal for short-term alvimopan treatment for post-operative ileus following bowel resection surgery.

On May 15, 2006, shortly after the submission of the complete response, DGP was informed about emerging cardiovascular adverse events from an ongoing study in patients with opioid-induced constipation. Study SB767905/014 is a 12-month randomized study of 805 non-cancer patients on chronic opioid therapy comparing alvimopan 0.5 mg bid to placebo treatment. In response to a DGP request, the sponsor submitted cardiovascular safety data from their planned 6-month safety interim analysis of this study. Eight serious cardiovascular events (six myocardial infarctions and one case each of congestive heart failure and unstable angina) were reported in alvimopan-treated patients. There were no serious cardiovascular events reported on placebo treatment. These events occurred within 38-111 days (mean 79 days) of alvimopan treatment in patients with $\geq$ 2 cardiac risk factors. The relative risk of having a myocardial infarction was 6.46 (0.4, 114) on alvimopan compared to placebo, and the myocardial infarction incidence rate on alvimopan in this study was 2.2/100 patient-years. Study SB767905/014 is still ongoing; an independent data monitoring committee was established to adjudicate cardiovascular adverse events and establish stopping rules for safety, as appropriate.

After it was discovered that all eight patients experiencing serious cardiovascular events in Study SB767905/014 had received alvimopan, all patients with serious cardiovascular events enrolled in opioid-induced constipation studies were unblinded. Patients enrolled in these studies were similar to those on Study SB767905/014 with regard to baseline cardiovascular risk factors. When all opioid-induced constipation studies $\geq$ 2 weeks duration were pooled (including Study SB767905/014), the incidence rate for serious cardiovascular adverse events on alvimopan was 6.27/100 patient-years vs. 4.12/100 patient-years for placebo treatment. The myocardial infarction incidence rate on alvimopan was 1.52/100 patient-years vs. 1.23/100 patient-years on placebo treatment. The sponsor contends that the myocardial infarction rates in these pooled opioid constipation studies are consistent with the expected rate of [redacted] patient-years in a US adult population on chronic opioid therapy with medium cardiovascular risk (i.e., with $\geq$ 2 cardiovascular risk factors; source IMS Lifelink Database). A detailed review by DGP revealed that there is no evidence that alvimopan increases blood pressure compared to placebo in either the post-operative ileus or opioid-induced constipation studies.

In summary, there is an as yet unexplained excess of cardiovascular events, primarily myocardial infarction, in a single study of opioid-induced constipation that enrolled chronic opioid users with medium cardiovascular risk. This study is also the single longest duration study (12 months) and is still ongoing. At this time, there is insufficient evidence in the literature to support either that opioids are cardioprotective or that opioid antagonists are cardiotoxic. Clinical experience with other approved opioid antagonists (naloxone and naltrexone) does not raise concerns about cardiovascular safety. From a pharmacokinetic standpoint, there is little accumulation of alvimopan with bid dosing, although an active degradant (ADL 08-0011) does appear to accumulate 6- to 9-fold after five days of dosing. Preclinical evaluation of alvimopan and this degradant does not raise any cardiovascular safety concerns.

The Division has concluded, and I agree, that efficacy for alvimopan 12 mg for the acceleration of recovery of upper and lower gastrointestinal tract motility following bowel resection surgery has been demonstrated. At this time, we do not believe there is a cardiovascular safety signal in post-operative ileus patients treated in the short-term with alvimopan ($\leq$ 8 days). However, an as yet unexplained excess of serious cardiovascular events in a single long-term study for a different indication has been identified. Although it is possible that this finding may have occurred purely by chance, the serious nature of the potential risk prompts our decision to wait for the completion of Study SB767905/014 to assess more fully the cardiovascular risk with longer term alvimopan exposure.

Thus, before this product may be approved for short-term use in patients following bowel resection surgery, the sponsor will need to submit the 12-month safety findings from Study SB767905/014, including detailed analyses of serious cardiovascular events, for review when they become available. The sponsor should also develop and submit a risk management plan that includes elements to a) communicate the possible cardiovascular risk of longer-term alvimopan exposure and b) minimize off-label use. This plan could include appropriate labeling for prescribers and patients, and restriction of alvimopan use to hospital settings.

With regard to the conduct of ongoing alvimopan studies, including Study SB767905/014, we find the recommendations of the sponsor's Global Safety Board, the charge of the Independent Cardiovascular Adjudication Board, and the sponsor's plans to communicate with regulatory agencies, investigators and IRBs, as outlined in the May 15, 2006 submission, to be generally acceptable. We recommend collection of blood samples to assess levels of alvimopan and of the active degradant (ADL 08-0011) in patients experiencing cardiovascular adverse events enrolled in ongoing alvimopan studies, if this is not already being done.

Tradename Review
The tradename "Entereg" is acceptable.

Labeling
Product labeling remains unresolved at this time.

Phase 4 Studies
No phase 4 studies are requested at this time.

Julie Beitz, MD
Director,
Office of Drug Evaluation III
CDER, FDA

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/s/

Julie Beitz
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DIRECTOR

MEMORANDUM

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

DATE: 10/31/2006

FROM: Ruyi He, MD
Medical Team Leader
Division of Gastroenterology Products/ODE III

SUBJECT: Medical Team Leader Review/Comments
NDA 21-775 ENTEREG (Alvimopan) complete response to approvable letter of June 21, 2005

APPLICANT: Adolor Corporation

DRUG: ENTEREG (Alvimopan), μ-opioid receptor antagonist

I. RECOMMENDATION:

I concur with Dr. Eric Brodsky's recommendation that ENTEREG (Alvimopan) be approvable for the acceleration of the time to upper and lower GI recovery following partial large or small bowel resection surgery with primary anastomosis (NDA 21-775). For approval of this application, the sponsor needs to provide final study summary of Study 014 with detail analyses of cardiovascular adverse events. A GI advisory committee meeting to discuss both safety and efficacy of alvimopan may be useful when the final results of Study 014 become available.

Study 014 is a 52-week ongoing safety trial of alvimopan in opioid-induced constipation (OIC) patients and it is the only study that has the study duration greater than 12 weeks. A planned 6-month interim analysis of Study 014 found a numerically higher incidence of serious cardiovascular events in the alvimopan treatment group, compared to the placebo group.

II. BACKGROUND:

Alvimopan, an investigational opioid-receptor antagonist (without any opioid-receptor agonist activity), is a new molecular entity that is not currently marketed in the United States or any other country.

Adolor originally submitted the NDA 21-775 on June 25, 2004 for postoperative ileus (POI). The Division took an approvable action on the NDA on July 7, 2005 because of insufficient proof of efficacy to support the POI indication for both patients with abdominal or pelvic surgery and recommended that Adolor provide at least one additional adequate and well-controlled study — in patients scheduled to have partial small or partial large bowel resection (BR) — that demonstrates statistically significant superiority and clinical meaningful results for the alvimopan group compared to the placebo group.

In this submission, Adolor submitted their complete response with the results of one additional controlled POI study in partial small and partial large BR surgery patients. Adolor changed their proposed indication from originally "to accelerate time to recovery of GI function following abdominal or pelvic surgery" to currently "to accelerate the time to upper and lower GI recovery following partial large or small bowel resection surgery with primary anastomosis".

On May 15, 2006, GlaxoSmithKline, a partner of Adolor in the development of alvimopan, informed the Division of a numerically higher incidence of serious CV events in the alvimopan treatment group, compared to the placebo group, in one of their ongoing, long-term alvimopan trials (Study 14) in opioid-induced constipation (OIC) patients. These serious CV events will be discussed in the safety section of this review.

In this review, I will focus mainly on clinical evaluations of efficacy and safety. For other information, please see the Division action package on the original NDA submission.

III. CLINICAL EVALUATION

1. Overview of Clinical Program for POI:

In this submission, the sponsor submitted the results of 49 studies (i.e., 48 completed clinical studies and the six-month interim analysis of 1 ongoing study). The entire safety database in the 49 studies consisted of 7715 of subjects/patients [of which 5185 (67.2%) and 2529 (32.8%) subjects/patients received alvimopan and placebo, respectively].

The 5 phase III clinical trials to support the efficacy of alvimopan in the treatment of POI in the BR surgery population included 1877 patients [of which 953 (50.8%) and 924 (49.2%) patients received the 12 mg alvimopan dose and placebo, respectively]. Study 314 was submitted in this second-cycle NDA.

2. Efficacy Summary

The five phase III efficacy POI trials (302, 308, 313, 001, and 314) were randomized, double-blind, placebo-controlled, parallel-group, multi-center trials in patients who were scheduled to partial large or small BR surgery with anastomosis; or total Abdominal Hysterectomy (TAH).

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

All five efficacy trials had the following design features:

- The initial dose was given preoperatively. After surgery, the study drugs were given twice a day beginning postoperative day (POD) 1 until POD 7 or until hospital discharge;
- Patients scheduled to received laparoscopic surgery or epidural anesthesia were excluded; and
- Patients who were taking chronic opioids before the surgery 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.

The primary efficacy endpoint was the time to recovery of both upper and lower GI tract motility following surgery. **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 pre-specified secondary efficacy endpoints DOW was measurement of the length of hospital stay. **DOW** was defined as the time from the end of surgery to the time that the hospital discharge order was written;

Efficacy Results

The efficacy results (**GI2**, time to recovery of the upper and lower GI tract motility) in BR surgery patients in the five POI efficacy studies are summarized in Table 1. The hazard ratios (HRs) of times 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. The change in time to achieve GI2 for the 12 mg alvimopan group, compared to the placebo group, increased from the 25^{th} to the 50^{th} to the 75^{th} percentiles in all five POI studies. The change in times to achieve GI2 at the 75^{th} 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 patients who received placebo at the 75^{th} percentile. One day earlier recovery is a clinically meaningful difference.

Table 1: Summary of Efficacy Results (GI2 in days) in BR patients in the POI studies

Study	Treatment Group	N	50th Percentile in days	Change from placebo in days	75th 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			

Table 2 displays the efficacy results of the time to achieve **DOW** in BR patients in the POI efficacy studies. The Hazard Ratios (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. 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. studies (i.e., Studies 302, 308, 313, and 314). Since there are significant differences in hospital discharge practices in Europe compared to the United States, the results of **DOW** from the European study (Study 001) is not included in this table.

Table 2: Summary of Efficacy Results (DOW in days) in BR patients in the U.S. POI studies

Study	Treatment Group	N	DOW at 50th Percentile in days	Change from placebo in days	DOW at 75th 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			

In conclusion, the clinical data from the five POI studies support the efficacy of 12 mg alvimopan treatment regimen for acceleration of the time to upper and lower GI recovery following partial large or small bowel resection surgery with primary anastomosis. For detail efficacy evaluation, please see Dr. Brodsky's review.

3. Safety Evaluation:

The entire alvimopan safety database contained the results of 49 studies (i.e., 48 completed clinical studies and the six-month interim analysis of 1 ongoing study). The entire safety database in the 49 studies consisted of 7715 of subjects/patients [of which 5185 (67.2%) and 2529 (32.8%) subjects/patients received alvimopan and placebo, respectively]. There were nine POI trials 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.

Subject disposition-overall POI population in the worldwide safety database is summarized in Table 3.

Table 3: Subject Dispositions – Overall POI Population in the Worldwide Safety Database

		Alvimopan		
	Placebo (N=1365) n (%)	**6 mg (N=898) n (%)**	**12 mg (N=1650) n (%)**	**Total[a] (N=2610) n (%)**
Randomized	1365 (100)	898 (100)	1650 (100)	2610 (100)
Treated	1365 (100)	898 (100)	1650 (100)	2610 (100)
Completed treatment	1044 (76.5)	726 (80.8)	1365 (82.7)	2140 (82.0)
Discontinued from treatment	321 (23.5)	172 (19.2)	285 (17.3)	470 (18.0)
Adverse event	152 (11.1)	69 (7.7)	126 (7.6)	202 (7.7)
Administrative	1 (0.1)	2 (0.2)	3 (0.2)	5 (0.2)
Withdrew	35 (2.6)	17 (1.9)	34 (2.1)	51 (2.0)
Protocol violation	72 (5.3)	46 (5.1)	75 (4.5)	121 (4.6)
Missing	11 (0.8)	3 (0.3)	3 (0.2)	12 (0.5)
Other	50 (3.7)	35 (3.9)	44 (2.7)	79 (3.0)
Completed study	1147 (84.0)	760 (84.6)	1439 (87.2)	2248 (86.1)
Discontinued from study	218 (16.0)	138 (15.4)	211 (12.8)	362 (13.9)
Adverse event	76 (5.6)	42 (4.7)	68 (4.1)	117 (4.5)
Administrative	3 (0.2)	1 (0.1)	0	1 (<0.1)
Withdrew	32 (2.3)	19 (2.1)	25 (1.5)	46 (1.8)
Protocol violation	80 (5.9)	54 (6.0)	79 (4.8)	136 (5.2)
Other	27 (2.0)	22 (2.4)	39 (2.4)	62 (2.4)

More subjects in the placebo group discontinued treatment due to AEs than subjects in either the alvimopan 6 mg or 12 mg groups.

Demographics in the overall POI population in the worldwide safety database are summarized in Table 4. As shown in Table 4, most subjects in the POI studies were Caucasian, <65 years of age, and female.

Table 4: Demographics - Overall POI Population in the Worldwide Safety Database

Demographic Factor Statistics	Placebo (N=1365) n (%)	Alvimopan 6 mg (N=898) n (%)	Alvimopan 12 mg (N=1650) n (%)	Alvimopan Total[a] (N=2610) 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)

Deaths

In the entire alvimopan development program there were 24 deaths. Of the 24 deaths, 22 occurred in the POI population and 2 occurred in the OIC population.

Of the 22 deaths in the POI population, 13 (13/2610, 0.5%) and 9 (9/1365, 0.66%) occurred in patients who received alvimopan and placebo, respectively. 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 are displayed Dr. Brodsky's review.

The percentage of subjects who reported SAEs was lower in the alvimopan 6 mg and alvimopan 12 mg groups compared with the placebo group (Table 5). In general, these SAEs and their frequency are consistent with that expected in subjects undergoing

surgery for the underline diseases. The numerically lower incidence of nonfatal SAE in the alvimopan groups was from a lower incidence of POI/small bowel obstruction (SBO). This lower incidence may be due to an efficacy benefit of alvimopan compared to placebo in the treatment of POI.

Table 5: All deaths and most common nonfatal SAEs in the POI population

Preferred term	Placebo N=1365 n (%)	Alvimopan		
		1 mg N=62 n (%)	6 mg N=898 n (%)	12 mg N=1650 n (%)
Total Deaths	9 (0.66)	0	5 (0.56)	8 (0.48)
All Nonfatal SAE	250 (18.3)	7 (11.3)	110 (12.2)	192 (11.6)
POI/SBO	86 (6.3)	0	18 (2.0)	32 (2.0)
Postoperative infection	19 (1.4)	0	10 (1.1)	18 (1.1)
Anastomotic leak	15 (1.1)	2 (3.2)	12 (1.3)	11 (0.7)
Pulmonary embolism	13 (1.0)	0	9 (1.0)	11 (0.7)
Wound dehiscence	6 (0.4)	1 (1.6)	3 (0.3)	15 (0.9)
Atrial fibrillation	5 (0.4)	1 (1.6)	5 (0.6)	12 (0.7)
Procedure complication	8 (0.6)	0	2 (0.2)	6 (0.4)

In summary, 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 (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 was numerically lower in the alvimopan groups, compared to the placebo group (7.9% and 11.9% of patients had discontinuations due to adverse events in the alvimopan and placebo groups, respectively). The difference in discontinuations due to adverse events was mostly due to a lower percentage of POI and vomiting reported in the alvimopan group, compared to the placebo group. Except potential higher incidence of MI in the OIC population following long-term use of Alvimopan (discussion in the next section), Alvimopan is well tolerated and safe in the POI population.

Summary of Cardiovascular Adverse Events

Short-Term POI Studies

Cardiovascular adverse events in the POI population are summarized in Table 6.

Table 6: Summary CV Adverse Events in POI Population#

Event	Alvimopan N=2610 n (%)	Placebo N=1365 n (%)	RR (95% CI)
Death (all causes)	13 (0.50)	9 (0.66)	0.76 (0.32, 1.76)
Death from CV events	5 (0.19)	2 (0.15)	1.31 (0.25, 6.73)
MI (fatal & nonfatal)*	13 (0.50)	7 (0.51)	0.97 (0.39, 2.43)
Unstable angina	0	4 (0.29)	
Nonfatal CVA**	3 (0.11)	4 (0.29)	0.39 (0.09, 1.75)
CHF (fatal & nonfatal)	19 (0.73)	17 (1.25)	0.58 (0.30, 1.12)
Serious Arrhythmia (fatal & nonfatal)	13 (0.50)	13 (0.95)	0.52 (0.24, 1.12)

#Based on the submission on October 5, 2006. *One subject in the Alvimopan group had a fatal MI.
**One additional Alvimopan 12mg subject had fatal events.

The data in Table 6 are summarized from the submission on October 5, 2006. The rates of MI (fatal and nonfatal) are similar in both groups (0.50% and 0.51% in the alvimopan and placebo groups, respectively). The proportion of patients with unstable angina, nonfatal CVA, CHF (fatal and nonfatal), serious arrhythmia (fatal and nonfatal) and death (all causes) were numerically lower in the alvimopan groups, compared to the placebo group. A total of 0.5% and 0.66% of patients died; 0% and 0.29% of patients had unstable angina; 0.73% and 1.25% of patients had CHF and 0.50% and 0.95% of patients had serious arrhythmia in the alvimopan and placebo groups, respectively.

In conclusion, the data indicate that there is no cardiovascular safety signal in POI population for Alvimopan at proposed dosage and regimen.

The long-term opioid-induced constipation (OIC) alvimopan studies (≥ 3 weeks)

On May 15, 2006, GSK (Adolor's partner for the OIC indication) informed the Division 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.

There were no differences in cardiac risk factors between the alvimopan and placebo treatment groups in Study 14. The overwhelming majority of patients who had MIs in Study 14 had typical symptoms, EKG changes, and elevated troponins. 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. Of the six MIs in Study 14, two occurred at one site in Scotland and two occurred in one site in the United States. There were no differences in the baseline CAD risk factors in patients in Study 14 compared to the patients in the other alvimopan OIC studies. Given the increased incidence of MI in the alvimopan groups in the OIC studies, an independent data monitoring committee was established to adjudicate CV cases and establish stopping rules in ongoing Study 14.

The rates of serious cardiovascular events in the alvimopan and placebo treatment groups in the controlled alvimopan trials ≥ 3 weeks duration are summarized in Table 7.

Table 7: Summary of Serious Cardiovascular Events in the Controlled Alvimopan Trials ≥ 3 Weeks Duration*

Event	Placebo N=911 % of Patients (Number of Events, Number of Patients)	Alvimopan All Doses N=2049 % of Patients (Number of Events, Number of Patients)	Relative Risk: Alvimopan/ Placebo (95% CI)	Incidence rate/100 patient-year (95% CI)
MIs	0.33% (6, 3)	0.39% (8, 8)	1.19 (0.34 – 4.01)	Placebo: 1.23 (0.25 – 3.61) Alvimopan: 1.52 (0.66 -3.00)
Unstable Angina	0	0.10% (3, 2)		
All Serious CV Events	1.10% (24, 10)	1.61% (40, 33)	1.47 (0.74 – 2.92)	Placebo: 4.12 (1.97 – 7.57) Alvimopan: 6.27 (4.32 – 8.81)

*Based on the submission on 9/28/2006 under [redacted]

Table 7 includes data from studies 007, 008, 011, 012, 013, 014 (6 month interim data only), 13C217 and 13C304.

The data above indicates a numerical increase for alvimopan treated patients compared to placebo in CV serious adverse events. With respect to the MI reports, when Study 014 interim data are taken into consideration, there is a numerical increase for alvimopan treated patients compared to placebo in the MI incidence rates expressed per 100 patient years. The apparent imbalance in reported MIs is driven by reports from Study 014 which is unprecedented and inconsistent with other studies. Four MI cases from Study 014 occurred within 12 weeks. The longest duration of exposure was 111 days and the shortest duration of exposure was 38 days (mean = 77 days). Narratives of 6 MI cases in Study 014 were summarized in Table 8. All MIs events occurred while patients on treatment and one patient died.

Table 8: Narratives of MIs Events in Study 014

Patient #	Days on Study Treatment	Narrative
759	38 days (Glasgow)	71 year old male with COPD and with stable angina and the following CV risk factors: hyperlipidemia, increased age, obesity (BMI=38.2), glucose intolerance, family history of CV disease. He received **alvimopan**. He had severe chest pain, ST depression, and positive troponin-I. Catheterization showed diffuse, triple vessel disease.
805	85 days (Glasgow)	75 year old female with OA and COPD with the following CV risk factors: HTN, smoker, obesity, hyperlipidemia received **alvimopan** and later developed chest pain, ST elevation, and positive troponin-I.
18322	65 days (Tampa, FL)	62 year old female with reflex sympathetic dystrophy and OA and peripheral vascular disease, HTN, hyperlipidemia, and smoker and received **alvimopan**. She had chest pain, q waves and ST elevations on EKG, and positive troponin. The catheterization showed critical LAD artery disease and got stented.
18321	111 days (Tampa, FL)	48 year old male with chronic back pain with history of CV disease, HTN and obesity and received **alvimopan**. He felt weak and had arm pain and developed syncope, ST segment elevation, and positive troponin. During hospitalization had AF and cardiogenic shock requiring intraaortic balloon pump (IABP) and vasopressors. Catheterization showed severe two-vessel disease and he had two stents placed.
1818	58 days	93 year old female with OA with ischemic heart disease and received **alvimopan**. She had SOB for one week and hospitalized. In hospital had cardiac arrest and intubated. ST wave elevation and positive troponin consistent with a MI. She died within 12 hours of admission.
17641	106 days	68 year old male, with chronic shoulder pain and DM, who received **alvimopan**. Had CP at rest, EKG showed inferior T wave inversions, positive troponin, and echocardiogram showed apical left ventricle hypokinesis with normal ejection fraction. Catheterization showed 5-vessel disease and he had a stent of the RCA placed and returned two weeks later for two additional stents. Patient resumed alvimopan treatment and 2 weeks later he was readmitted with CV symptoms for 3 days. The alvimopan was discontinued during the hospitalization. He was discharged from the hospital. Short after discharge, on the same day, he had more symptoms and was readmitted and had an angioplasty.

Other 2 CV events in Study 014 were 1 CHF and 1 unstable angina. Narratives are summarized as follow:

Patient 807 was a 75 year old female with osteoarthritis (OA) with a history of AF, CHF, hypertension (HTN), transient ischemic attack (TIA), hyperlipidemia, obesity, smoker, and aortic valve regurgitation. She received alvimopan for 85 days. She had SOB and edema and was hospitalized. Troponin positive (0.08) and echo showed severe mitral regurgitation (MR), moderate to severe tricuspid regurgitation (TR) and severe hypokinesis of the left ventricle.

Patient 3202 was a 47 year old female with history of cerebral vascular accident (CVA) CV disease (coronary stent placed), HTN, hyperlipidemia and received alvimopan for 83 days. Developed unstable angina and was hospitalized.

Study 014 is the only study with the duration more than 12 weeks (52 weeks) and is ongoing currently.

Based on the results from this 6-month interim safety analysis, 8 patients (1.5%) had severe cardiovascular events in the alvimopan treated group, compared to none event in the placebo group. The result indicated that there is a potential increase in the incidence of MI or cardiovascular adverse events patients treated by alvimopan compared to placebo in the long-term opioid-induced constipation alvimopan.

In the OIC population (i.e., Studies 217, 304, 11, 12, 13, and 14), there were two deaths and both patients received alvimopan.

The first patient was a 64 year old female (with a history of COPD, asthma, chronic bronchitis, CAD, HTN, GERD and history of cancer with right lung lobectomy) with chronic pain on methadone. She received alvimopan 0.5 mg/day and on Study Day 9 was diagnosed and treated with an outpatient pneumonia and COPD exacerbation. She did not take the study drug on Days 11, 13-18, and 20. She stopped the study medication on Day 21. She was started on fluconazole for a "fungal lung infection". On Study Day 32 she was admitted to a hospital with SOB, upper abdominal pain, nausea, vomiting, and diarrhea. She was found to have an acute respiratory acidosis and hypoxia. Later on Day 32, she developed asystole thought secondary to respiratory failure.

The second patient was listed under study 014. She was a 93 year old female with OA with ischemic heart disease and received alvimopan. She had SOB for one week and hospitalized. In hospital she had cardiac arrest and intubated and EKG showed ST wave elevation and positive troponin consistent with a MI. She died within 12 hours of admission.

Although the death of the first patient was unlikely related to alvimopan, it can not rule out that the death in the second patient in Study 014 (i.e., acute MI) was possibly related to alvimopan. However, other factors (e.g., she had ischemic heart disease and she was 93 years old) may be the only reason for her death.

VI. CONCLUSIONS

In conclusion, the clinical data from the POI studies support the efficacy of 12 mg alvimopan treatment regimen for acceleration of the time to upper and lower GI recovery following partial large or small bowel resection surgery with primary anastomosis. Alvimopan is well tolerated and safe in the POI population and the data indicated that there is no cardiovascular safety signal in POI population for Alvimopan at proposed dosage and regimen. The data from long term OIC studies indicated a numerical increase for alvimopan treated patients compared to placebo in CV serious adverse events. With respect to the MI reports, when Study 014 interim data are taken into consideration, there is a numerical increase for alvimopan treated patients compared to placebo in the MI incidence rates expressed per 100 patient years. The apparent imbalance in reported MIs is driven by reports from Study 014 which is the only study with the duration greater than 12 weeks (52 weeks) and is ongoing currently.

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/s/

Ruyi He
10/31/2006 12:40:19 PM
MEDICAL OFFICER

SECOND-CYCLE ENTEREG® CLINICAL REVIEW

Application Type	NDA (second-cycle)
Submission Number	21-775
Submission Code	000
Letter Date	5/9/06
Stamp Date	5/9/06
PDUFA Goal Date	11/9/06
Reviewer Name	Eric Brodsky, M.D.
Review Completion Date	10/30/06
Established Name	Alvimopan
(Proposed) Trade Name	ENTEREG®
Therapeutic Class	μ-opioid receptor antagonist
Applicant	Adolor Corporation
Priority Designation	Second-cycle submission
Formulation	Oral capsule
Proposed Dosing Regimen	Initial dose: One 12 mg alvimopan capsule 0.5 to 5 hours prior to the scheduled start of the surgery on postoperative day (POD) 0. Subsequent doses: One 12 mg alvimopan capsule BID for a maximum of 7 days while the patient is hospitalized or until hospital discharge (whichever is earlier).
Proposed Indication	"To accelerate the time to upper and lower GI recovery following partial large or small bowel resection surgery with primary anastomosis".
Intended Population	Patients undergoing partial small or large bowel resection surgery with primary anastomosis

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This medical officer recommends an **approvable** action for the 12 mg dose of ENTEREG® (alvimopan) Capsules to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis. To obtain approval of the 12 mg dose of alvimopan for this post-operative ileus (POI) indication, the sponsor must provide the results of their one-year, ongoing, alvimopan phase 3 trial in opioid-induced constipation patients [i.e., SB-767905/014 (Study 14)] including detailed analyses of myocardial infarction, unstable angina, and other serious cardiovascular events.

This medical officer concludes that efficacy of alvimopan for the POI indication was demonstrated and there was no evidence of a significant safety signal — including a cardiovascular (CV) signal — with short-term alvimopan use (i.e., $\leq$ 7.5 days) in a large safety database.

However, there may be CV toxicity associated with the long-term use of alvimopan. Thus, this medical officer recommends submission of CV data from ongoing Study 14 prior to approval of alvimopan for the short-term POI indication for adequate labeling (e.g., CV WARNINGS) and to determine if a risk management plan is necessary.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Risk management activities are not indicated.

1.2.2 Required Phase 4 Commitments

Phase 4 commitments are not indicated.

1.2.3 Other Phase 4 Requests

Other phase 4 requests are not indicated.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Adolor Corporation (Adolor) submitted this **second-cycle new drug application** (NDA 21-775) on May 9, 2006 to support the approval of oral ENTEREG® (alvimopan) Capsules, an opioid-receptor antagonist (without opioid-receptor agonist activity), in the treatment of POI. POI is a disorder characterized by temporary impairment of gastrointestinal (GI) tract motility — without complete blockage of the GI tract — following surgery. In this second-cycle new drug application (NDA), Adolor requested the following POI indication: alvimopan is indicated "to accelerate the time to upper and lower GI recovery following partial large or small bowel resection surgery with primary anastomosis".

Adolor originally submitted this NDA on June 25, 2004 for the treatment of POI. The Division of Gastroenterology Products (DGP) took an approvable action on this NDA on July 7, 2005 because of "insufficient proof of efficacy" to support the POI indication and recommended that Adolor 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 and clinical meaningful results for the alvimopan group compared to the placebo group.

To satisfy the deficiencies in their original submission, Adolor submitted this second-cycle NDA submission containing the results of one additional adequate and well controlled POI study in partial small and partial large bowel resection surgery patients (i.e., Study 314).

In this second-cycle NDA submission, Adolor submitted the results of **49 studies** (i.e., **48 completed clinical studies** and the six-month interim analysis of **1 ongoing study**). The entire safety database in the 49 studies consisted of 7715 of subjects/patients [of which 5185 (67.2%) and 2529 (32.8%) subjects/patients received alvimopan and placebo, respectively].

The most important 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]:

- One trial (i.e., Study 314) was submitted in this second-cycle NDA; and
- Four trials (i.e., Studies 302, 308, 313, and 001) were submitted in the first-cycle NDA.

The most important 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 constipation (OIC) trials** (i.e., $\geq$ 3 weeks) in noncancer 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 302, 308, 313, 001, and 314);
- One phase 3 trial with primary safety endpoints (i.e., Study 306); and
- Three efficacy/safety phase 2 trials (i.e., Studies 206, 214, and 213).

The six OIC trials included:

- Three 3-6 week studies [i.e., (13C217, 13C304, and SB-767905/011 (Study 11)]
- Study summaries of two recently completed 12-week studies [i.e., SB-767905/012 (Study 12) and SB-767905/013 (Study 13)]; and
- Six-month interim analysis of one, ongoing, one-year study [i.e., SB-767905/014 (Study 14).

On May 15, 2006, GlaxoSmithKline (GSK), a partner of Adolor in the development of alvimopan, informed the DGP of a numerically higher incidence of serious CV events in the alvimopan treatment group, compared to the placebo group, in one of their ongoing, long-term, OIC trials (Study 14). In response to a DGP request, GSK submitted CV safety data from their planned 6-month safety interim analysis of ongoing Study 14.

1.3.2 Efficacy

The five most important 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 important 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 this 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)]; 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 most important pre-specified, secondary efficacy endpoints in the five important efficacy studies were 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.

This medical officer believes that the primary efficacy endpoints were adequate because they evaluated the recovery of both upper and lower GI track motility following surgery. However, this medical officer believes that **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, this medical officer believes that **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

Table I delineates the efficacy results of **GI2** (i.e., time to recovery of upper and lower GI tract motility) 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. This medical officer believes that 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. 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 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 I: GI2 in days in BR patients in the POI studies

Study	Treatment Group	N	Median Time	Difference in Medians	75th Percentile	Difference in 75th Percentile	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			

1 The 6 mg alvimopan dose is not shown in Studies 302, 308, 313, and 001 because the sponsor proposes only the 12 mg alvimopan dose.
2 N is the number of BR patients in the efficacy database; 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. The p-values of the results of Studies 302, 308, 313, and 001 are not bolded because **GI2** was not the primary efficacy endpoint and multiplicity adjustments were not made for the multiple alvimopan doses.
Reference: Please see Table 19 in this review for complete references.

Table II 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, this medical officer did not include the results of **DOW** from the one European POI efficacy/safety trial (i.e., Study 001) in Table II. 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 II: DOW in days in BR patients in the four U.S. POI trials

Study	Treatment Group	N	50th Percentile in days	Change from placebo in days	75th 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			

1 Since there are significant differences in hospital discharge practices in Europe, compared to the United States, the results of **DOW** from the European study (i.e., Study 001) are not included.
2 The 6 mg alvimopan dose is not shown in Studies 302, 308, 313, and 001.
3 N is the number of BR patients in the efficacy database; the TAH patients were not included.
Reference: Please see Table 21 in this review for complete references.

This medical officer believes that efficacy of the 12 mg alvimopan dose in the treatment of POI — in BR surgery patients — was established because the 12 mg alvimopan dose, compared to placebo, 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.

Thus, alvimopan has achieved one of the efficacy requirements that the DGP stated at a sponsor/DGP October 2000 end of phase 1 meeting: "A clinically meaningful difference in recovery time will be one that is on the order of a day or so, not just a few hours". 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).

In summary, the clinical data from the five important adequate and well-controlled POI trials **established the efficacy** of the sponsor's proposed 12 mg alvimopan treatment regimen for the sponsor's proposed POI indication: "acceleration of the time to upper and lower GI recovery following partial large or small bowel resection surgery with primary anastomosis". In addition, this medical officer believes that use of the 12 mg of alvimopan regimen in BR surgery patients in the treatment of POI represents effective treatment of a serious aspect (prolonged hospitalization) of a serious disease (POI) that has no currently approved products.

1.3.3 Safety

The entire alvimopan safety database included the results of **49 studies** (i.e., **48 completed clinical studies** and the six-month interim analysis of **1 ongoing study**). The entire safety database in the 49 studies consisted of 7715 of subjects/patients [of which 5185 (67.2%) and 2529 (32.8%) subjects/patients received alvimopan and placebo, respectively].

The most important 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] and **six longer-term OIC trials** in noncancer patients (i.e., Studies 13C217, 13C304, 11, 12, 13, and 14) with 2518 patients [of which 1728 (68.6%) and 790 (31.4%) 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, the percentages of deaths [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 was numerically lower in the alvimopan groups compared to the placebo group (i.e., 7.9% and 11.9% of patients had discontinuations due to adverse events in the alvimopan and placebo groups, respectively). The difference in discontinuations due to adverse events was mostly due to a lower percentage of POI and vomiting adverse events in the alvimopan group compared to placebo.

After the sponsor informed the DGP of a numerically higher incidence of serious CV events in the alvimopan treatment group, compared to the placebo group, in one of their ongoing, long-term trials in OIC patients (Study 14); an extensive CV evaluation of the POI database was performed. This medical officer believes there was **no evidence of a CV alvimopan-associated signal in the short-term POI studies** because of the following:

- According to the investigator CV AE reports, there is no overall CV signal for all cause death, CHF, nonfatal CVA, nonfatal MI, serious arrhythmia, and unstable angina (i.e., there is no difference in these six combined events between the alvimopan and placebo groups). In the alvimopan groups, there were 89 of these selected CV events out of 2610

(3.4%) patients; and in the placebo group, there were 69 of these selected CV events out of 1365 (5.1%) patients. The relative risk (95% confidence intervals) of these CV events was 0.66 (0.48, 0.93);

- Unblinded adjudication of MIs by this medical officer and Dr. Nhi Beasley, a medical officer in the Division of Cardiovascular and Renal Products, demonstrated that the proportion of treatment-related MIs in the alvimopan and placebo groups were similar. Treatment-related MIs were MIs that had a reasonable temporal relationship between the drug administration and the MI. In the alvimopan groups, there were 7 treatment-related MIs out of 2610 (0.3%) patients and in the placebo groups there were 3 MIs out of 1365 (0.2%) patients. The relative risk (95% confidence intervals) of these unblinded adjudicated MIs was 1.22 (0.28 ,7.33);
- Blinded adjudication by Dr. Karen Hicks, a cardiologist in the Division of Cardiovascular and Renal Products, found that the proportion of possible or likely MIs in the two treatment groups were similar; and
- The POI safety database (i.e., 3975 patients in which 2610 and 1365 received alvimopan and placebo, respectively) was large and the safety surveillance was reasonable to detect serious MIs.

However, in the six-month interim safety analysis of Study 14, the alvimopan group, compared to placebo, had a greater incidence of MI according to the sponsor's non-adjudicated reports and this medical officer's unblinded adjudication. In the alvimopan group, 6 patients had a MI out of 538 (1.1%) patients; whereas, in the placebo group, no patients had a MI out of 267 patients (according to this medical officer's unblinded adjudication). Since there was about a 2:1 ratio of alvimopan patients to placebo patients in Study 14, the effective MI ratio was 3 to 0 (according to this medical officer's unblinded adjudication). Therefore, this medical officer **cannot rule out long-term CV toxicity after prolonged exposure to alvimopan**. Given this uncertainty, this medical officer recommends a full assessment of the long-term CV risk of alvimopan (i.e., submission of the complete results of ongoing Study 14).

1.3.4 Dosing Regimen and Administration

If no there is no CV toxicity associated with long-term alvimopan use or the CV toxicity of long-term use can be minimized with CV WARNINGS and/or a risk management plan, this medical officer will recommend the following 12 mg of alvimopan dose regimen in the treatment of POI in partial small BR and partial large BR adult surgery patients:

- 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; then
- Following surgery, 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 hospital discharge (whichever is earlier).

1.3.5 Drug-Drug Interactions

There are no important drug-drug interactions.

1.3.6 Special Populations

There are no special alvimopan dosing considerations for age, gender, and race.

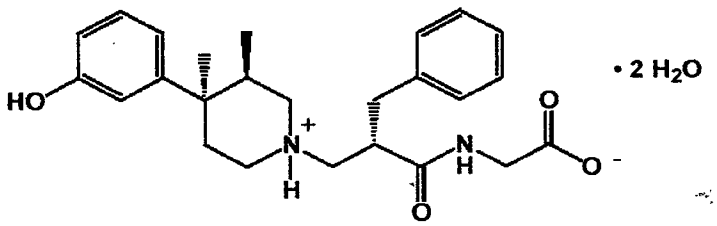
There are no special alvimopan dosing considerations for patients with mild to moderate hepatic insufficiency. However, one out of the three patients with severe hepatic insufficiency who received alvimopan had alvimopan levels ten times higher than patients with no hepatic disease.

Although there were no studies in patients with severe renal insufficiency or patients on dialysis, there are no special alvimopan dosing considerations for patients with mild to severe renal insufficiency.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

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



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

Original Proposed Indication in the Original NDA Submission: To accelerate time to recovery of GI function following abdominal or pelvic surgery.

Proposed Age Group: Adults

Pharmacologic Class: μ-opioid receptor antagonist

Route of Administration, Description, and Formulation: Oral hard gelatin capsules that are blue [redacted]

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: $C_{25}H_{32}N_2O_4 \cdot 2H_2O$

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

2.2 Currently Available Treatment for Indications

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®).

2.3 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.

2.4 Important Issues With Pharmacologically Related Products

Three opioid antagonists [naloxone hydrochloride (Narcan®), naltrexone hydrochloride (ReVia®, Depade®), and nalmefene hydrochloride (Revex®)] are approved in the United States (see Table 1). Methylnaltrexone (N-methylnaltrexone bromide, MNTX), an opioid antagonist, is being developed (in phase 3 trials) for the treatment of opioid-induced constipation (OIC) in patients with advanced medical illness (see Table 1).

There have not been recent labeling changes or recent safety and/or effectiveness concerns regarding these opioid antagonists. These opioid antagonists are not addictive and do not have abuse potential.

Table 1: Approved opioid antagonists and investigational opioid antagonists in phase 3 of development

	[redacted]	[redacted]	[redacted]	[redacted]
Naloxone hydrochloride (Narcan®)	NDA 16-636	1971	IV, IM, SC	1) Complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids opiate agonist-induced respiratory depression 2) Diagnosis of suspected or known acute opioid overdosage
Naltrexone hydrochloride (ReVia®, Depade®)	NDA 18-932	1984	PO	1) Adjuvant treatment of opiate agonist dependence 2) Adjuvant treatment of alcoholism
Nalmefene hydrochloride (Revex®)	NDA 20-459	1995	IV, IM, SC	1) Complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids 2) Management of known or suspected opioid overdose
Alvimopan (ENTEREG®)	NDA 21-775	Not approved	PO	1) To accelerate the time to upper and lower GI recovery following partial large or small BR surgery with primary anastomosis 2) The treatment of OIC in patients taking opioids for pain
Methylnaltrexone (N-methylnaltrexone bromide, MNTX)	INDs 64,583 & 67,452	Not approved	SC, IV	[redacted] 2) The treatment of OIC in patients taking chronic opioid therapy for pain

1 ROA = routes of administration (SC=subcutaneously; IM=intramuscularly, IV=intravenously, and PO=orally)
2 Alvimopan and methylnaltrexone are investigational drugs and these are there proposed indications
Reference: Adapted from the current drug product labels

2.5 Presubmission Regulatory Activity

Alvimopan is not approved in the United States (or any other country). The highlights of the regulatory activity in the United States include the following:

- In November 1993, Eli Lilly and Company established an IND [redacted] for LY246736 Dihydrate, a μ-opioid receptor antagonist, for the [redacted]
- In February 1997, Eli Lilly and Company transferred [redacted] to Roberts Pharmaceutical Corporation (Roberts);
- In June 1998, Roberts licensed [redacted] to Adolor Corporation (Adolor) and subsequently transferred all rights to [redacted] to Adolor;
- In August 1998, Adolor submitted IND# 56,553 for LY246736 Dihydrate, which was renamed to ADL 8-2698, for the [redacted]
- In December 1999, Roberts withdrew [redacted] for "administrative reasons"; and
- In October 2000, the Division of Gastroenterology Products (formerly known as the Division of GI and Coagulation Drug Products) and Adolor met to discuss proposed phase

2 and phase 3 studies for the treatment of POI with ADL 8-2698 (under IND# 56,553). During this meeting the Division of Gastroenterology Products (DGP) stated the following:

- Rapid recovery from POI needs to be clinically meaningful and defined prospectively and a "clinically meaningful difference in recovery time will be one that is on the order of a day or so, not just a few hours";
- The "primary endpoint should be assessed as success vs. failure. Effectiveness should be measured by comparing proportions of patients who experience success among treated vs. placebo patients";
- The DGP and Adolor agreed that the primary efficacy endpoint should be a composite variable assessing the recovery of upper (gastric) and lower (colonic) GI motility;
- The DGP and Adolor agreed that appropriate secondary endpoints include the following: the severity of GI symptoms (including nausea, vomiting, abdominal bloating/distention), daily pain, time until hospital discharge, time to achieve adequate oral hydration, and need for reinsertion of nasogastric tube; and
- Approximately 1000 patients exposed to ADL 8-2698 would probably a reasonable safety database for the short-term indication of treatment of POI.

➢ In March 2001, the DGP and Adolor met for an end-of-phase 2 meeting for the treatment of POI with ADL 8-2698 (under IND# 56,553). During this meeting, the DGP and Adolor "agreed that the achievement of both time to recovery of upper GI function and time to recovery of lower GI function are necessary to demonstrate efficacy"; and
➢ In March 2002, the DGP and Adolor met to discuss Adolor's revised clinical development plans for ADL 8-2698 (renamed alvimopan). During this meeting, the following occurred:

- Adolor agreed with the DGP to conduct an additional single dose, phase 1 bioavailability study of alvimopan;
- Adolor stated that they uncovered an active metabolite of alvimopan;
- The DGP stated that Adolor needed to provide the following biopharmaceutical data to support a future NDA: plasma protein binding, pharmacological activity of the major metabolite, absolute bioavailability, dose proportionality, food effect, and a severe hepatic impairment subgroup; and
- Adolor agreed to perform an additional phase 1 study of 12 mg of alvimopan in Crohn's disease patients to assess bioavailability in this population.

➢ In February 2004, the DGP granted the alvimopan development program (for the treatment of POI) **fast tract status** because POI "is a serious condition for which no drugs have been approved" and alvimopan "appears to be a safe and effective treatment for this medical need";
➢ In February 2004, the DGP and Adolor met for a pre-NDA meeting. During this meeting, the DGP stated the following:

- Given the "highly variable data on PK in patients with severe hepatic impairment, the label may contraindicate the use of alvimopan in this group of patients;

- The thorough QT/QTc study can be submitted in the 120-day safety update;
- The clinical and non-clinical data appeared sufficient to support submission of an NDA for alvimopan for the treatment of POI;
- Pediatric trials will be deferred until a regulatory decision on the NDA has been made; and
- "Carcinogenicity studies are not needed for" the short-term POI indication.

➢ In May 2004, the DGP accepted Adolor's proposed plan for the "**Pilot 1 Continuous Marketing Application** Reviewable Units for Fast Track Products". Adolor agreed to submit the non-clinical pharmacology and toxicology unit on May 5, 2004; the chemistry, manufacturing, and controls unit on May 30, 2004; and the complete NDA on June 30, 2004.

2.6 Other Relevant Background Information

Regulatory History during the First-Cycle NDA Review
During the first cycle NDA review process (i.e., June 25, 2004 to July 25, 2005) the DGP met with Adolor two times (i.e., November 2004 and March 2005).

➢ In November 2004, the DGP and Adolor met to discuss several issues during the NDA review. The DGP explained to the sponsor the DGP's rationale for denying alvimopan a priority review. The DGP stated the need for an Advisory Committee Meeting to evaluate the efficacy of alvimopan in the treatment of POI. The DGP stated that there were two main reasons to seek recommendations from an Advisory Committee Meeting: 1) the FDA never approved a drug product in this new indication and 2) the equivocal nature of the efficacy results. The DGP confirmed that a general surgeon and a gynecologic surgeon will be on the Advisory Committee. Additionally, The DGP asked the sponsor to clarify several design features in the important trials. Adolor explained that Study 306 was a primary safety study (with primary safety endpoints and secondary efficacy endpoints).
➢ 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 (GI^3) 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;"
- An Advisory Committee Meeting will not be necessary at this time;
- 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.

➢ In the March 2005 meeting between the DGP and Adolor, Adolor asked the following:

- [redacted]

- [redacted]

➢ On April 8, 2005, Adolor submitted the final study report for Study 001.

Approvable Action of the First-Cycle NDA
On July 7, 2005, Dr. Julie Beitz (the acting office director for the Office of Drug Evaluation III) took an approvable action on the ENTEREG NDA for POI. In the approvable letter to Adolor, Dr. Beitz, stated the following:

"Before the NDA is approved, it will be necessary for you to resolve the following: (There is) Insufficient proof of efficacy to support your proposed indication of acceleration of time to recovery of gastrointestinal function following bowel resection surgery. In Study 14CL302, the 6 mg alvimopan dose, but not the 12 mg dose, was statistically superior to placebo treatment in time to recovery of gastrointestinal motility as measured by GI3. In contrast, the 12 mg alvimopan dose in Study 14CL313 was statistically superior to placebo treatment while the 6 mg dose was not. Two additional studies (14CL308 and SB767905/001) failed to show statistical superiority for either dose compared to placebo treatment. When both doses are considered together, time to gastrointestinal recovery when assessed at 108 hours post-surgery ranged from one hour longer to 17 hours shorter relative to placebo treatment. The following are our recommendations for resolution of your above cited deficiency:

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. Your 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 your 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.

Product labeling remains unresolved at this time. Please include revised draft product labeling with submission of your NDA amendment."

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."
- "A conclusion of efficacy for your primary endpoint (time to GI recovery) will be based on the results of the hazard ratio analysis. Then, as supportive evidence, clinically meaningful differences can be considered. It is inappropriate to use the estimate of mean time -to-event to describe the magnitude of treatment effect because the mean is biased in the presence of censoring and the inherent skewness of time -to-event data. For descriptive purposes, magnitude of the treatment effect is best described using the median. For characterization of the treatment effect over time it is best to present both the hazard ratio and the survival curves. While the mean may better summarize the length of time to recovery in this data set, the application of this method is data-driven. The Draft Guidance for Industry: Clinical Studies Section of Labeling for Prescription Drugs and Biologics – Content and Format, Section III.D.3., states that, "When time–to-event endpoints (e.g., mortality) are used, median or mean survival alone is not usually an adequate descriptor. Survival curves (or event-free survival curves) and hazard ratios are often effective ways to display such data."
- The following clinical endpoints have utility and may provide valuable information when appropriately defined: Postoperative NG tube reinsertion, prolonged hospital admission for complications of POI, re-admission for complications of POI, and clearly defined prolonged POI/EPSBO, as well as responder analyses of GI recovery (e.g., GI2 or GI3), DOW, and Ready. Several cut-off points (e.g. by post-surgical day) can be used for the responder analyses. The protocol for Study 314 did not define the duration of a "prolonged hospital stay", "prolonged POI", "EBSBO", and the timeframe for readmission to the hospital.
- We expect the label to comment on the results from the gynecologic subpopulation from Studies 302, 306, 308, 313, and 001.
- Your proposed indication (to accelerate time to recovery of GI function following BR surgery) does not match your study BR population in your three completed phase 2 trials and your four completed phase 3 efficacy trials. An alternative indication is the following: Alvimopan is indicated "to accelerate the time to recovery of upper and lower GI tract motility following partial large or small BR surgery with primary anastomosis."

During the September 7, 2005 post-action meeting, Adolor gave a slide presentation regarding their proposals to characterize the clinical benefit of alvimopan. Adolor presented:

- Pooled analyses of the BR surgery population in Studies 302, 308, and 313 (analyses of Study 001 were not included); and
- Pooled analyses of the time to GI2 endpoint (a secondary endpoint for Studies 308 and 313; but a post-hoc endpoint for Study 302).

In their September 7, 2005 post-action meeting presentation, Adolor proposed the following:

- Introduction of a new postoperative morbidity (POM) endpoint. Patients with POM would have one of the following two events during the trial: 1) postoperative NGT insertion [any postoperative insertion of an NGT for an intervention for an acute event (e.g., nausea, vomiting, abdominal bloating, and abdominal distension)] and 2) prolonged stay or readmission (within 30 days of initial discharge) for complications of POI and/or EPSBO (e.g., POI, paralytic ileus, adynamic ileus, EPSBO, and nausea, vomiting, abdominal bloating, abdominal distension, and constipation) based on SAEs collected.
- Describe the differences in the treatment groups (alvimopan and placebo) using quartile analyses; and
- Have three main measures of efficacy: acceleration of GI recovery (i.e., GI2), shortened hospital stay (i.e., DOW), and POM;

In an October 6, 2005 letter to Adolor, in response to Adolor's proposals, the DGP stated the following:

- Your phase 3 BR surgery studies (Studies 302, 308, 313, and 001) are complete and are unblinded; therefore, we consider your proposed POM endpoint to be a post-hoc analysis in these studies;
- For Study 314, your proposed POM endpoint needs to be assessed with the protocol defined primary and the secondary endpoints; and
- Consider performing responder analyses of important clinical endpoints (e.g., DOW and Ready).

Regulatory History of the Second-Cycle NDA Review

On May 15, 2006, about one week after their second-cycle NDA submission for POI, GlaxoSmithKline (GSK) — Adolor's partner for the OIC 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 OIC studies;
6) In their original submission, GSK found that in the phase 2 and phase 3 pooled OIC 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 OIC studies, an independent data monitoring committee was established to adjudicate CV cases and establish stopping rules in ongoing Study 14.

On September 29, 2006, this medical officer presented the following topic at an Internal Regulatory Briefing: "ENTEREG® (Alvimopan), an Investigational Opioid Antagonist, for the Treatment of Post-Operative Ileus (POI) with Possible Long Term, Serious Cardiovascular Events". No consensus was reached at this regulatory briefing. Some members of the committee recommended approval of alvimopan with CV WARNINGS. Other members recommended an approvable action because Study 14 (i.e., the ongoing, one-year OIC study) was not complete (only the planned six-month interim analysis was submitted) and they expressed concern that a larger MI signal may emerge after completion of the one-year study. Additionally, some members stated that alvimopan could not be appropriately labeled without full assessment of the long-term use MI signal and they recommended an approvable action until submission of the complete results from Study 14.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

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 (please see his April 26, 2005 review for more details).

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 the following labeling changes: "The applicant should delete the words [redacted] and add "inactive ingredient" in front of polyethylene glycol in the labeling description section. The established name (alvimopan) and dosage form should be displayed in the same line instead of displayed in separate lines (please see her October 18, 2006 review for more details).

3.2 Animal Pharmacology/Toxicology

According to Dr. Tamal Chakraborti, the pharmacology/toxicology reviewer, based on the pharmacology/toxicology perspective "this NDA may be approved." Dr. Chakraborti did not recommend additional phase 4 commitments (please see his November 4, 2004 review for more details).

According to Dr. Chakraborti, alvimopan "exhibited no significant target organs of toxicity when administered at sufficiently high oral doses up to 13 weeks in mice and up to 6 months in rats and dogs." "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 (24 mg/day or 17.8 mg/m^2), respectively, based on body surface area. Alvimopan and its active metabolite ADL 08-0011 did not show any potential for genotoxicity. In fertility and reproductive performance study in rats, alvimopan did not cause any adverse effect. It was not teratogenic in rats or rabbits."

The *in vitro* assays for cardiovascular effects including the effect of alvimopan and its metabolite (ADL 08-0011) on cloned hERG channels expressed in mammalian cells and isolated dog Purkinje fibers were completely negative for any significant cardiovascular (CV) pharmacologic effect. According to Dr. Chakraborti, alvimopan did not have any significant CV toxicity in the animal studies including studies on conscious dogs and anesthetized dogs.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Six randomized, double-blind, placebo-controlled, parallel-group, multi-center phase 3 trials and three phase 2 trials of alvimopan in the treatment of POI were evaluated by this medical officer during this review. The six phase 3 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). In this review, the six phase 3 trials — Studies 14CL302, 14CL308, 14CL313, 14CL314, 14CL306, and SB-767905/001 will be identified as Studies 302, 308, 313, 314, 306 and 001, respectively. Of these six phase 3 studies, five studies (Studies 302, 308, 313, 306, and 001) were originally submitted during the first-cycle NDA submission and one study (Study 314) was submitted in this second-cycle NDA.

All of the study reports were submitted electronically.

Since this investigational product is not marketed anywhere in the world, foreign post-marketing reports are not part of the sources of information for this review.

4.2 Tables of Clinical Studies

The most important POI trials for this review include **five** POI phase 3 trials of BR surgery patients [**one** U.S. safety/efficacy trial submitted to this second-cycle NDA (314), **three** U.S. safety/efficacy trials originally submitted to the first-cycle NDA (302, 308, and 313), and **one** European trial safety/efficacy trial originally submitted to the first-cycle NDA (001)]. Please see Table 5 for a tabular listing of these important trials.

Forty-nine alvimopan clinical studies (**10 bolded studies submitted in this second-cycle,** 36 studies submitted in the first-cycle, 2 studies completed during the second-cycle NDA review period, and 1 ongoing study with six-month interim safety data) are listed in the following tables:

1) Table 2 lists the 9 single-dose studies in healthy subjects (14C114, 14CL115, RC99-CP006, 13C111, 14CL124, 14CL127, **14CL130**, **SB-767905/019**, and **17CL133**);
2) Table 3 lists the 11 multiple-dose studies in healthy subjects (H3G-LC-BGGA, 14CL118, 14CL119, RC99-CP007, 13C109, RC98-CP001, H3G-LC-BGGC and SB-767905/016, **14CL128**, **14CL201**, and **SB-767905/018**);
3) Table 4 lists the 5 studies in special populations (14CL116, 14CL117, 14CL123, 14CL125, 14CL126);
4) Table 5 lists the 9 POI studies in surgery patients in Europe and the United States (13C206, 13C213, 13C214, 302 , 306, 308, 313, 001, and **314**)
5) Table 6 lists the 8 OIC studies in chronic (non-cancer) pain patients (RC99-CT001, RC99-CT002, 13C210, 13C208, 13C209, 13C217, 13C304, and **SB-767905/011**);
6) Table 7 lists the 2 OIC studies in chronic cancer pain patients (13CL223 and 13CL224);

7) Table 8 lists the 2 idiopathic chronic constipation studies (**SB-767905/004** and **SB-767905/007**); and
8) Table 9 lists the 2 OIC studies in chronic (non-cancer) pain patients that were completed during the second-cycle NDA review period [SB-767905/012 (Study 12) and SB-767905/013 (Study 13),] and the 1 one-year OIC study in chronic, non-cancer pain patients that is ongoing [SB-767905/014 (Study 14)].

In addition, Table 9 shows two additional ongoing alvimopan OIC trials in chronic cancer pain patients (SB-767905/008 and SB-767905/ABD101684).

Table 2: Completed single-dose alvimopan studies in healthy subjects

STUDY	TITLE	OBJECTIVE	N	TREATMENT GROUPS	DAYS
1) 14C114	A single center, open-label study to evaluate the absorption, metabolism, and excretion following oral administration of [^{14}C] alvimopan in normal healthy male subjects	To evaluate absorption, metabolism, and excretion following oral dose of radio-labeled alvimopan	6	Alvimopan 12 mg	1
2) 14CL115	A phase I, single-blind, PC study of the temporal safety and tolerability of alvimopan on opioid withdrawal in normal healthy volunteers	Temporal safety and tolerability of alvimopan on opioid withdrawal in subjects taking MS Contin for 7 or 10 days	18	Placebo Alvimopan 12 mg	1
3) RC99-CP006 (CP006)	A phase I study assessing use of a peripherally selective μ opioid antagonist to prevent opioid-induced delayed GI transit in normal subjects	Determine if alvimopan would prevent delay of GI transit that occurred with administration of therapeutic dose of morphine sulfate	6 14	Phase 1: Alvimopan 2 mg Phase 2: (crossover) Placebo and Alvimopan 2 mg	1 in each period
4) 13C111	A phase I, R, DB, PC, crossover, dose-ranging, MC study to assess the use of alvimopan in reducing the frequency and severity of opioid-induced nausea in subjects with a prior history of opioid-induced nausea	Effect of alvimopan on morphine induced nausea in subjects with confirmed history of opioid induced nausea	42	(Crossover) Alvimopan 1 mg Alvimopan 3 mg Alvimopan 9 mg	1 in each period
5)14CL124	Pharmacokinetics of alvimopan and its metabolite (ADL 08-0011) in the fed and fasted states	PK of alvimopan 12 mg and its metabolite in the fed and fasted states	24	Alvimopan 12 mg	1 in each period
6) 14CL127	A study of the bioavailability of alvimopan from oral capsule relative to that from oral solution and the absolute bioavailability of alvimopan in normal healthy volunteers	Bioavailability of alvimopan 12 mg from oral capsules (2 x 6 mg) relative to that from an oral solution (12 mg total) and an IV formulation (12 mg total) in normal healthy volunteers	36	Crossover of 12 mg of Alvimopan Oral capsule Oral solution IV	1 in each period
7) 14CL130	Phase 1, open-label, single dose, 2-sequence crossover bioequivalence study of capsule strength	Bioequivalence study of the 6 mg alvimopan capsules and the 12 mg alvimopan capsules	88	1) Two 6 mg alvimopan doses and then one 12 mg alvimopan dose	1

				2) One 12 mg alvimopan dose and then two 6 mg alvimopan doses	
8) SB-767905/019*	A DB, R, PC, PG single dose ascending study to investigate the safety and pharmacokinetics of alvimopan and its metabolites in Japanese healthy male subjects	PK of alvimopan and its metabolites	50	Alvimopan 0.5, 1, 3, 6, or 12 mg Placebo	1
9) 17CL133*	A phase I study, R, DB, double-dummy, PG comparison of the effects of alvimopan versus placebo on remifentanil-induced nausea and vomiting in healthy female volunteers	The effects of alvimopan on opioid-induced nausea and vomiting	37	12 mg of oral Alvimopan 2 mg of IV Alvimopan Placebo	1

R (randomized), DB (double-blind), PC (placebo-control), MC (multi-center), and PG (parallel group)
1 N = number of subjects/patients randomized;
* The shaded studies in this table were submitted during this second-cycle
Reference: Final Study Report Study 314, ISS, Table 73, Pages 140-153

Table 3: Completed multiple-dose alvimopan studies in healthy subjects

STUDY	TYPE	OBJECTIVES	N	TREATMENT GROUPS	DAYS
1) H3G-LC-BGGA	Alvimopan: Dose-escalation safety trial	Evaluate the safety and tolerability, and the PK profile of alvimopan after a single dose and after single doses for three consecutive days. To evaluate GI physiology during administration of alvimopan for three consecutive days.	8	Placebo Alvimopan doses ranged from 1.2 mg/day to 120 mg/day	Periods 1, 2, & 3 = 1 day Periods 4 & 5 = 3 days
2) 14CL118	A single-blind, PC study of the plasma PK of intravenous morphine after single and repeat doses of alvimopan in healthy volunteers	Effect of single and repeated doses of alvimopan on IV morphine PK.	10	(Crossover) Placebo BID Alvimopan 12 mg BID	4.5
3) 14CL119	A DB, PC study of the pharmacokinetics of repeat doses of alvimopan in healthy volunteers	PK of alvimopan and metabolite following repeated doses of alvimopan in healthy subjects	40	Placebo BID Alvimopan 6 mg, 12 mg, 18 mg, and 24 mg BID	4.5
4) RC99-CP007 (CP007)	A phase I, double-blind, placebo-controlled, dose ranging study of the reversal of opioid-induced delay in GI transit in subjects	Determine if alvimopan would prevent delayed GI transit that occurs with administration of therapeutic dose of MS Contin without reversing morphine-induced analgesia in healthy subjects	13	(Crossover) Placebo TID Alvimopan 3 mg TID	4
5) 13C109	A DB, R, PC study of the effect of alvimopan on opioid-induced side effects and analgesia in patients after third molar extraction	Determine if alvimopan would reduce subjective opioid GI symptoms without reversing opioid-induced analgesia or pupillary constriction	63	Placebo Alvimopan 2 mg First dose 60 minutes before surgery and second dose 60 minutes	1

				after surgery	
6) RC98-CP001 (CP001)	An ascending dose safety study of alvimopan in man	Evaluate the safety of oral alvimopan by determining if there was a dose-related toxicity with the drug in the proposed dose range and to estimate the tolerated dose	44	Placebo TID Alvimopan doses ranging from 0.25 mg to 36 mg TID	4
7) H3G-LC-BGGC	Alvimopan: multiple-dose trial in subjects with loperamide-induced constipation	Evaluate the safety and tolerability, the PK profile and the pharmacology and duration of activity of multiple-dose alvimopan compared with placebo in subjects with loperamide-induced constipation.	8	(Crossover) Placebo; Loperamide BID & Alvimopan 24 mg TID; Loperamide BID & Alvimopan 2.4 mg TID; and Loperamide BID	4 to 5
8) SB-767905/016 **	A R, PC study to evaluate the effect of single and multiple oral doses of alvimopan on cardiac conduction as assessed by 12-lead ECG in healthy subjects	Exclude a greater than 10 msec effect of single and multiple oral doses of alvimopan 6 mg BID and 24 mg BID on the QTc interval, compared to placebo.	162	Placebo Alvimopan 6 mg and 24 mg BID Moxifloxacin 400 mg per day	7
9) 14CL128*	Phase 1, R, DB, PC of the effect of alvimopan on gastric, small bowel, and colonic transit in healthy subjects	Effects of alvimopan on gastric, small bowel, and large bowel motility	19 17 19 18	Alvimopan 12 mg BID + Codeine 30 mg QID; Alvimopan 12 mg BID; Codeine 30 mg QID; Placebo	2-3
10) 14CL201*	A Phase 1/2, complex, 4-part study of the safety of repeat dosing with IV alvimopan and its effect on opioid-induced changes in GI transit	Effects of alvimopan on opioid-induced changes in the GI tract	12 8 24 84 2	Part A: 6 mg PO BID & loperamide 2 mg QID Part B: 12 mg IV or placebo Part C: 6 mg IV BID or placebo Part D: IV (0.1 mg, 0.45 mg, 1 mg, 3 mg, 6 mg) & loperamide 2 mg QID	4 3 7 2 4
11) SB-767905/018 *	A single center, DB, PC, R, multiple oral dose study to evaluate the safety, tolerability, and PK of multiple oral doses of alvimopan in Japanese healthy male subjects	PK of alvimopan	18	Alvimopan 1 mg BID or placebo BID	8

* These shaded studies submitted during this second-cycle
** Study SB-767905/016 is the thorough QT/QTc submitted during the first-cycle.
Reference: Final Study Report Study 314, ISS, Table 73, Pages 140-153

Table 4: Completed single-dose alvimopan studies in special populations

STUDY	TITLE	OBJECTIVES	N	TREATMENT ARM(S)	DAYS
1) 14CL116	Pharmacokinetics of alvimopan in subjects with renal impairment.	Characterize 1) the PK of alvimopan and its primary metabolite (ADL 08-0011) in plasma, following a single oral dose of 12 mg in patients with mild, moderate, or severe renal impairment; 2) the urinary excretion of alvimopan and ADL 08-0011 in patients with mild, moderate, or severe renal impairment.	24	Alvimopan 12 mg	1
2) 14CL117	Pharmacokinetics of alvimopan in subjects with hepatic impairment	Characterize 1) the PK of alvimopan and its primary metabolite in plasma, following a single oral dose of 12 mg in healthy subjects and patients with mild or moderate hepatic impairment, as defined by Child-Pugh classification and 2) the urinary excretion of alvimopan and ADL 08-0011 after a single oral dose of 12 mg in healthy subjects and patients with mild or moderate hepatic impairment.	20	Alvimopan 12 mg	1
3) 14CL123	Pharmacokinetics of oral alvimopan and its metabolite (ADL 08-0011) in elderly subjects 65 years of age or older	Characterize the PK of alvimopan and its metabolite in the elderly after a single 12 mg alvimopan dose.	18	Alvimopan 12 mg	1
4) 14CL125	A phase I study of the plasma levels of alvimopan and presence of Its metabolite in patients with Crohn's disease.	Describe the PK of alvimopan and ADL 08-0011 in patients with Crohn's disease. Evaluate whether the PK of alvimopan and ADL 08-0011 in patients with active or quiescent Crohn's disease are similar to those observed in previous studies of healthy volunteers after a single dose of 12 mg of alvimopan.	12	Alvimopan 12 mg	1
5) 14CL126	Pharmacokinetics of alvimopan in subjects with severe hepatic impairment	Characterize the PK of alvimopan and its metabolite in plasma, following a single oral capsule administration of a dose of 12 mg in healthy subjects and patients with severe hepatic impairment. Evaluate the safety of alvimopan in patients with severe hepatic impairment compared to controls.	10	Alvimopan 12 mg	1

Reference: Final Study Report Study 314, ISS, Table 73, Pages 140-153

Table 5: Completed alvimopan studies: the treatment of POI

STUDY	TITLE	OBJECTIVES	N	TREATMENT GROUPS	DAYS
1) 13C206	A Phase II , DB, PC, Parallel Study of Efficacy for Shortening the Duration of POI	Determine if Alvimopan shortened the duration of POI after partial colectomy or TAH in patients receiving IV opioids for postoperative pain.	79	Placebo Alvimopan 1 mg Alvimopan 6 mg	Up to 8 days
2) 13C213	A MC Phase II/III, DB, Dose Ranging, PC, Parallel Study of Alvimopan in Opioid-Induced Postoperative Bowel Dysfunction/POI	Determine the clinically optimal dose of alvimopan	153	Placebo Alvimopan 3 mg Alvimopan 6 mg Alvimopan 12 mg	Up to 8 days
3) 13C214	A MC, Phase II, DB, PC Study Assessing Efficacy of Alvimopan for Speeding Recovery from Postoperative Opioid-Induced Bowel Dysfunction	Determine if alvimopan would shorten the duration of POI as assessed by faster recovery of bowel function following intra-abdominal surgery (excluding planned BRs). Determine whether 12 mg of alvimopan was safe for use in a population of patients who had undergone intra-abdominal surgery	65	Placebo Alvimopan 12 mg	Up to 8 days
4) 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
5) 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
6) 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
7) 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
8) SB-767905/001 (001)[2]	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
9) 13CL314 (314)[3]	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	654	Placebo Alvimopan 12 mg	Up to 8 days

		GI function in patients undergoing partial small or large BR with primary anastomosis			

N = number of patients
1 For the original 8 POI studies, the first dose was administered at least 2 hours prior to surgery, and the next doses BID for up to 7 days or until hospital discharge (which ever is sooner) and for Study 314 the first dose was administered 0.5 to 1.5 hours prior to surgery, and the next doses BID for up to 7 days or until hospital discharge (which ever is sooner)
2 Study SB-767905/001 (001) was conducted in Europe, Australia, and New Zealand
3 Study 13CL314, which is shaded, was submitted in this second-cycle
Reference: Final Study Report Study 314, ISS, Table 74, Pages 154-158

Table 6: Completed alvimopan studies: the treatment of OIC in chronic (non-cancer) pain patients

STUDY	TITLE	OBJECTIVES	N	TREATMENT ARMS	DAYS
			7	Alvimopan 0.125 mg on visit 1 0.25 mg on visit 2 1 mg on visit 3 3 mg on visit 4	1
			8	Placebo or Alvimopan day 1: 0.125 (or 0.25) mg day 2: 0.25 (or 1) mg day 3: 1 mg day 4 & 5: 3 mg	5
			26	Placebo or Alvimopan day 1: 0.5 mg day 2: 1.5 mg day 3: 3 mg day 4: 4.5 mg	4
			62	Placebo Alvimopan 0.5 mg Alvimopan 1.5 mg Alvimopan 3 mg	1
			13	Placebo Alvimopan 0.5 mg Alvimopan 1.5 mg Alvimopan 3 mg	1
			20	Placebo Alvimopan 0.5 mg/day Alvimopan 1 mg/day	21
			168	Placebo	21

[redacted]		Alvimopan 0.5 mg/day Alvimopan 1 mg/day	
[redacted]	522	Placebo Alvimopan 0.5 mg BID Alvimopan 1 mg/day Alvimopan 1 mg BID	42

* This study, which is shaded in this table, was submitted in this second-cycle
Reference: Final Study Report Study 314, ISS, Table 75, Pages 159-165

Table 7: Completed alvimopan studies: the treatment of OIC in chronic cancer pain patients

STUDY	DESIGN	OBJECTIVES	N	TREATMENT GROUPS	DAYS
1) 13CL223	A phase II, open-label study of alvimopan in subjects receiving chronic opioid therapy for cancer pain	Characterize the safety of alvimopan administered as needed for up to 21 days in cancer patients receiving chronic opioid therapy for treatment of cancer-related pain. Assess the overall satisfaction of these subjects with the quality and number of BMs during treatment.	16	Alvimopan 0.25 mg to 1 mg prn achievement of satisfactory BM	Up to 21 days
2) 13CL224	A phase II, open-label study of alvimopan in subjects receiving chronic opioid therapy for cancer pain	Gather long-term safety data on alvimopan administered as needed in cancer patients receiving chronic opioid therapy for treatment of cancer-related pain. Assess the overall satisfaction of these subjects with their bowel habits on study.	7	Alvimopan 0.25 mg to 1 mg prn achievement of satisfactory BM	Up to 21 days

Reference: Final Study Report Study 314, ISS, Table 75, Pages 159-165

Table 8: Completed alvimopan studies: the treatment of idiopathic chronic constipation

STUDY	DESIGN	OBJECTIVES	N	TREATMENT GROUPS	DAYS
1) SB-767905/004*	A single center, PC, DB, R, 2-period crossover study of the effect of alvimopan, 3 mg BID, on whole bowel transit in subjects with functional constipation	Assess the whole bowel transit of alvimopan in functional constipation patients	24	Placebo BID Alvimopan 3 mg BID	7
2) SB-767905/007 (Study 7)*	A phase 2, MC, R, PC, dose-ranging study of the safety and efficacy of alvimopan capsules (1 mg, 3 mg and 8 mg) administered BID for treatment of chronic constipation in adults	Assess the efficacy and safety of alvimopan in patients with chronic constipation	212	Placebo BID Alvimopan 1 mg BID Alvimopan 3 mg BID Alvimopan 8 mg BID	56

* Both of these studies were submitted in this second-cycle
Reference: Final Study Report Study 314, ISS, Table 76, Pages 166

Table 9: Ongoing alvimopan studies: the treatment of OIC in cancer and noncancer patients

STUDY	TITLE	OBJECTIVES	N	TREATMENT GROUPS	DAYS
[redacted]			519	2 alvimopan groups (n=346) Alvimopan 0.5 mg BID Alvimopan 0.5 mg/day Placebo (n=173)	365
			491	2 alvimopan groups (n=327) Alvimopan 0.5 mg BID Alvimopan 0.5 mg/day Placebo (n=164)	84
			805	Alvimopan 0.5 mg BID (n=537) Placebo (n=268)	84
			236	2 alvimopan groups (n=157) Alvimopan 0.5 mg BID Alvimopan 1 mg BID Placebo (n=79)	21 to 42[3]
			1	Alvimopan 0.5 mg BID Alvimopan 1 mg BID Placebo	*

1 N is the number enrolled at the time of the May 16, 2006 briefing package.
2 Days are the number of planned days in these ongoing studies.
3 Study 8 was originally 6 weeks in duration; however, it was modified to 3 weeks.
* The duration of Study will be at least 8 weeks. According to the sponsor, the treatment period will continue until alvimopan is commercially available, [redacted]

Reference: Final Study Report Study 314, ISS, Table 76, Pages 166

4.3 Review Strategy

This medical officer is responsible for the entire safety and efficacy reviews for the POI indication in BR surgery patients.

For the efficacy review of the POI indication, this medical officer believes that there are **five** important alvimopan phase 3 trials [**one** study from this second-cycle NDA (Study 314) and **four** studies from the first-cycle NDA (302, 308, 313, and 001)]. Of these five trials, the most important trial is Study 314 because:

- Of the five studies, Study 314 contained the largest number of patients in the efficacy BR surgery population (i.e., MITT) for the proposed 12 mg alvimopan dose. Studies 302, 308, 313, 001, and 314 had 98, 139, 160, 238, and 317 BR surgery patients, respectively (i.e., the MITT population) in the 12 mg alvimopan treatment group. Thus, Study 314 contained 33.3% (317/952) of the total efficacy BR surgery population in the 12 mg alvimopan treatment group.
- Study 314 was the only study that had **GI2** (a two-component composite endpoint assessing toleration of solid food and BM) as the primary efficacy endpoint [the other four studies had **GI3** (a three-component composite endpoint assessing toleration of solid food, BM, and flatus) as the original, pre-specified primary efficacy endpoint]. This medical officer believes that **GI2** assesses GI recovery better than **GI3** because **GI3** contains flatus — which may not be able to be assessed reliably and which may not accurately measure the efficacy of treatments in POI.
- Study 314 was the only study had contained only GI surgery patients; the other four studies contained GI and gynecologic surgery patients (alvimopan demonstrated no efficacy in the gynecologic surgery subpopulation in these four studies).
- Study 314 contained only one alvimopan treatment group (i.e., the 12 mg dose); whereas, the other four studies had two alvimopan doses (the 6 mg and 12 mg doses). For this second-cycle the sponsor has proposed [redacted] the 12 mg alvimopan dose for the POI indication.

The other four trials are also important for the efficacy review. This medical officer believes that these remaining four trials are equally important because they all had the following similarities:

- The same complex dosing regimen for up to eight days in the hospital (the first dose two hours prior to surgery, and the next doses BID for 7 postoperative days or until hospital discharge);
- The same three doses (placebo, 6 and 12 mg of alvimopan);
- The same two surgical types (BR and TAH);
- The same prohibited medications;
- The same primary endpoint (**GI3**), six identical secondary endpoints, and one similar secondary endpoint (the responder analysis). Studies 302, 308, and 313 totaled seven pre-specified secondary endpoints and Study 001 had a total of 25 pre-specified secondary endpoints; and

- Large (between 451 to 911 patients), adequate, and well-controlled studies (they were all randomized, double-blinded, placebo-controlled, multi-center, parallel group phase 3 studies.

For the integrated safety review of the POI indication, this medical officer believes that all 49 alvimopan trials should be evaluated. The most important POI trials for the safety of alvimopan in the proposed indication are the nine POI trials including the three phase 2 POI trials (13C206, 13C213, and 13C214) and five phase 3 POI trials (302, 308, 313, 001, 306, and 314). These nine trials are the most important because these trials are in the proposed population (surgery patients) and they contain the proposed doses (the first dose administered prior to surgery and then BID for a maximum of 7 postoperative days).

Since there was a possible alvimopan-associated CV signal seen in one of the long-term OIC studies (i.e., Study 14), this medical officer will thoroughly evaluate the CV safety of alvimopan in the nine POI trials. In addition, this medical officer will assess the CV safety of alvimopan in the longer-term ($\geq$ 3 week duration) OIC studies and the implications of a possible CV OIC safety signal for the short-term POI population. The 3-12 week OIC studies are Studies 13C217, 13 C304, 11, 12, and 13 and the ongoing, one-year OIC study is Study 14. The complete results of the OIC studies are not available because two studies were completed during this second cycle NDA review (i.e., Studies 12 and 13) and one study is ongoing (i.e., Study 14).

4.4 Data Quality and Integrity

Five sites were selected for Division of Scientific Investigations (DSI) audits in the first-cycle NDA: three sites in Study 313 (site 04 in Atlanta, GA; site 09 in Grand Rapids, MI; and site 06 in Salt Lake City, Utah) and two sites in Study 308 (site 33 in San Diego, CA and site 10 in Denver, CO). The three sites in Study 313 and the two sites in Study 308 had the largest number of patients per site in the respectively trials. In Study 313, sites 04, 09, and 06 treated 38, 35, and 32 patients, respectively, and in study 308, sites 33 and 10 treated 70 and 59 patients, respectively. On initial review before the filing meeting, the proposed alvimopan dose (12 mg) appeared to demonstrate the best efficacy (compared to placebo) in the primary efficacy endpoint in Study 313 and the 12 mg dose appeared to demonstrate the second best efficacy (compared to placebo) in the primary efficacy endpoint in Study 308.

Dr. Khairy W. Malek, the medical reviewer for the Division of Scientific Investigations, reviewed the inspection of four sites (sites 04, 09, 33, and 10). Dr. Malek, in his May 5, 2005 review, stated that the data from all four sites can be used to support the NDA. He found "multiple instances of protocol deviations" that "do not seem to affect the overall validity and reliability of the data." The mild protocol deviations included the following minor protocol violations: not performing laboratory testing; not correctly recording surgery start times; not correctly recording the time to tolerate first solid food; inaccurate recording of treatment compliance (inaccurate recording of missing doses); and performing a PK analysis two hours after the scheduled time. Please see Dr. Malek's May 5, 2005 review for more details.

Since there were no concerning findings on the inspections of five sites during the first-cycle NDA, the DGP did not request any additional DSI audits of the new POI study (Study 314).

Medical Reviewer's Comments: This medical officer believes that incorrect recording of surgery start times and incorrect recording of the time to tolerate first solid food may have influenced the results of the primary efficacy endpoint and the important secondary endpoints. However, the DSI audits only uncovered two patients who had an incorrect recording of the time to tolerate first solid food and one patient who had an incorrect recording of the time surgery ended. Therefore, the low prevalence of these incorrect recordings probably did not influence the overall results of the primary and secondary endpoints.

4.5 Compliance with Good Clinical Practices

According to the sponsor, all nine phase 2 and phase 3 studies in the treatment of POI (Studies 13C206, 13C213, 13C214, 302, 306, 308, 313, 001, and 314) were conducted in compliance with good clinical practice (GCP) guidelines, as described in the International Conference on Harmonization (ICH) Harmonised Tripartite Guidelines for Good Clinical Practice 2000 and the United States Code of Federal Regulations (CFR) dealing with clinical studies. A signed informed consent form was obtained for each patient and IRB approval was obtained by the principal investigators in accordance with 21 CFR 50 and 56. According to the sponsor, all of the trials were conducted in accordance with acceptable ethical standards.

4.6 Financial Disclosures

The sponsor has submitted FDA Form 3454 certifying that the clinical investigators in the nine submitted POI trials:

- Did not participate in any financial arrangement with the sponsor, whereby the value of compensation to the investigators for conducting the study could be affected by the outcome of the study [as defined in 21 CFR 54.2(a)]:
- Had no proprietary interest in this product or significant equity interest in the sponsor [as defined in 21 CFR 54.2(b)]: and
- Was not the recipient of significant payments of other sorts [as defined in 21 CFR 54.2(f)].

5 CLINICAL PHARMACOLOGY

5.1 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 degradant (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 1/2 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." Please see Dr. Sue Chih Lee's review for more details regarding the pharmacokinetics of alvimopan and its metabolite.

5.2 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 "Ki 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."

According to Dr. Sue Chih Lee, in the thorough QT/QTc study, "there was some trend of (an) increase in QTcF with (the) alvimopan dose. However, the increase (in QTc did not) appear to be as apparent as (the increase in QTc after) moxifloxacin 400 mg" dosing. Please see her review for more details.

5.3 Exposure-Response Relationships

In this second-cycle NDA, the sponsor [redacted] proposes the 12 mg alvimopan regimen for the treatment of POI.

The sponsor [redacted] proposed [redacted] 12 mg alvimopan regimens for the treatment of POI. There did not appear to be a dose response (i.e., improved efficacy) with the use of the 12 mg dose compared to the 6 mg dose (for details of the dose response see this medical officer's July 12, 2005 review of the original NDA).

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

In the original first-cycle NDA submission, the sponsor proposed indication was the following: "alvimopan is indicated to accelerate time to recovery of GI function following abdominal or pelvic surgery". During the NDA review cycle, the sponsor changed their proposed indication to the following: "alvimopan is indicated to accelerate time to recovery of GI function following major abdominal or complex pelvic surgery." In this second cycle NDA submission, the sponsor proposes the following new indication: "alvimopan is indicated to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis".

6.1.1 Methods

For the efficacy review of the POI indication, this medical officer believes that there are **five** important alvimopan phase 3 trials [**one** study from this second-cycle NDA (Study 314) and **four** studies from the first-cycle NDA (302, 308, 313, and 001)]. Of these five trials, the most important trial is Study 314 because:

- Of the five studies, Study 314 contained the largest number of patients in the efficacy BR surgery population (i.e., MITT) for the proposed 12 mg alvimopan dose. Studies 302, 308, 313, 001, and 314 had 98, 139, 160, 238, and 317 BR surgery patients, respectively (i.e., the MITT population) in the 12 mg alvimopan treatment group. Thus, Study 314 contained 33.3% (317/952) of the total efficacy BR surgery population in the 12 mg alvimopan treatment group.
- Study 314 was the only study that had **GI2** (a two-component composite endpoint assessing toleration of solid food and BM) as the primary efficacy endpoint [the other four studies had **GI3** (a three-component composite endpoint assessing toleration of solid food, BM, and flatus) as the original, pre-specified primary efficacy endpoint]. This medical officer believes that **GI2** assesses GI recovery better than **GI3** because **GI3** contains flatus — which may not be able to be assessed reliably and which may not accurately measure the efficacy of treatments in POI.
- Study 314 was the only study had contained only GI surgery patients; the other four studies contained GI and gynecologic surgery patients (alvimopan demonstrated no efficacy in the gynecologic surgery subpopulation in these four studies).
- Study 314 contained only one alvimopan treatment group (i.e., the 12 mg dose); whereas, the other four studies had two alvimopan doses (the 6 mg and 12 mg doses). For this second-cycle the sponsor has proposed only the 12 mg alvimopan dose for the POI indication.

The other four trials are also important for the efficacy review. This medical officer believes that these remaining four trials are equally important because they all had the following similarities:

- The same complex dosing regimen for up to eight days in the hospital (the first dose two hours prior to surgery, and the next doses BID for 7 postoperative days or until hospital discharge);
- The same three doses (placebo, 6 and 12 mg of alvimopan);
- The same two surgical types (BR and TAH);
- The same prohibited medications;
- The same primary endpoint (GI3), six identical secondary endpoints, and one similar secondary endpoint (the responder analysis). Studies 302, 308, and 313 totaled seven pre-specified secondary endpoints and Study 001 had a total of 25 pre-specified secondary endpoints and
- Large (between 451 to 911 patients), adequate, and well-controlled studies (they were all randomized, double-blinded, placebo-controlled, multi-center, parallel group phase 3 studies.

6.1.2 General Discussion of Endpoints

Primary Efficacy Endpoint (**time to GI2**): The pre-specified, primary efficacy endpoint was the time to recovery of both the upper and lower GI tracts, following partial small or large bowel resection surgery with primary anastomosis:

1) The first component of the primary endpoint was the recovery of the **upper GI tract**: 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).
2) The second component of the primary endpoint was the recovery of the **lower GI tract**: the time from the end of surgery to the first BM.

This two-component, composite endpoint, identified **as GI2**, was the time from the end of surgery to recovery of the upper GI tract and the lower GI tract (whichever occurred last). **GI2** was mathematically expressed as follows: **GI2** = max (solid food, BM).

In Studies 308, 313, and 001, **GI2** was a pre-specified secondary efficacy endpoint; whereas, in Study 302, **GI2** was a post-hoc endpoint.

Medical Reviewer's Comments: Important endpoints for investigational POI trials have not been standardized by the DGP. This medical officer believes that the primary efficacy endpoint (i.e., time to GI2) in Study 314 is an acceptable endpoint because it assesses both upper and lower GI tract recovery after surgery.

In several DGP/sponsor meetings during the development of alvimopan, the DGP stressed the importance that this composite endpoint must be both statistically significant and

clinically meaningful. In an October 2000 meeting between the DGP an the sponsor, the DGP stated that "A clinically meaningful difference in recovery time will be one that is on the order of a day or so, not just a few hours." This medical officer believes that a 24 hour difference (or greater) in recovery of both upper and lower GI tract motility between alvimopan and the placebo would be clinically meaningful. However, this medical officer believes that a 10 hour difference (or less) in recovery of both upper and lower GI tract motility between alvimopan and the placebo may not be clinically meaningful.

This medical officer believes that the following factors will help determine the clinical meaningfulness of the primary efficacy endpoint (i.e., GI2) results:

- **The relative change in time to discharge (i.e., DOW and Ready) of alvimopan compared to placebo;**
- **The responder analyses of the time to GI recovery and the time to discharge events;**
- **The duration of time to GI recovery and discharge. If the mean time to the first BM and the mean time to DOW are 10 days, then a 10 hour difference is probably not clinically meaningful; and**
- **Confounding factors in the efficacy analysis including the relative amount of opioids (e.g., in morphine equivalents) and possibly the relative amounts of 5-HT3 antagonists administered in the immediate pre-operative period, the operative period, and the double-blind post-operative treatment period in the alvimopan and placebo groups.**

The sponsor used GI3, a three component composite endpoint, as the primary efficacy endpoint in their first four POI efficacy studies (i.e., Studies 302, 308, 313, and 001). GI3 was identical to GI2 except the recovery of the lower GI tract was the time from the end of surgery to the time of the first BM or the first flatus (whichever occurred first) and it was expressed mathematically as follows: GI3 = max [upper GI tract, lower GI tract] = max [solid food, min (flatus, BM)]. This medical officer agrees with the sponsor's argument that GI3 may not assess the recovery of the lower GI tract as well has 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.

Pre-specified secondary endpoints: In Study 314, the original, pre-specified 14 secondary endpoints were the following:

1) Time from the end of surgery to the time of the first flatus (identified as **Flatus**);
2) Time from the end of surgery to the time of the first BM (identified as **BM**);
3) Time from the end of surgery to the time of first toleration of solid food (identified as **Solids**);
4) 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 (identified as **Ready**);
5) Time from the end of surgery to the time that the hospital discharge order was written (identified as **DOW**);

6) Time from the end of surgery to the time of actual hospital departure (identified as **Departure**);
7) Proportion of patients with a postoperative nasogastric tube (NGT) insertion;
8) Proportion of patients who had a postoperative chest x-ray (CXR) and the primary reason for obtaining the CXR;
9) Proportion of patients with DOW $\geq$ POD 7;
10) Proportion of patients readmitted to the hospital (for any cause) within 10 days of actual hospital discharge;
11) SAEs of POI;
12) Gastrointestinal Quality of Life Index (GIQLI) with 36 questions;
13) SF-8 Health Survey with 8 questions; and
14) Cleveland Global Quality of Life (CGQL) with 3 questions.

The sponsor added the following two additional secondary efficacy endpoints in an amendment to the original protocol on August 9, 2004:

15) Adolor-Inflexxion Questionnaire (RI-49) with 49 questions; and
16) Proportion of patients who had a postoperative abdominal x-ray performed and the primary reason of obtaining the test.

In their January 10, 2006 amendment to the statistical analysis plan (SAP) for Study 314, the sponsor amended their original pre-specified secondary endpoints. According to the sponsor, these amendments to the SAP were performed prior to un-blinding of the completed Study 314 (Study 314 was completed on December 20, 2005). In their January 2006 SAP, the sponsor's **42** secondary efficacy 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 (6 endpoints);
7) The proportion of **Ready** responders* by PSD 3, 4, 5, 6, 7, and 8 (6 endpoints);
8) The proportion of **GI3** responders* by PSD 3, 4, 5, 6, 7, and 8 (6 endpoints);
9) The proportion of BM responders* by PSD 3, 4, 5, 6, 7, and 8 (6 endpoints);
10) The proportion of **DOW** responders* by PSD 3, 4, 5, 6, 7, and 8 (6 endpoints);
11) The proportion of **Departure** responders* by PSD 3, 4, 5, 6, 7, and 8 (6 endpoints); 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. Therefore, non-responders would be patients who were censored; patients who did not achieve the event; who had the event, but subsequently had a prolonged hospitalization due to prolonged POI; and patients who had the event, but subsequently were readmitted for POI within seven days of discharge.

In addition to the 1 primary efficacy endpoint, the 42 secondary efficacy endpoints, the January 10, 2006 final SAP had the following **10** other efficacy endpoints:

1) Time to Solids;
2) Time to Flatus;
3) The proportion of patients with postoperative morbidity (referred to as POM);
4) The proportion of patients with readmission for all causes within 10 days of the actual hospital departure;
5) The proportion of patients who had a postoperative abdominal x-ray;
6) The proportion of patients who had a postoperative CXR;
7) Differences in the following QOL questionnaires: GIQLI, SF-8, CGQL and Adolor-Inflexxion Recovery Index (4 endpoints).

Medical Reviewer's Comments: **This medical officer believes that 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).**

This medical officer believes that treatments that demonstrate reduction of time to GI recovery but do not demonstrate reduction of time to discharge (i.e., Ready and DOW) may not be clinically meaningful. This medical officer would expect therapies that demonstrate reduction of time to GI recovery also demonstrate reduction of time to discharge. This medical officer will assess the results of both the time to GI recovery endpoints and the time to discharge endpoints.

This medical officer agrees with the sponsor that 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.

The relative importance of Ready versus DOW in the efficacy evaluation of alvimopan is equivocal. DOW may be more relevant endpoint than Ready if alvimopan contributes to a non-GI serious adverse event (SAE) that delays hospitalization. However, Ready may be more clinically relevant than DOW if the events that delay discharge are not related to the BR surgery no alvimopan-related AEs occur.

This medical officer also believes that the responder analyses of the important primary (i.e., time to GI2) and the important secondary endpoints (i.e., time to DOW and time to Ready) at the six cutoff points (i.e., by PSD 3, 4, 5, 6, 7, and 8) are valuable endpoints in the efficacy assessment of alvimopan. This medical officer also agrees with the sponsor's decision to define non-responders as patients who had prolongation of their hospitalization due to prolonged POI or patients who readmitted for POI within seven days of discharge. However, this medical officer believes that the duration of a "prolonged POI" should have

been pre-specified in the original protocol because surgeons have different definitions of a prolonged POI. See the following for different definitions of a "prolonged POI":

- **All BR surgery patients because all of these patients have intestinal dysmotility following surgery;**
- **BR surgery patients who continue to have intestinal dysmotility after a certain time frame (e.g., one week post-surgery);**
- **BR surgery patients who have had reinsertion of their NG tubes; and**
- **BR surgery patients who cannot take significant oral intake (e.g., tolerate liquids, tolerate solids) after a certain time frame.**

The disparate definitions of a "prolonged POI" may confound these responder analyses. This medical officer recommends that the sponsor prospectively define "prolonged POI" — in the responder definition — if the sponsor plans future POI studies.

6.1.3 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 313.

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 Objective: The primary objective of this study was to 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 bowel resection with primary anastomosis. The secondary objectives were to evaluate the safety of alvimopan 12 mg and to assess the postoperative effects of alvimopan on the patients' quality of life.

Study 314 Design: 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 (see Table 10).

Table 10: Post-Surgery Day (PSD)

Post-Surgery Day (PSD)	Time of Assessment – Hours Relative to End of Surgery
0	≤24
1	24 to 48
2	48 to 72
3	72 to 96
...	...
10	240 to 264

Reference: Adapted from Volume 173, Table 5, Page 50.

Medical Reviewer's Comments: Study 314 was well-controlled and well-designed. 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 11 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 11: 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	GI[2]	GI[3]
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: Table 12 displays the eligibility criteria of Study 314.

Table 12: Eligibility criteria of Study 314

Inclusion Criteria: To be eligible to participate in the study, patients had to have met the following criteria:	**Exclusion Criteria:** If patients had the following conditions, they were not eligible to participate in the study:
➢ 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.	➢ 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).

Reference: Adapted from Clinical Study Report for Study 314, pages 34-36.

Medical Reviewer's Comments: 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.

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 (the 6 mg and 12 mg doses) 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's 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.

Medical Reviewer's Comments: 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).

The dosing regimen used in the phase 3 studies exposed patients to one dose of study medication before the development of a POI. Additionally, some patients were exposed to one dose of study medication unnecessarily because they received the first dose and then

their surgery was canceled. This medical officer believes that the sponsor should have experimented with different dosing regimens during the phase 2 POI studies to avoid unnecessary exposure to study medication. The sponsor should have investigated the administration of the first dose of study drug after surgery.

In addition, the sponsor should have considered different alvimopan dosing throughout the treatment period to correspond to the amount of opioids typically administered. Since most of the opioids are given between POD 0 and POD 2 and fewer opioids are given during PODs 3-7, the sponsor could have experimented with higher alvimopan doses during PODs 0-2 and lower alvimopan doses during PODs 3-7.

Schedule of Procedures and Evaluations in Study 314: See Table 13 for a list of the procedures and evaluations during Study 314.

Table 13: 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.

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.

Four quality of life questionnaires (i.e., GIQLI, SF-8, Health Survey, CGQL, and Adolor-Inflexxion Questionnaire) were administered during the screening period (the Adolor-Inflexxion Questionnaire was added as an amendment to the original protocol).

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.

Medical Reviewer's Comments: The five efficacy phase 3 trials (i.e., Studies 302, 308, 313, 001, and 314) had very similar evaluations and procedures. In the 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 one European trial (Study 001), the last possible study day was POD 14.

Prohibited medications in Study 314: The use of the following medications was prohibited in Study 314: epidural opioids, epidural local anesthetics, 5-HT4 receptor agonists, prophylactic cathartics (i.e., magnesium citrate, magnesium hydroxide, magnesium sulfate, castor oil, sodium phosphate, sodium biphosphate, polyethylene glycol, and enemas), and low-dose naloxone infusions. However, the use of naloxone and/or cathartics was allowed for treatment. The routine use of ketorolac or cyclooxygenase-2 (COX-2) inhibitors was restricted to a maximum of two doses during the perioperative and postoperative periods.

Medical Reviewer's Comments: This medical officer agrees with the prohibited medications during the study. This medical officer believes that all NSAIDs (including ketorolac) should have been prohibited during the treatment period because all NSAIDs could reduce the opioid requirements. This medical officer will closely analyze the amount of perioperative and postoperative opioids used in the treatment groups.

This medical officer agrees with prohibiting cathartics because cathartics may decrease the time to first BM, a component of the primary efficacy endpoint. The sponsor should also have prohibited the use of all stimulant laxatives (including bisacodyl). This medical officer will analyze the proportion of patients in the treatment groups who received laxatives during the treatment period.

This medical officer agrees with the sponsor's decision to prohibit prophylactic naloxone. This medical officer will analyze the proportion of patients who received opioid antagonists (including naloxone) in the treatment groups during the treatment period.

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.

Medical Reviewer's Comments: 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., 10-18 hours) a safety follow-up visit several days after the last alvimopan dose would be useful.

Statistical Methods in Study 314: The following three patient populations were pre-specified in Study 314:

1) Intention to Treat (ITT): All patients who received at least one dose of study medication; had protocol specified surgery; and had at least one postsurgery assessment for flatus, BM, or tolerability of solid food. The ITT population was the pre-specified primary population for the primary efficacy analysis;
2) Efficacy evaluable (EE): All ITT patients who did not have violation of any eligibility criteria and did not have more than one dosing error. Efficacy data collected prior to the start date of prohibited medication was included in the EE population data analysis. However, efficacy data collected after the start date of prohibited medication was not included in the EE analysis. The EE population was the pre-specified secondary population for the secondary efficacy analyses in Study 314.
3) Safety: All patients who received at least one dose of study medication and who had at least one safety assessment following administration of study medication. The safety population was used for all safety analyses.

In their January 10, 2006 amendment to the statistical analysis plan (SAP) for Study 314, the sponsor amended their original pre-specified populations. According to the sponsor, these amendments to the SAP were performed prior to un-blinding of the completed Study 314 (Study 314 was completed on December 20, 2005). In their January 2006 SAP, the sponsor's populations were the following:

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, which will include, but not limited to, the following:

   - Entered study without meeting all inclusion/exclusion criteria;
   - Did not receive protocol-specified surgery (i.e., partial small/large BR);
   - Received epidural anesthesia/analgesia;
   - Intravenous opioid PCA was not started postoperatively;
   - NGT was not removed before the scheduled first postoperative study medication dose;
   - Was not treated per randomization during the study period (e.g., the patient received study medication that did not match his or her randomized treatment assignment); or
   - Received prohibited concomitant medication. However, patients who received a prohibited medication may be considered partially EE depending on both the time the medication is given and its potential to confound study endpoints.

Medical Reviewer's Comments: The sponsor's final SAP for Study 314 (i.e., the January 10, 2006 SAP) was almost identical to the SAPs of the four important POI studies that were submitted in the first-cycle NDA (Studies 302, 308, 313, and 001). The sponsor's original SAP for Study 314 differed from the SAPS of the four important POI studies. To reduce confusion between the disparate definitions used in the original and final SAPs for Study 314, this medical officer will use the final SAP because it was done prior to un-blinding and it is consistent with the SAPs of the four POI studies previously submitted.

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.

This medical officer agrees with the sponsor's selected primary populations — in their final SAP for Study 314 — for the efficacy analyses (i.e., the MITT population) and safety analyses (i.e., the safety population).

Statistical Methods in Study 314: 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 GI[2] 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. The estimates for time

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.

For the four QOL questionnaires, summary tables, including the proportion of patients who responded to each category for each question at each time point, were made. The change from baselines in the QOL questionnaires was also analyzed at each post baseline time point.

Medical Reviewer's Comments: **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. In addition, the QOL secondary endpoints have multiple analyses (i.e., the change in SF-8, CGQL, and Adolor-Inflexxion Questionnaire scores, compared to baseline, from PODs 2, 5, 14, and 28).

Dr. Sonia Castillo, the statistical reviewer, provided more information regarding the statistical analyses in Study 314 and the other POI studies in her review. Please see her review.

6.1.4 Efficacy Findings

Disposition of patients: In the five important POI efficacy studies (Studies 302, 308, 313, 001, and 314), 953 and 942 BR patients were part of the MITT population (the primary statistical population for efficacy evaluation) for the 12 mg alvimopan and placebo treatment groups, respectively (see Table 14). The gynecologic surgery patients in Studies 302, 308, 313, and 001 are not included in Table 14 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 14 because the sponsor did not desire approval of this dosage regimen. Study 314 did not have a 6 mg alvimopan dose.

Table 14: Disposition of BR patients in the five major POI studies[1]

Study	Treatment Groups	Total number of ITT 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[2]	Placebo	312
	12 mg alvimopan	317
Total	Placebo	924
	12 mg alvimopan	953
All BR efficacy patients[3]		1877

1 The five major efficacy studies were Studies 302, 308, 313, 001, and 314. Study 314, which is shaded was submitted in this second-cycle. The MITT population was the primary statistical population for efficacy evaluation.

2 Study 314 only contained two treatment groups (12 mg of alvimopan and placebo). However, Studies 302, 308, 313, and 001 had three treatment groups (6 mg and 12 mg of alvimopan and placebo). The 6 mg alvimopan dose is not displayed because the sponsor [redacted] proposed the 12 mg alvimopan dose in this second cycle NDA submission.

3 The BR population is the only surgical population under efficacy consideration because the gynecologic surgery population demonstrated no efficacy.

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

Medical Reviewer's Comments: 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 15 features baseline demographics (including age, race, gender, and BMI) and baseline characteristics of the BR population in the five important POI studies (i.e., Studies 302, 308, 313, 001, and 314). Table 15 displays only the 12 mg alvimopan and placebo treatment groups because the sponsor is not seeking approval of the 6 mg alvimopan dose. 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 15: Demographics of the BR population in Studies 302, 308, 313, 001, and 314

	Study 14CL302		Study 14CL308		Study 14CL313		Study 14CL314		Study GSK001	
Characteristic	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

Medical Reviewer's Comments: 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 16 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 16 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 16: Surgery characteristics for the MITT BR population in the important POI studies[1]

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	239	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 btn 1st dose and surgery (hours)										
Mean (SD)	3.2 (1.63)	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)

1 The five important efficacy studies were Studies 302, 308, 313, 001, and 314
Reference: Final Study Report for Study 314, ISE, Table 6.

Table 17 displays the pooled BR surgery characteristics of the important POI studies.

Table 17: Surgery characteristics from the pooled important POI studies[1] (MITT BR population)

Small BR	62 (6.7)	74 (7.8)	136 (7.2)
Total large BR	862 (93.3)	879 (92.2)	1741 (92.8)
Left large BR	490 (53)	496 (52.0)	986 (52.5)
Right large BR	334 (36.1)	352 (36.9)	686 (36.5)
Other	38 (4.1)	31 (3.3)	69 (3.7)

1 The five important efficacy studies were Studies 302, 308, 313, 001, and 314
Reference: ISE, Table 3.1, Page 160

Medical Reviewer's Comments: **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. This medical officer recommends that the sponsor 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. Patients with

prior abdominal surgery have a greater likelihood of developing adhesions, and these patients may be at higher risk for POI. Therefore, in future POI trials, the sponsor should collect past surgical history of abdominal and/or pelvic surgeries.

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 18. 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 18: Primary indications for surgery in the BR population in the five POI efficacy studies[1]

Colon or Rectal Cancer	133 (67.5)	151 (53.7)	174 (57.6)	353 (75.4)[2]	265 (42.1)	1076 (57.3)
Diverticular Disease	38 (19.3)	50 (17.8)	35 (11.6)	N/A	100 (15.9)	223 (11.9)
Ostomy Reversal	7 (3.6)	23 (8.2)	20 (6.6)	N/A	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)	N/A	75 (11.9)	121 (6.4)
Rectal Prolapse	3 (1.5)	3 (1.1)	9 (3.0)	N/A	10 (1.6)	25 (1.3)
Intestinal Fistula	2 (1.0)	5 (1.8)	6 (2.0)	N/A	5 (0.8)	18 (1.0)
Small Bowel Cancer	0 (0)	7 (2.5)	3 (1.0)	N/A	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)

1 The five important efficacy studies were Studies 302, 308, 313, 001, and 314
2 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.

Medical Reviewer's Comments: 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.

Efficacy Results:

Pre-specified primary endpoint in Study 314: In Study 314, the pre-specified, two-component, composite, primary efficacy endpoint (**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 **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 **GI2** from placebo was 0.4, 0.7, and 0.9 days, respectively (sees Table 19).

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 0.8, 0.9, 1.2, 0.8, and 0.9 days, respectively. The 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.

Table 19: Time to GI2[1] in days in BR patients in the POI studies

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 **GI2** was the primary efficacy endpoint in Study 314; it was one of seven secondary endpoints in Studies 308 and 313; it was one of 25 secondary endpoints in Study 001; and it was a post-hoc endpoint in Study 302.
2 The 6 mg alvimopan dose is not shown in Studies 302, 308, 313, and 001.
3 N is the number of patients in the efficacy database in the BR patients (the TAH patients were not included).
4 The p-value of the results of Study 314 is bolded because **GI2** was the pre-specified primary efficacy endpoint. The p-values of the results of Studies 302, 308, 313, and 001 are not bolded because GI2 was not the primary efficacy endpoint and there were multiple alvimopan doses in these studies.

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.

Medical Reviewer's Comments: 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.

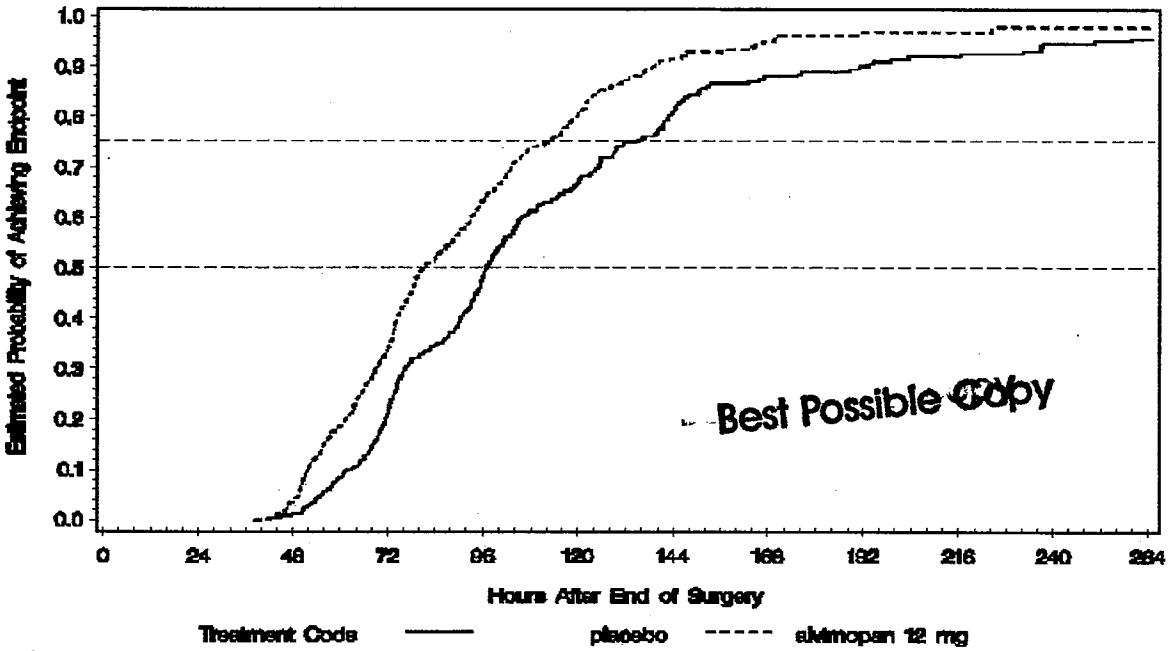
Demonstration of a large change in time to GI2 at the 25th percentile is more clinically meaningful than demonstration of a large change in time to GI2 at the 75th percentile. In other words, the earlier a study treatment improves recovery of the upper and lower GI tracts, compared to placebo, the better the treatment. However, this medical officer believes that 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.

This medical officer believes that the reduction of time to recovery of the upper and lower GI tracts at the 75th percentile of the 12 mg alvimopan group, compared to the placebo group, (i.e., 0.8 to 1.2 days) is clinically meaningful. 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).

The sponsor has achieved one of the requirements that the DGP stated at the October 2000 end of phase 1 meeting between the sponsor and the DGP. In this meeting the DGP stated that "A clinically meaningful difference in recovery time will be one that is on the order of a day or so, not just a few hours".

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 (the primary efficacy endpoint) in Study 314



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

Medical Reviewer's Comments: **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 significantly 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). In Study 314, Ready and DOW were two of 14 original pre-specified endpoints; in Studies 302, 308, and 313, they two of 7 pre-specified secondary endpoints; and in Study 001 they were two of 25 pre-specified secondary endpoints.

Ready (an important pre-specified secondary endpoint): Table 20 presents **Ready**, an important secondary endpoint, in the BR surgery subpopulation in the five important POI trials (i.e., Studies 302, 308, 313, 001, and 314).

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 0.9, 0.8, 1.0, 0.2, and 0.8 days, 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.

Table 20: Time to Ready[1] in days in BR patients

Study	Treatment Group	N	25th Percentile (SE)	50th Percentile (SE)	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

1 Ready was one of 7 secondary endpoints in Studies 302, 308, and 313; one of 25 secondary endpoints in Study 001; and one of 14 original secondary endpoints in Study 314.
2 The 6 mg alvimopan dose is not shown in Studies 302, 308, 313, and 001
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.

Medical Reviewer's Comments: **This medical officer agrees with the sponsor that 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 two important secondary endpoints (time to Ready and DOW). Therefore, this medical officer will consider 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).**

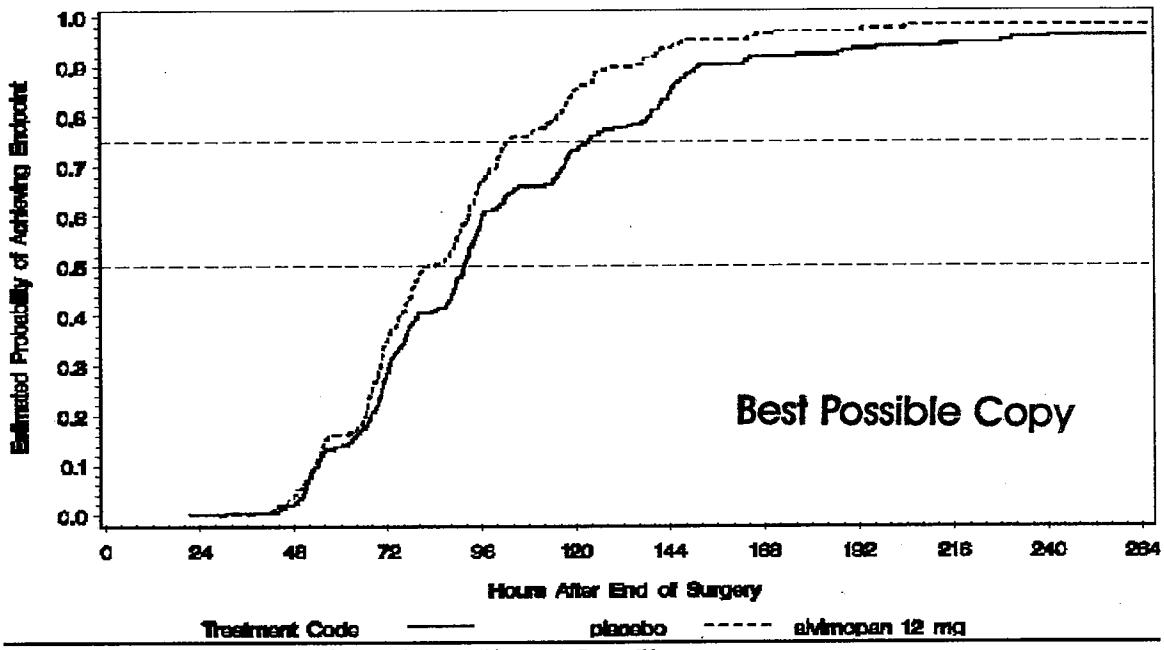
As expected, the times to Ready at the 25th, 50th, and 75th percentiles were greater than the times to GI recovery (i.e., GI2 and GI3) for the treatment groups. One would expect that the upper and lower GI tracts to recover before surgeons believed the patients were ready to be discharged from a GI surgical standpoint.

This medical officer believes that 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 (i.e., 0.8 to 1 day) are clinically meaningful. 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 1 day). Therefore, the results of the important time to upper and lower GI tract recovery endpoint (i.e., GI2) correlated with the results of

the important time to discharge endpoint (i.e., Ready). This correlation supports the efficacy of 12 mg alvimopan dose in the treatment of POI.

Figure 2 displays the Kaplan-Meier estimates for **Ready** (an important secondary efficacy endpoint) for the 12 mg alvimopan and the placebo treatment groups in Study 314.

Figure 2: Kaplan-Meier estimates for time to Ready in Study 314



Reference: Final Study Report for Study 314, Figure 4, Page 73.

Medical Reviewer's Comments: **The Kaplan-Meier curves of the time to achieve Ready demonstrate that after about 60 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 about 60 hours, the patients in the alvimopan group achieve Ready significantly earlier than patients in the placebo group.**

DOW (an important pre-specified secondary endpoint): Table 21 displays the time to **DOW**, an important secondary endpoint, in the BR surgery subpopulation in the five important POI trials (i.e., Studies 302, 308, 313, 001, and 314).

The change in **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. The HRs for the **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 21: Time to DOW[1] in days in BR patients

Study	Treatment Group[2]	N	25th Percentile (Median Time to Event)	75th Percentile (Median Time to Event)	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

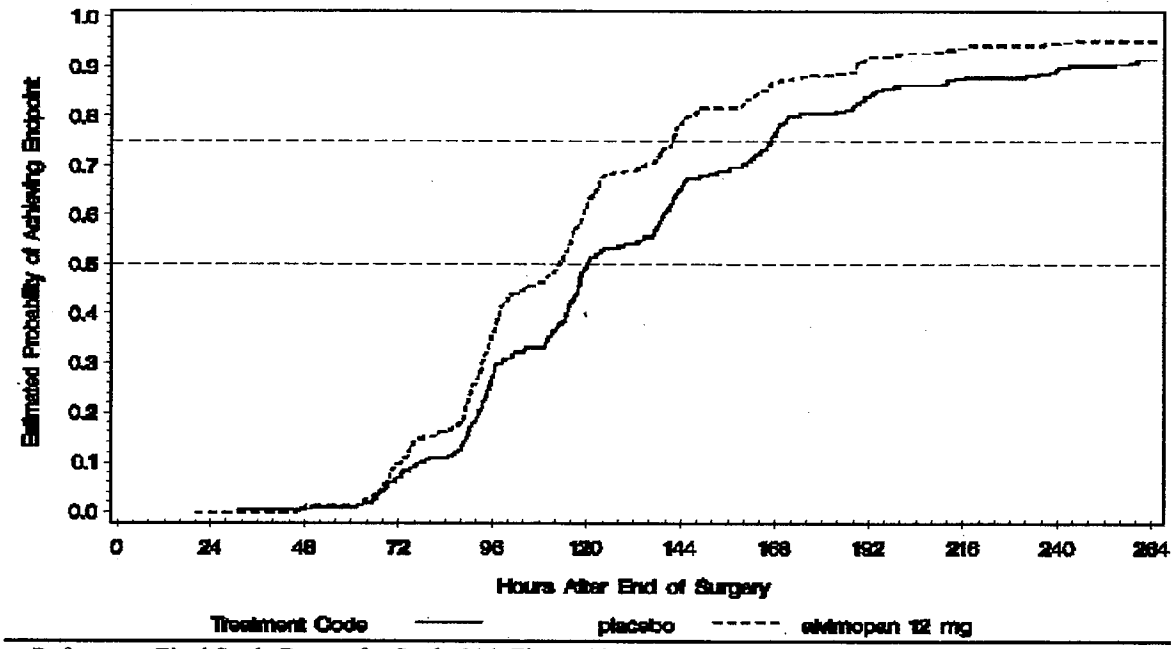
1 **DOW** was one of 7 secondary endpoints in Studies 302, 308, and 313; one of 25 secondary endpoints in Study 001; and one of 14 secondary endpoints in Study 314.
2 The 6 mg alvimopan dose is not shown in Studies 302, 308, 313, and 001
Reference: Final Study Report for Study 314, Table 15, Page 83; 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.

Medical Reviewer's Comments: 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.

This medical officer believes that the change in the times to achieve DOW at the 75th percentile for the 12 mg alvimopan dose, compared to placebo, in Studies 302, 308, 313, and 314 (i.e., 0.8 to 1.5 days) are clinically meaningful. 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 1 day. 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 1 day. 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.

Figure 3 displays the Kaplan-Meier estimates for **DOW** (an important secondary efficacy endpoint) for the 12 mg alvimopan and the placebo treatment groups in Study 314.

Figure 3: Kaplan-Meier estimates for time to DOW in Study 314



Reference: Final Study Report for Study 314, Figure 10, Page 82.

Medical Reviewer's Comments: **The Kaplan-Meier curves of the time to achieve DOW demonstrate that after about 72 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 about 72 hours, the patients in the alvimopan group achieve DOW significantly earlier than patients in the placebo group.**

Unlike the Kaplan-Meier curves of the time to achieve GI2, the Kaplan-Meier curves of the time to achieve DOW are step-like. This is probably because surgeons write discharge orders when they make inpatient rounds during the day and patients are not likely to be discharge during the night.

The 12 mg alvimopan and placebo Kaplan-Meier curves for the times to GI2, Ready, and DOW begin to separate at about 48, 60, and 72 hours, respectively. One would expect that patients would achieve GI recovery (e.g., GI2) first, and then be ready to be discharged from a surgical standpoint (e.g., Ready), and finally be ready to be discharged, considering all their medical issues (e.g., DOW).

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 22 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 22 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 22: Time to GI3[1] (in hours) in BR patients

Study	Treatment	N	25th Percentile (95% CI)	50th Percentile (95% CI)	75th Percentile (95% CI)	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**[2]
	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	142.5		
	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**[2]
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

1 GI3 was the primary efficacy endpoint in Studies 302, 308, 313, and 001. In the middle of Study 001, the primary endpoint was changed to GI2. GI3 was a post-hoc endpoint in Study 314.

2 Statistically significant for the primary efficacy endpoint

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.

Medical Reviewer's Comments: **For the 12 mg alvimopan group, the results of time to GI3 were not as efficacious as the results of the time to GI2. This medical officer believes that 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.**

This medical officer believes that 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 23 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). The timing of "prolonged hospital stay" was determined by the investigator.

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 and PSD 8 to 15.7% by PSD 5.

Table 23: Responder Analyses by PSD for the GI2, Ready, and DOW time-to-event endpoints in Study 314

	PSD	Placebo (%) n=242	Alvimopan 12 mg (%) n=242	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.

<u>Medical Reviewer's Comments</u>: **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 24 displays the mean length of hospital stay by POD in the BR population in the five important POI studies. Table 24 presents results by POD; in contrast, the DOW and Ready endpoints assesses length of hospital stay by PSD. In addition, Table 24 presents departure (i.e., the time from the end of surgery to the time the patient leaves the hospital); in contrast, DOW and Ready assess time to discharge order written and time to Ready (the time the surgeon believes the patient is ready to go home).

Table 24: Mean length of hospital stay in days (by POD) in the BR population in the five important POI studies

	[redacted]				
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

Medical Reviewer's Comments: The results by POD are consistent with the results of Ready and DOW. This adds support to the efficacy of the 12 mg alvimopan dose in the treatment of POI in BR patients.

Subgroup Exploratory Efficacy Analyses:
The POI studies included three main types of surgery (i.e., large BR, small BR, and TAH). 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. This medical officer found that there was no efficacy in the gynecology surgery subgroup (i.e., TAH) in the POI studies that were submitted in the first-cycle. Because efficacy was not established in the gynecology subpopulation in the first cycle, TAH surgery patients were not enrolled in the sponsor's POI study submitted to this second-cycle (i.e., Study 314).

Additionally, the sponsor changed their proposed surgery population in their proposed POI indication. In the first-cycle NDA the original proposed indication was acceleration of the "time to recovery of GI function following abdominal or pelvic surgery" and in this second-cycle the currently proposed indication is acceleration of the "time to upper and lower GI recovery following partial large or small bowel resection surgery with primary anastomosis".

Tables 25 and 26 present **GI2** and **DOW** according to the two GI surgery types (i.e., partial small BR and partial large BR).

Table 25: Time to GI2 in hours in large BR and small BR patients

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	72 (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)		

1 The hazard ratio (HR) of alvimopan to placebo was calculated from a Cox proportional hazards model
2 Nominal p-values were calculated by the Wald Chi-square tests for pair-wise comparisons between alvimopan and placebo
The 6 mg alvimopan dose is not shown in Studies 308, 313, and 001. Study 302 is not presented because there were no small BR surgery patients.
Reference: Dr. Sonia Castillo's exploratory analysis

Table 26: Time to DOW in hours in large BR and small BR patients

Surgery Type	Study	Treatment Group	N	Median (95% CI)	Hazard Ratio (95% CI)	p-value
Large Bowel	308	Placebo	126	140	1.48 (1.15,1.91)	0.002
		Alvimopan 12 mg	128	119 (21)		
	313	Placebo	130	122	1.34 (1.04,1.73)	0.024
		Alvimopan 12 mg	137	118 (4)		
	314	Placebo	290	121	1.36 (1.15,1.61)	<0.001
		Alvimopan 12 mg	286	114 (7)		
Small Bowel	308	Placebo	16	134	3.96 (1.60,9.85)	0.003
		Alvimopan 12 mg	11	90 (44)		
	313	Placebo	12	126	1.84 (0.87,3.87)	0.11
		Alvimopan 12 mg	23	90 (36)		
	314	Placebo	22	115	1.77 (1.01,3.11)	0.047
		Alvimopan 12 mg	31	90 (25)		

1 The hazard ratio (HR) of alvimopan to placebo was calculated from a Cox proportional hazards model
2 Nominal p-values were calculated by the Wald Chi-square tests for pair-wise comparisons between alvimopan and placebo
The 6 mg alvimopan dose is not shown in Studies 308, 313, and 001. Study 302 is not presented because there were no small BR surgery patients. Study 001 is not presented here because of different discharge practices in Europe, Australia, and New Zealand
Reference: Dr. Sonia Castillo's exploratory analysis

Medical Reviewer's Comments: Even though the numbers of patients who received partial small bowel surgery were small, there appears to be efficacy of the 12 mg alvimopan dose in this population. Therefore, this medical officer agrees with the sponsor's proposal to include the following two surgery types in the POI indication: partial small BR and partial large BR.

Opioid Use and Efficacy:
Table 27 displays the median and mean opioid consumption (in morphine equivalents) prior to surgery, during surgery, and after surgery in the BR surgery patients.

Table 27: Median and mean (SD) opioid consumption[1] pre, intra, and post operatively in BR patients

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)

1 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

Medical Reviewer's Comments: 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.

This medical officer believes that no clear relationship exists between pre, intra, and postoperative opioid use and the efficacy of alvimopan in the treatment of POI (i.e., GI2 and DOW). Therefore, this medical officer believes that the efficacy of alvimopan, compared to placebo, in the treatment of POI is not confounded by opioid consumption.

6.1.5 Clinical Microbiology

A clinical microbiology review is not applicable to this product.

6.1.6 Efficacy Conclusions

This medical officer believes that efficacy of the 12 mg alvimopan dose in the treatment of POI — in BR surgery patients — was established because the 12 mg alvimopan dose, compared to placebo, 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.

In summary, the clinical data from the five important adequate and well-controlled POI trials support the efficacy of the sponsor's proposed 12 mg alvimopan treatment regimen for the sponsor's proposed POI indication "acceleration of the time to upper and lower GI recovery following partial large or small bowel resection surgery with primary anastomosis". In addition, this medical officer believes that use of the 12 mg of alvimopan regimen in BR surgery patients in the treatment of POI represents effective treatment of a serious aspect (prolonged hospitalization) of a serious disease (POI) that has no currently approved products.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

In the entire alvimopan development program consisting of 49 studies (i.e., 48 completed alvimopan studies and data from the six-month interim analysis from ongoing OIC Study 14) there were 24 deaths. Of the 24 deaths, 22 occurred in the POI population and 2 occurred in the OIC population; none occurred in the chronic constipation and healthy subject populations.

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%) patients died who received alvimopan and 9 out of 1365 (0.66%) patients died 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 28, 29, 30, respectively.

Table 28: Narratives of the eight deaths in the 12 mg alvimopan treatment group in the POI trials

	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
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 [redacted]
2	14CL302-22-01118	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 [redacted]
3	14CL313-13-13015	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	5/14/02 **Left Large BR**	5/22/02 [redacted]

			underwent unsuccessful PTCA and stent placement in his RCA. Post-procedure had ventricular fibrillation and had cardioversion. On POD 9 had tachypnea and hypoxia and died on POD 10.		
4	GSK001-273	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. Study medication was withdrawn on POD 5. On POD 9 had anastomosis leak with peritonitis. Had exploratory laparotomy. Died on POD 16.	5/13/03 **Large BR**	5/15/03
5	**GSK001-448**	Death unknown cause	63 year old male (with history of AAA) had left large BR for rectal cancer. Postoperative course complicated by mild wound infection. Stopped treatment on POD 7. Discharged on POD 13. Died during sleep at home on POD 16. No autopsy was performed.	5/5/04 **Left Large BR**	5/21/04
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**	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.	2/3/05 **Left Large BR**	2/6/05
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**	

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.

Medical Reviewer's Comments: This medical officer believes that the CV death in Patient 14CL302-22-01118 (i.e., CHF), was unlikely related to alvimopan because this patient had an improbable temporal sequence from the administration of alvimopan (he only received one dose of alvimopan and developed CHF 6 days later and died 13 days later) and his death can be reasonable explained by other factors (i.e., his underlying CAD).

This medical officer believes that the CV death in Patient 14CL313-13-13015 (i.e., acute MI) was possibly related to alvimopan because there was a reasonable temporal sequence and the possibility of alvimopan involvement cannot be excluded because of the existence of

reports of MIs associated with alvimopan use in the longer-term OIC trials. However, other factors (e.g., he was high risk for MI prior because of his underlying DM, increased age, and surgical stress) may be the only reason for his death. This medical officer will look at a possible CV signal in section 7.4.1 of this review.

This medical officer believes that the CV death in Patient GSK001-273 (i.e., acute CVA) was possibly related to alvimopan because there was a reasonable temporal sequence and the possibility of alvimopan involvement cannot be excluded because of the existence of reports of serious CVs associated with alvimopan use in the longer-term OIC trials. However, other factors (e.g., she was high risk for a CVA because of increased age and she had known carotid artery disease and a recent TIA within one month of surgery) may be the only reason for her death. This medical officer will look at a possible CV signal in section 7.4.1 of this review.

This medical officer believes that the possible CV death in Patient 14CL314-360240 (i.e., acute MI and CHF but also had ARF, acute liver failure, and acute respiratory failure) was possibly related to alvimopan because there was a reasonable temporal sequence and the possibility of alvimopan involvement cannot be excluded because of the existence of reports of serious CVs associated with alvimopan use in the longer-term OIC trials. However, other factors (e.g., she was high risk for an MI because of many CV risk factors like increased age and HTN and she had a stressful surgical procedure) may be the only reasons for her death. This medical officer will look at a possible CV signal in section 7.4.1 of this review. In addition, it is not clear if this patient had a primary CV death or if this patient had a secondary MI and CHF due to her multiorgan failure (ARF, acute liver failure, and acute respiratory failure).

This medical officer believes that the four non-CV deaths in the 12 mg alvimopan group in the POI studies were unlikely related to alvimopan because the deaths had an improbable temporal sequence from the administration of alvimopan and/or the deaths can be reasonable explained by other factors (e.g., complications of underlying disease).

Table 29: Narratives of the five deaths in the 6 mg alvimopan treatment group in the POI trials

	Patient ID	Cause of Death	Medical History	Surgery Date / Type	Date of Onset / 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 [redacted] 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 [redacted]
2	**14CL308-31-01182**	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 [redacted]
3	**14CL313-05-05005**	Autopsy showed acute purulent peritonitis, severe CAD	47 year old white female [with a past history of morbid obesity, 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 [redacted] On POD 23 [redacted], she was found at home unresponsive.	6/24/02 **small BR**	7/17/02 [redacted]
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 [redacted]
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 [redacted] 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 [redacted] Her septic shock worsened and she died on POD 20 [redacted]	1/14/04 **Left Large BR**	1/18/04 [redacted]

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

Medical Reviewer's Comments: This medical officer believes that the CV death in Patient 14CL308-31-01182 (i.e., pulmonary embolus) was unlikely related to alvimopan because this patient had a pulmonary embolus at baseline prior to surgery and had major risk factors for PE (e.g., metastatic cancer liver cancer, metastatic colon cancer, recent surgery). Furthermore, there was an improbable temporal sequence from the administration of alvimopan to onset of the PE symptoms on POD 13.

This medical officer believes that the four non-CV deaths in the 6 mg alvimopan group in the POI studies were unlikely related to alvimopan because the deaths had an improbable temporal sequence from the administration of alvimopan and/or the deaths can be reasonable explained by other factors (e.g., complications of underlying disease).

Table 30: Narratives of the nine deaths in the placebo treatment group in the POI trials

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 [redacted]
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 [redacted] She was readmitted on [redacted] for abdominal abscess and gram negative septic shock. She developed aspiration pneumonia.	11/6/02 **Right Large BR**	11/21/02 [redacted]
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 [redacted]
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 [redacted]
5	001-263	Cause of death not reported	61 year old male (with history of colon cancer) discharged on POD 7. POD 9 [redacted] died	11/13/03	[redacted]
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 [redacted] On POD 6 [redacted] developed wound infection then hypotension. Laparotomy showed abdominal abscess, peritonitis, and anastomotic leakage. Had ileostomy. On POD 8 [redacted] she died due to septic shock.	3/12/04 **Right Large BR**	3/16/04 [redacted]
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 [redacted]. Treatment was discontinued because of reinsertion of nasogastric tube. On POD 7 [redacted] because of worsened abdominal distension and tenderness had an exploratory laparotomy and found to have infected	7/21/04 **Left Large BR**	8/29/04 [redacted]

			free fluid and greater omentum fat necrosis (probably from pancreatitis). His condition was improving, but on POD 39 [redacted] had massive UGIB and died on POD 40		
8	14CL314-40191	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 [redacted]
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 [redacted]

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.

OIC population:

In the OIC population (i.e., Studies 217, 304, 11, 12, 13, and 14), there were two deaths in patients who received alvimopan (see Table 31). The Study 14 results are based on the six-month safety interim analysis that was submitted.

Table 31: Narrative of the two deaths in the OIC trials[1]

Patient #[2]	Cause of Death	Narrative Text	Date of Onset & Date of Death
13C304-003-001	COPD exacerbation	64 year old female (with a history of COPD, asthma, chronic bronchitis, CAD, HTN, GERD and history of cancer with right lung lobectomy) with chronic pain on methadone. She received **alvimopan** 0.5 mg/day and on Study Day 9 was diagnosed and treated with an outpatient pneumonia and COPD exacerbation. She did not take the study drug on Days 11, 13-18, and 20. She stopped the study medication on Day 21. She was started on fluconazole for a "fungal lung infection". On Study Day 32 she was admitted to a hospital with SOB, upper abdominal pain, nausea, vomiting, and diarrhea. She was found to have an acute respiratory acidosis and hypoxia. Later on Day 32, she developed asystole thought secondary to respiratory failure.	Day 24 [redacted]
Study 14-1818	Acute MI	93 year old female with OA with ischemic heart disease and received **alvimopan**. She had SOB for one week and hospitalized. In hospital had cardiac arrest and intubated. ST wave elevation and positive troponin consistent with a MI. She died within 24 hours of admission.	Day 51 [redacted]

1 The OIC studies included Studies 304, 217, 11, 12, 13, and the 6-month interim safety analysis of Study 14.
2 The shaded events were CV deaths
Reference: Final Study Report for Study 13C304, Section 12.3.4.1, Pages 123-124 and May 15, 2006 [redacted] submission, Page 17.

Medical Reviewer's Comments: This medical officer believes that the death of Patient 13C304-003-001 was unlikely related to alvimopan because she had known COPD and probably restrictive lung disease (lobectomy) and obstruction lung disease (COPD). This patient had COPD exacerbations in the past without being on alvimopan. In addition, she was off alvimopan when her symptoms of her COPD exacerbation started.

This medical officer believes that the CV death in Patient Study 14-1818 (i.e., acute MI) was possibly related to alvimopan because there was a reasonable temporal sequence and the possibility of alvimopan involvement cannot be excluded because of the existence of reports of serious CVs associated with alvimopan use. However, other factors (e.g., she had ischemic heart disease and she was 93 years old) may be the only reason for her death. This medical officer will look at a possible CV signal in section 7.4.1 of this review.

7.1.2 Other Serious Adverse Events

This section contains the most frequent nonfatal SAEs in the four populations (i.e., POI, OIC, chronic constipation, and healthy subjects).

POI population:
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 32 for a listing of the most common nonfatal SAEs in the POI studies.

Table 32: Nonfatal SAEs (≥0.5% of the population) in the nine POI trials

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

Medical Reviewer's Comments: 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.

For a discussion of the serious CV events in the POI trials see Section 7.1.4.

OIC population:
Of the 28 nonfatal SAEs in the OIC population, 23 and 5 occurred in patients who received alvimopan and placebo, respectively [23 out of 578 (4.0%) patients had nonfatal SAEs who received alvimopan and 5 out of 207 (2.4%) patients had nonfatal SAEs who received placebo]. See Table 33 for a listing of the most common nonfatal SAEs in the OIC studies in noncancer patients that were originally submitted in this NDA (i.e., Studies 217, 304, and 11). Two phase 3, 12-week OIC studies in noncancer patients were ongoing at the time of this second-cycle submission and therefore were not submitted in this second-cycle. These two phase 3 studies were completed during the NDA review cycle. Additionally, Study 14, the ongoing OIC study, was not submitted and thus its results are not presented in Table 33.

Table 33: Nonfatal SAEs (≥0.3% of the population) in the OIC trials[1]

Patients with at least one nonfatal SAE	5 (2.4)	7 (3.2)	16 (4.9)	0 (0)	23 (4.0)
Abdominal pain	0 (0)	0 (0)	3 (0.9)	0 (0)	3 (0.5)
Chest pain	1 (1.5)	1 (0.5)	1 (0.3)	0 (0)	2 (0.3)
Asthma	0 (0)	0 (0)	2 (0.6)	0 (0)	2 (0.3)
Back pain	0 (0)	1 (0.5)	1 (0.3)	0 (0)	2 (0.3)
Pyelonephritis	0 (0)	1 (0.5)	1 (0.3)	0 (0)	2 (0.3)

1 The OIC population included patients in the submitted single dose studies (Studies 13C208 and 13C209) and submitted 3-6 week studies (Studies 13C217, 13C304, and 11). Since the complete results of OIC Studies 12, 13, and 14 have not been submitted, they are not included in this table.
Reference: Adapted from ISS, Table A.3.6.2, Page 3262

Medical Reviewer's Comments: There were very few SAEs in this OIC population in both treatment groups. There were no significant differences in SAES in this OIC population.

The OIC patients had a lower percentage of SAEs compared to the POI patients. This is probably because the OIC patients were healthier than the POI patients. The mean age of POI patients was about 60 years old and about 57% of the POI patients had cancer. In contrast, the mean age of the OIC patients was about 51 and these OIC patients were likely to be cancer free (patients with a nonskin cancer malignancy within the past five years were excluded from participation).

Chronic constipation population:
There were two nonfatal SAEs in the chronic constipation population. One patient in the placebo group had myocarditis and one patient in the alvimopan 8 mg group had GERD.

Healthy subject population:
There was only one nonfatal SAE (i.e., cellulitis in a patient who received alvimopan and loperamide in Study 28CL201) in the healthy subject population. This event was unrelated to the study drug.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Table 34 delineates the most common reasons for discontinuation in the nine POI studies.

Table 34: The most common reasons for study discontinuation in the POI population

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
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.

Medical Reviewer's Comments: 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.

7.1.3.2 Adverse events associated with dropouts

This section contains the most frequent treatment-emergent AEs (TEAEs) that resulted in study discontinuation in the POI population (see Table 35).

Table 35: Patients who had TEAEs (≥ 0.3% in any group) causing discontinuation in the POI population

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
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.

Medical Reviewer's Comments: 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.

7.1.3.3 Other significant adverse events

Please see Section 7.14 for a complete discussion of the CV events in the POI and OIC studies.

7.1.4 Other Search Strategies

Since a possible CV signal was seen in the longer-term OIC studies, this medical officer analyzed CV events in the submitted POI and OIC studies.

CV Safety in the POI Studies

Sponsor's CV Safety Results in the POI Population: Table 36 displays selected CV results — **from the sponsor** — in the POI safety population. The incidence and relative risk of the following CV events are presented in Table 36: all cause death; CV death; CHF (fatal and nonfatal); nonfatal unstable angina; serious arrhythmia (fatal and nonfatal); and the four-component, composite Antiplatelet Trialist's Collaboration (APTC) endpoint which includes four mutually exclusive events — nonfatal MI, nonfatal CVA (i.e., ischemic and hemorrhagic CVA), vascular death (i.e., cardiac, cerebrovascular, venous thromboembolic, hemorrhagic, or other vascular death), and death due to unknown cause. The APTC composite endpoint does not include the following nonfatal CV events: unstable angina, TIA, or peripheral vascular events. The events in Table 36, reported by the sponsor, were not adjudicated — no independent data monitoring committee (IDMC) was established during the conduct of these nine POI trials.

Table 36: Sponsor's results — Incidence and Relative Risk (95% CI) of selected CV events in the POI population[1]

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Death (all cause)[6,7]	n, (%)	9 (0.66)	5 (0.56)	8 (0.48)	13 (0.50)
	RR[2] (95% CI)		**0.84** (0.28,2.51)	**0.74** (0.28,1.90)	**0.76** (0.32,1.76)
Death (CV)[3,6,7]	n, (%)	2 (0.15)	1 (0.11)	4 (0.24)	5 (0.19)
	RR[2] (95% CI)		**0.76** (0.07,8.4)	**1.65** (0.30,9.0)	**1.31** (0.25,6.7)
CHF[7] (fatal & nonfatal)	n, (%)	17 (1.25)	6 (0.67)	13 (0.79)	19 (0.73)
	RR[2] (95% CI)		**0.54** (0.21,1.36)	**0.63** (0.31,1.30)	**0.58** (0.30,1.12)
Unstable angina[7] (nonfatal)	n, (%)	4 (0.29)	0	0	0
	RR[2] (95% CI)		—	—	—
Serious arrhythmia[7] (fatal & nonfatal)	n, (%)	28 (2.05)	16 (1.78)	26 (1.58)	42 (1.61)
	RR[2] (95% CI)		**0.87** (0.47,1.60)	**0.77** (0.44,1.30)	**0.78** (0.49,1.26)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
1) Nonfatal MI[5]	n, (%)	7 (0.51)	5 (0.56)	7 (0.42)	12 (0.46)
	RR[2] (95% CI)	[illegible]	**1.09** (0.35,3.41)	**0.83** (0.29,2.35)	**0.90** (0.35,2.27)
2) Nonfatal CVA[6]	n, (%)	4 (0.29)	2 (0.22)	1 (0.06)	3 (0.11)
	RR[2] (95% CI)	[illegible]	**0.76** (0.14,4.1)	**0.21** (0.02,1.85)	**0.39** (0.09,1.75)
3) Death (vascular)[6]	n, (%)	0	1 (0.11)	2 (0.12)	3 (0.11)
	RR[2] (95% CI)	[illegible]	—	—	—
4) Death (unknown cause)[6]	n, (%)	1 (0.07)	0	1 (0.06)	1 (0.04)
	RR[2] (95% CI)	[illegible]	—	**0.83** (0.05,13.2)	**0.52** (0.03,8)

1 The POI population included the following nine trials: Studies 206, 213, 214, 302, 306, 308, 313, 314, and 001.
2 The RR (relative risk) of the alvimopan group compared to the placebo group
3 CV death includes death due to MI, CHF, arrhythmia, pericarditis, pulmonary emboli, and cerebrovascular causes.
4 Antiplatelet Trialist's Collaboration (APTC) composite endpoint includes non-fatal MI, non-fatal CVA, death with unknown cause, and vascular death. These APTC events were mutually exclusive.
5 The sponsor combined the following three MedDRA terms to classify an MI: MI, acute MI, and myocardial ischemia.
6 One patient with an MI in the 12 mg alvimopan group died. This patient is included in the death from all cause, CV death, and vascular death categories; however, this patient is not included in the nonfatal MI category. One patient with a CVA in the 12 mg alvimopan category died. This patient is included in the death from all cause, CV death, and vascular death categories; however, this patient is not included in the nonfatal CVA category.
7 These events were not mutually exclusive.
Reference: September 13, 2006 submission, Table 3.1, Pages 12-13; September 13, 2006 submission, Table 4.1, Page 16; September 25, 2006 submission, Table 4.1, Pages 44-45; and September 25, 2006 submission, Table 4.2, Page 46.

<u>Medical Reviewer's Comments</u>: The CV events in Table 36 were not adjudicated by the sponsor because no CV signal was seen at the time of the conduct of the nine efficacy/safety POI trials (from January 2000 to December 2005). A possible alvimopan-associated CV signal was seen by the sponsor after the completion of the POI studies (i.e., in the spring of 2006). Since the sponsor did not have IDMCs adjudicate CV events during the conduct of the POI studies; the events in Table 36 were obtained from investigator reports. This medical officer believes that since no CV signal was seen during the conduct of the POI trials the need for IDMCs could not have been foreseen by the sponsor.

From these selected investigator CV reports, there is no CV signal in the alvimopan groups compared to placebo. The relative risks of alvimopan compared to placebo for the following CV events are < 1: death, CHF, unstable angina, serious arrhythmia, nonfatal MI, nonfatal CVA, and death due to unknown cause. The only event that had a higher incidence in the alvimopan groups compared to placebo was CV death (vascular death, a subset of CV death, also had a higher incidence in the alvimopan groups compared to placebo). However, as noted above, the incidence of all cause death was lower in the alvimopan groups compared to placebo. The small number of CV deaths may explain the slight imbalance in the incidence of CV death in the alvimopan and placebo groups. Additionally, the imbalance of CV deaths in the alvimopan and placebo groups may have been due to chance.

The lower incidence of CHF in the alvimopan groups, compared to the placebo group, may have been due to a shorter hospital stay in the alvimopan groups. Surgery patients with fewer days in the hospital may have received less fluid and therefore may be less likely to develop CHF.

Thus, according to the investigator CV AE reports, there is no evidence of a CV signal associated with alvimopan use in the POI population.

Medical Reviewer's Unblinded Adjudication of CV Events in the POI Population: Since a possible alvimopan-associated CV signal (i.e., MI) was seen in one of the longer-term OIC trials, this medical officer and Dr. Nhi Beasley, a medical officer in the Division of Cardiovascular and Renal Products, adjudicated possible MIs in the POI population. This medical officer reviewed the narratives of the 19 nonfatal MI (12 and 7 MIs in the alvimopan and placebo groups, respectively), the narrative of the 1 fatal MI, and the narratives of all deaths (see Tables 28, 29, and 30 in Section 7.1.1). According to the sponsor, the following three MedDRA terms were used to code the MIs presented in Table 36: acute myocardial infarction, myocardial infarction, and myocardial ischemia. This medical officer and Dr. Beasley adjudicated events into the following three categories: definite MI, likely MI, and unlikely MI. A definite MI was classified as having two of the following three characteristics, as reported in the narratives: symptoms typical of a MI, ECG changes, and elevated cardiac enzymes. Additionally, events that had certain cardiac tests (including echocardiograms and catheterizations) that "confirmed" an MI and events that required coronary intervention (i.e., PTCA, stents, and/or CABG) were characterized as definite MI. A likely MI was delineated when the investigator reported that a MI occurred but less than two of the three MI characteristics were missing (i.e., symptoms, ECG changes, and/or enzymes). Finally, an unlikely MI was defined as an event that did not fit into the definite MI or likely MI categories.

Table 37 displays the narratives of this medical officer's unblinded adjudicated definite and likely MIs. This medical officer did not include the narratives of the unlikely MIs in Table 37. After adjudication, there were 14 likely or definite MIs (11 and 3 in the alvimopan and placebo groups, respectively) in the POI studies.

Table 37: Narratives of definite and likely MIs in the POI trials

	Subject # (Study #)	Definite or Likely MI (# of study drug doses)	Narrative
1	05-0006 (213)	Likely MI (4 doses)	67 year old male with CAD (s/p MI, PTCA and stent), colon cancer, HTN, hyperlipidemia, COPD, CFR, gout) was randomized to **placebo** and underwent a left large BR on 1/19/01 (POD 0). On POD 0 had hypotension and on POD 1 had non-Q wave MI and ARF. Stopped study drug on POD 2. On POD 4 had GI bleed and on POD 11 had wound dehiscence and intestinal perforation. On POD 22, EGD showed EE. Discharged on POD 48.
2	13-1235 (308)	Definite MI (8 doses)	71 year old female (with diverticulitis, colon polyp, SBO, GERD, lower GI bleed, CAD, HTN, TIA, pneumonia, COPD, asthma, morbid obesity, sleep apnea, depression, osteoarthritis, osteoporosis, lysis of GI adhesions, smoker) received **placebo** and underwent left LB resection on [redacted] (POD 0). On POD 2 had AF which resolved also had elevated CPK and CPK MB but troponin T was negative. On POD 4 her troponin T levels were increased and she was diagnosed with a non-Q wave MI. Also had AF with RVR and mild CHF. Last study drug was given on AM of POD 4. On POD 10 she was discharged. At home on POD 12 had CP and diagnosed with unstable angina (post-infarct angina) and COPD exacerbation and troponin was negative and ECG was negative. On POD 15, cath showed single vessel CAD with thrombus resolving.
3	08-0733 (314)	Likely MI (1 dose)	50 year old male (with Crohn's disease, myocarditis, CAD, obesity, gastric ulcers) received **placebo** (only one dose) and underwent a small bowel resection on [redacted] (POD 0). On POD 0 after the surgery had an MI (had CP). He discontinued study drug before POD 1. He was discharged on POD 7.
4	02-0022 (001)	Definite MI (1 dose)	82 year old female (with CABG, AF, CHF, ischemic heart disease, DM type II, colon cancer) received **6 mg of alvimopan** then underwent BR for colon cancer on [redacted] OD 0). Only received one dose (study drug not given on POD 1). On POD 0 developed a gap metabolic acidosis and required prolonged intubation postsurgery in ICU. The acidosis resolved (thought maybe due to metformin). On POD 2 developed AF with RVR and a MI (positive troponin I, ST changes)
5	34-0520 (001)	Definite MI (1dose)	58 year old female (with colon cancer) received **6 mg of alvimopan** on [redacted] POD 0) before large BR for colon cancer. During anaesthesia induction, 2.5 hours after receiving alvimopan she developed an arrhythmia leading to a MI (treated with adrenaline). The surgery was canceled. An echo and cardiac cath confirmed the MI.
6	53-1306 (302)	Likely MI (6 doses)	53 year old male (with colon cancer of the ascending colon, MI in 1996, PTCA with stents, hyperlipidemia, GERD, anemia) received **6 mg of alvimopan** on [redacted] POD 0) then underwent a right large BR. On POD 0 had nausea. Last study drug on AM POD 3. End of the study ECG on POD 3 there was "age undetermined inferior posterior infarct" (the investigator thought this was clinically significant). The screening ECG was normal. No signs or symptoms and no treatment was given. Discharged on POD 3. No additional AEs on follow-up contact on POD 11.
7	03-3014 (313)	Definite MI (10 doses)	69 year old male (with colon cancer, HTN, diverticulitis, DM, obesity) received **12 mg of alvimopan** then underwent right LB resection on [redacted] POD 0). Received study drug until AM of POD 5 and he was discharged on POD 5. On POD 33 had CP and diagnosed with a MI. Cath showed 3-vessel disease and had 3-vessel CABG on POD 35 (CPK MB elevated on POD 35). On POD 37 had AF.
8	01-0702 (314)	Definite MI (2 doses)	75 year old female (with chronic diverticulitis with colon obstruction, gout, HTN, CVA with residual facial drop, depression, DM type II, CVD s/p carotid endarterectomy, constipation, GERD, CAD, obesity) received **12 mg of alvimopan** on [redacted] (POD 0) before undergoing a left large BR and ventral hernia repair. On POD 1 had hypoventilation due to excessive narcotics (treated with stopping narcotics and naloxone). Later on POD 1 had ECG changes associated with elevated enzymes (diagnosed with acute MI). Last study dose received in AM on POD 1. Concurrent with MI had multisystem organ dysfunction and required parental

			nutrition. On POD 13 had surgical wound dehiscence which was repaired. On POD 32 required intubation which resolved and she was discharged on [redacted] (around POD 68).
9	25-0025 (314)	Likely MI (3 doses)	70 year old male (with cecal colon cancer, CAD (s/p stent), aborted lateral MI, HTN, remote smoker, COPD, PUD, RA) had a right colon resection after had received the **12 mg alvimopan** dose then had right large BR on [redacted] POD 0). On POD 1, he had a MI and CHF. On POD 2, he had a POI which required a NGT. He discontinued study medication after PM POD 1 dose. Later he was discharged.
10	36-0240 (314)	Likely MI (6 doses)	78 year old female (with colon cancer with liver metastasis, HTN, s/p gastric ulcer surgery, osteoarthritis, s/p left hip arthroplasty) received **12 mg of alvimopan** and then had a left large BR resection and ureteral stent placed on [redacted] POD 0). On POD 3, she had an MI, ARF, CHF, and respiratory failure and study medication was discontinued after AM POD 3 dose. On POD 4, she had acute liver failure. Discharged to hospice care on POD 6 and she died of acute liver and renal failure on POD 9. Also had AF with rapid ventricular response.
11	15-0970 (001)	Definite MI (10 doses)	75 year old male (with CAD, 90% RCA stenosis, colon cancer) **received 12 mg of alvimopan** on [redacted] (POD 0) before large BR for colon cancer. Received study drug until POD 5 [redacted] On POD 1, positive troponin CPK, and CPK MB (ECG non ST elevation MI) and no symptoms. On [redacted] POD 6) had CP and ECG showed ST wave elevations and had PTCA of RCA with stent. On POD 7 had AF and on POD 8 had pacemaker placed. Thought to have had two MIs.
12	19-0257 (001)	Definite MI (3 doses)	68 year old male (with HTN, smoking, CAD, PVD s/p fem-pop, PVD stent) received **12 mg of alvimopan** on [redacted] POD 0) before large BR for rectal cancer. Stopped study drug after PM dose on POD 1 because of stoma (protocol violation). On POD 5 [redacted] developed femoral artery occlusion and had thrombectomy and stent. On POD 6 (but POD 1 from PVD stenting) ECG showed MI, CPK elevated, troponin I elevated, and no symptoms. Discharged on POD 14.
13	14C1313-13-13015	Definite MI[2] (12 doses)	64 year old male (with a history of recurrent colon cancer, prostate cancer, renal cell carcinoma, and DM) received **12 mg of alvimopan** then underwent 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.
14	32-0586 (314)	Likely MI (2 doses)	73 year old male (with colon cancer, chronic gastritis, HTN, COPD, DM type II, hyperlipidemia, chronic AF, CHF, bladder cancer, chronic alcohol use, severe obstructive sleep apnea, PVD, peripheral neuropathy) received **12 mg of alvimopan** on [redacted] (POD 0) before undergoing a left large BR. His last dose was the AM POD 1 dose. On POD 1 he experienced acute respiratory failure and alcohol withdrawal. Both of these events resolved on POD 37. Also noted he had a "small demand MI", AF exacerbation, UTI, malnutrition.

1 This patient also developed multiorgan failure including CHF, acute renal, liver, and respiratory failure and subsequently died.
2 This patient also died.
Reference: Narratives from original study reports and information requests.

<u>Medical Reviewer's Comments</u>: The following is a summary of the 11 POI patients who had adjudicated definite or likely MIs in the alvimopan groups:

- **Mean age of 69.5 years;**
- **9 of 11 (82%) patients had prior vascular disease or diabetes;**
- **10 of 11 (91%) patients had prior vascular disease, diabetes, or were at increased CV risk of having a MI;**
- **The median postoperative day of the MI was POD 3;**
- **The median postoperative day of the last alvimopan dose was POD 2.5; and**
- **The median number of alvimopan doses received during the study was 3 doses.**

Therefore, the patients in the alvimopan groups who had definite or likely MIs were at extremely high risk of having a MI.

Of the 11 POI patients on alvimopan who had a MI, the following 3 patients had their events several days after the last alvimopan dose:

- **Patient #7 (03-3014) had his alvimopan dose on POD 5 and developed a MI on POD 33;**
- **Patient #12 (19-0257) had his alvimopan dose on POD 1 and developed a MI on POD 6; and**
- **Patient #14 (32-0586) had his last alvimopan dose on POD 1 and developed a MI on POD 23.**

This medical officer believes that these three MIs were not likely related to alvimopan given the temporal sequence of alvimopan administration and the MI.

Table 38 displays definite or likely MIs in the POI trials from this medical officer's adjudication and the sponsor's MI results.

Table 38: Comparison of FDA and sponsor's analyses of MI in the POI trials

FDA[1]	3 (0.22)	11 (0.42)	1.9 (0.5-6.7)
FDA[2]	3 (0.22)	7 (0.27)	1.2 (0.3-7.3)
Sponsor[3]	7 (0.51)	13 (0.50)	1.0 (0.4-2.4)

1 This is from this medical officer's and Dr. Beasley's adjudication. This represents definite or likely MIs. Please see "Medical Reviewer's Unblinded Adjudication of CV Events in the POI Population" in this section for the adjudication rules.
2 This is derived from FDA[1] analyses. This excludes the three patients (who received alvimopan) who did not have a strong temporal relationship between alvimopan administration and development of the MI.
3 This includes 1 fatal MI and 19 nonfatal MIs in Table 36. The 19 nonfatal MIs are under the nonfatal MI category; whereas, the one fatal MI is classified under the CV death category (it is also classified under the vascular death and all cause death categories).
Reference: Table 36 and the sponsor's narratives from the original study reports and the responses to information requests.

<u>Medical Reviewer's Comments</u>: **Excluding the three alvimopan cases which do not appear to have a temporal relationship of alvimopan administration and the development of a MI, this medical officer believes a MI signal is less likely in the POI population.**

The lack of an overall CV signal for all cause death, CV death, CHF, nonfatal CVA, nonfatal MI, serious arrhythmia, and unstable angina, supports the CV safety of alvimopan for short-term use in POI. Moreover, the large total POI safety database of

3975 surgery patients (2610 and 1365 received alvimopan and placebo, respectively, supports the lack of a CV signal in the POI population.

CV Safety in the OIC Studies

Sponsor's CV Safety Results in the OIC Population: Table 39 displays the APTC results — **from the sponsor** — in the OIC safety population [consisting of the 3-12 week OIC studies (i.e., Studies 13C217, 13C304, 11, 12, and 13) and the planned 6-month interim analysis of the ongoing, one-year safety study (i.e., Study 14)]. The APTC is a four-component composite endpoint which includes four mutually exclusive events — nonfatal MI, nonfatal CVA (i.e., ischemic and hemorrhagic CVA), vascular death (i.e., cardiac, cerebrovascular, venous thromboembolic, hemorrhagic, or other vascular death), and death due to unknown cause. The APTC composite endpoint does not include the following nonfatal CV events: unstable angina, TIA, or peripheral vascular events.

The events in Table 39, reported by the sponsor, were not adjudicated — no IDMC was established during the conduct of these OIC trials. After a higher proportion of patients in the alvimopan group, compared to the placebo group, developed MIs in Study 14, an IDMC was established. Therefore, all future CV events that occur in ongoing Study 14 will be adjudicated by the IDMC.

Table 39: Sponsor's results — Incidence and Relative Risk (95 % CI) of APTC events in the OIC population[1]

			OIC (3-12 Weeks)		Study 14 (6-month Interim Analysis)	
			Placebo (N=2610)	Alvimopan[2] (N=1365)	Placebo (N=407)	Alvimopan[3] (N=388)
	APTC[5]	n (%)	2 (0.08)	1 (0.07)	0	0
		RR[4] (95% CI)		0.44 (0.04-4.85)		
1)	Nonfatal MI	n (%)	2 (0.08)	1 (0.08)	0	6 (1.55)
		RR (95% CI)		0.22 (0.02-1.69)		
2)	Nonfatal CVA	n (%)	1 (0.19)	1 (0.08)	0	1 (0.19)
		RR (95% CI)		0.44 (0.03-7.35)		
3)	Death (Vascular)	n (%)	0	1 (0.08)	0	1 (0.19)
		RR (95% CI)				
4)	Death (Unknown Cause)	n (%)	0	0	0	0
		RR (95% CI)				

1 The 3-12 week OIC population included patients in Studies 13C217, 13C304, 11, 12, and 13; whereas, the 6-month interim analysis of CV events are presented for ongoing, one-year Study 14.
2 Alvimopan doses were 0.5 mg q day, 1 mg q day, 0.5 mg BID, and 1 mg BID.
3 Alvimopan dose is 0.5 mg BID
4 The RR (relative risk) of the alvimopan group compared to the placebo group.
5 APTC composite endpoint includes the following mutually exclusive events: non-fatal MI, non-fatal CVA (ischemic and hemorrhagic), death with unknown cause, and vascular death (cardiac, cerebrovascular, venous

thromboembolic, hemorrhagic, or other vascular death). This does not include unstable angina, TIA, or nonfatal peripheral vascular events.
6 The sponsor combined the following two MedDRA terms to classify an MI: MI and acute MI.
7 The one vascular death in the alvimopan group was due to a fatal MI.
Reference: September 13, 2006 submission (response to our September 6, 2006 information request), Table 3.2, Pages 14-15 and Table 4.2, Page 17 and September 21, 2006 submission (response to our September 6, 2006 information request), Table 3, Pages 23-24, and Table 3, Page 28

Medical Reviewer's Comments: In the 3-12 week OIC studies, there were few CV events. In the 3-12 week OIC studies, 3 and 3 patients on the alvimopan and placebo groups, respectively, had a nonfatal MI, nonfatal CVA, vascular death, or death due to unknown cause with a RR (95% CI) of 0.44 (0.08,2.38). Thus, there is no evidence of a CV signal in the shorter term OIC studies (i.e., 3-12 weeks).

There were a higher proportion of CV events in 6-month interim analysis of ongoing Study 14 compared to the 3-12 week OIC studies.

In the sponsor's non-adjudicated 6-month interim analysis of Study 14, there was an imbalance of CV events in the alvimopan groups, compared to placebo. There were 8 APTC events in the alvimopan group, compared to no APTC events in the placebo group. Of the 8 APTC events in the alvimopan group, 7 were MIs (6 nonfatal and 1 fatal). Since there was about a 2:1 ratio of alvimopan patients to placebo patients, the effective MI ratio was 3.5:0.

Medical Reviewer's Unblinded Adjudication of CV Events in the Study 14: This medical officer and Dr. Beasley reviewed the narratives of the 6 MIs in Table 39 and the narratives of the deaths (see Table 31 in Section 7.1.1) in 6-month interim analysis of Study 14. According to the sponsor, the following two MedDRA terms were used to code the MIs presented in Table 39: acute myocardial infarction and myocardial infarction. This medical officer and Dr. Beasley adjudicated events into the following three categories: definite MI, likely MI, and unlikely MI. A definite MI was classified as having two of the following three characteristics, as reported in the narratives: symptoms typical of a MI, ECG changes, and elevated cardiac enzymes. Additionally, events that had certain cardiac tests (including echocardiograms and catheterizations) that "confirmed" an MI and events that required coronary intervention (i.e., PTCA, stents, and/or CABG) were characterized as definite MI. A likely MI was delineated when the investigator reported that a MI occurred but less than two of the three MI characteristics were missing (i.e., symptoms, ECG changes, and/or enzymes). Finally, an unlikely MI was defined as an event that did not fit into the definite MI or likely MI categories.

Table 40 displays the narratives of this medical officer's unblinded adjudicated definite and likely MIs in Study 14. This medical officer did not include the narratives of the unlikely MIs in Table 40. After adjudication, there were 7 likely or definite MIs in the alvimopan group (6 nonfatal and 1 fatal) and no MIs in the placebo group in Study 14.

Table 40: Narratives of definite or possible MIs in Study 14

	Patient (Study)	Day of study treatment (Site)	Event	Narrative
1[1]	759 (Study 14)	38 days (Glasgow)	Definite MI	71 year old male with COPD and with stable angina and the following CV risk factors: hyperlipidemia, increased age, obesity (BMI=38.2), glucose intolerance, family history of CV disease. He received **alvimopan**. He had severe chest pain (CP), ST depression, and positive troponin-I. Catheterization showed diffuse, triple vessel disease.
2	805 (Study 14)	85 days (Glasgow)	Definite MI	75 year old female with OA and COPD with the following CV risk factors: HTN, smoker, obesity, hyperlipidemia received **alvimopan** and later developed CP, ST elevation, and positive troponin-I.
3	18322 (Study 14)	65 days (Tampa, FL)	Definite MI	62 year old female with reflex sympathetic dystrophy (RSD) and OA and peripheral vascular disease (PVD), HTN, hyperlipidemia, and smoker and received **alvimopan**. She had CP, q waves and ST elevations on EKG, and positive troponin. The catheterization showed critical LAD artery disease and got stented.
4	18321 (Study 14)	111 days (Tampa, FL)	Definite MI	48 year old male with chronic back pain with history of CV disease, HTN and obesity and received **alvimopan**. He felt weak and had arm pain and developed syncope, ST segment elevation, and positive troponin. During hospitalization had AF and cardiogenic shock requiring intraaortic balloon pump (IABP) and vasopressors. Catheterization showed severe two-vessel disease and he had two stents placed.
5	1818 (Study 14)	58 days	Definite MI[1]	93 year old female with OA with ischemic heart disease and received **alvimopan**. She had SOB for one week and hospitalized. In hospital had cardiac arrest and intubated. ST wave elevation and positive troponin consistent with a MI. She died within 12 hours of admission.
6[2]	17641 (Study 14)	106 days	Definite MI	68 year old male, with chronic shoulder pain and DM, who received **alvimopan**. Had CP at rest, EKG showed inferior T wave inversions, positive troponin, and echocardiogram showed apical left ventricle hypokinesis with normal ejection fraction. Catheterization showed 5-vessel disease and he had a stent of the RCA placed and returned two weeks later for two additional stents. Patient resumed alvimopan treatment and 2 weeks later he was readmitted with CV symptoms for 3 days. The alvimopan was discontinued during the hospitalization. He was discharged from the hospital. Short after discharge, on the same day, he had more symptoms and was readmitted and had an angioplasty.
7[3]	**807 (Study 14)**	30 days	Possible MI, Definite CHF[3]	75 year old female with osteoarthritis with a history of AF, CHF, HTN, TIA, hyperlipidemia, obesity, smoker, and aortic valve regurgitation. She received alvimopan. She had SOB and CHF and was hospitalized. Her echo showed severe mitral regurgitation (MR), moderate to severe tricuspid regurgitation (TR) and severe hypokinesis of the left ventricle.

1 This patient died of an MI (fatal MI). She was not included in the vascular component of the 4 component APTC endpoint; not the nonfatal component.
2 This patient had evidence of re-challenge.
3 This patient was coded by the sponsor as a MI. However, this medical officer adjudicated this as CHF.
Reference: From the sponsor's response to our information requests.

Medical Reviewer's Comments: This medical officer and Dr. Beasley adjudicated a total of 6 MIs (5 nonfatal and 1 fatal). In contrast, the sponsor's non-adjudicated reports had a total of 7 MIs (6 nonfatal and 1 fatal). The discrepancy is with Patient # 807 (shown in row 7) in Table 40. This medical officer and Dr. Beasley thought this patient, with a history of severe valvular disease and CHF, most likely developed CHF without an MI.

Thus, according to the sponsor the effective ratio of MIs in the alvimopan group compared to the placebo group is 3.5:0 and according to my adjudication the effective ratio was 3:0. This discrepancy does not change the conclusions regarding CV toxicity with long-term alvimopan use in OIC patients.

The following is a summary of the 6 OIC patients in Study 14 who had a definite MI (by this medical officer's and Dr. Beasley's unblinded adjudication) in the alvimopan group:

- **The mean age was 69.5 years old**
- **5 out of 6 (83%) of patients had vascular disease or diabetes;**
- **6 out of 6 (100%) of patients had vascular disease, diabetes, or multiple CV risk factors; and**
- **The mean time to event was 77.2 days and the median time to event was 75 days.**

Thus, the patients who had MIs in the alvimopan group were at very high risk of having a MI.

Please see Section 7.29 for a discussion of the CV risk factors and Section 7.1.8.3 for blood pressure results in the alvimopan and placebo groups in the OIC studies.

In conclusion, there may be a CV signal associated with alvimopan use in longer-term OIC patients.

Opioid withdrawal symptoms

Because alvimopan is an opioid antagonist, it has the potential to reverse the analgesic effects of opioids and/or contribute to opioid withdrawal. The opioid withdrawal symptoms are less likely in the POI population because patients who took a significant amount of opioids the week prior to surgery were excluded from participation. In Studies 302, 308, 313, and 001, patients who took more than one opioid dose the week before surgery were excluded and in Study 314 patients who took more than three opioid doses the week before surgery were excluded. The opioid withdrawal symptoms are more likely in the OIC population because these patients had to be on chronic opioids prior to enrollment in the studies and these OIC studies were much longer in duration then the POI studies (e.g., about 1 week for the POI studies and 3 to 6 weeks for the OIC studies). Thus, this medical officer will examine withdrawal symptoms and/or reversal of analgesia in the POI and OIC studies.

Medical Reviewer's Comments: In the POI trials, patients were excluded from participation if they were taking a significant amount of opioids prior to surgery (e.g., in

Studies 302, 308, 313, and 001, patients who 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 — were excluded). In addition, patients in the chronic constipation and the majority of the healthy subject trials were not allowed to participate if they were taking opioids. In contrast to the POI, chronic constipation, and healthy subject populations; the OIC population only included patients on chronic opioid therapy (i.e., cancer and noncancer patients with OIC who required chronic opioid therapy for pain relief). Table 41 displays the most common treatment-emergent AEs in the completed multiple-dose OIC studies (i.e., Studies 13C217, 13C304, and 011). Opioid withdrawal is characterized by the following symptoms: return of the pain, abdominal pain, diarrhea, shaking, drug craving, nausea, vomiting, insomnia, restlessness, rhinorrhea, sneezing, yawning, sweating, tears, muscle aches, and tachycardia. Table 41 displays a higher incidence of abdominal pain, nausea, diarrhea, vomiting, hyperhidrosis (excessive sweating) in the patients who received alvimopan compared to the placebo group. In addition, there appears to be a higher incidence of the abdominal pain, nausea, and diarrhea as the dose of alvimopan increases. This may suggest possible opioid withdrawal. These multiple dose studies from to 3- 6 weeks studies did not include a subjective opioid withdrawal scale as part of the safety monitoring; thus, one cannot conclusively state if true opioid withdrawal has occurred in these patients.

Table 41: Most common TEAEs (≥ 3% in any alvimopan group or ≥ 1% in the placebo group) in the OIC studies[1]

Adverse event	Placebo (N=187) n (%)	Alvimopan 0.5 mg QD (N=66) n (%)	Alvimopan 0.5 mg BID (N=130) n (%)	Alvimopan 1 mg QD (N=197) n (%)	Alvimopan 1 mg BID (N=130) n (%)
Abdominal pain	25 (13)	9 (14)*	22 (17)*	37 (19)*	36 (28)*
Nausea	15 (8)	4 (6)	9 (7)	20 (10)*	13 (10)*
Headache	9 (5)	1 (2)	15 (12)*	11 (6)*	9 (7)*
Diarrhea	7 (4)	2 (3)	9 (7)*	22 (11)*	18 (14)*
Flatulence	8 (4)	2 (3)	8 (6)*	13 (7)*	10 (8)*
Vomiting	6 (3)	4 (6)	6 (5)*	11 (6)*	5 (4)*
Hyperhidrosis	5 (3)	0	10 (8)*	7 (4)*	4 (3)
Abdominal distension	9 (5)	1 (2)	4 (3)	5 (3)	8 (6)*
Back pain	4 (2)	0	8 (6)*	8 (4)*	5 (4)*
Fatigue	9 (5)	0	8 (6)*	5 (3)	2 (2)
Gamma-glutamyltransferase increased	6 (3)	3 (5)*	2 (2)	3 (2)	2 (2)
Weight increased	6 (3)	0	6 (5)*	1 (<1)	5 (4)*
Rhinorrhea	3 (2)	0	6 (5)*	3 (2)	2 (2)
Dyspepsia	4 (2)	0	5 (4)*	3 (2)	(<1)
Gastroenteritis viral	1 (<1)	3 (5)*	1 (<1)	4 (2)	1 (<1)
Tremor	0	0	5 (4)*	1 (<1)	1 (<1)
Nasal congestion	4 (2)	3 (5)*	0	2 (1)	0
Insomnia	0	0	5 (4)*	1 (<1)	0

1 The OIC population included patients in the submitted single dose studies (Studies 13C208 and 13C209) and submitted 3-6 week studies (Studies 13C217, 13C304, and 11). Since OIC Studies 12, 13, and 14 have not been submitted, they are not included in this table.
Reference: ISS, Table 52, Page 91.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

All of the phase 2 and 3 POI trials had similar procedures to evaluate AE data. AEs were obtained from abnormalities in physical exams (PEs) including vital signs (measured twice daily during the Treatment Period), laboratory tests (measured prior to and at hospital discharge), and ECGs (collected prior to and at hospital discharge). Laboratory testing included CBC with differential, hepatic panel, basic metabolic panel, LDH, and urinalysis. During the Treatment Period (POD 0 to POD 10 or until hospital discharge), patients received routine postoperative care including frequent vital signs, daily brief physical exams, possible laboratory testing, and possible other special studies. Investigators interviewed patients twice daily and they monitored the patient's hospital records.

The follow-up procedures for eliciting AEs differed in the phase 2 and 3 trials. Safety Study 306 had the most complete follow-up. In Study 306, patients had a follow-up visit 7- 10 days after the last dose of study drug. In Study 306, if the patients were home, they would follow-up with investigators during a clinic visit; or if the patients were hospitalized, they would be visited by investigators in the hospital. The follow-up visit included a complete PE with vital signs, laboratory tests including EKGs, and assessments of AEs.

Patients in the other POI trials (i.e., Studies 206, 213, 214, 302, 308, 313, 314, and 001) had suboptimal follow-up. In these studies, a follow-up visit was scheduled if the patient was still hospitalized; however, no follow up visit was obtained for outpatients. In Studies C206 and 214 and in the initial 302 protocol, outpatients were called within 14 days after hospital discharge. In Studies 213, 308, 313, 314, 001, and in the amended 302 study, outpatients were called 5-7 days after the last dose of study medication. During the telephone call, AE assessments were obtained; however, no PEs, vital signs, laboratory tests, or ECGs were obtained. In these patients, the last thorough evaluation was obtained on the hospital discharge day. If the outpatients did not respond to three telephone calls, then a certified letter was sent to the patients.

Medical Reviewer's Comments: Study 306's follow-up clinic visit to evaluate possible AEs — 7-10 days after the last dose of study treatment — was acceptable because of the following reasons:

1) **95% of alvimopan and its metabolite are out of the body in five days after the last dose (according to Dr. Sue Chih Lee, the pharmaceutics reviewer); and**
2) **The proposed duration of alvimopan use is short (i.e., up to 7.5 days of therapy or a maximum of 15 doses).**

However, the eight other studies (206, 213, 214, 302, 308, 313, 314, and 001) did not have optimal follow-up periods. Hospitalized patients in one of the POI clinical trials may have achieved the primary efficacy endpoint (e.g., GI2 or GI3) in the morning and may have been sent home later that day. In this example, the discharge procedures (including physical exam, laboratory testing, and ECG testing) 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, these patients may have had suboptimal post-treatment follow-up. A follow-up telephone call five to seven days after hospital discharge may not have elicited all AEs.

The essential question is whether the follow safety evaluations were adequate to detect the overwhelming number of MIs in the POI population. Table 42 presents the post-discharge safety surveillance of the BR patients in the United States. About 88% of the BR patients had a follow-up telephone call and about 75% of patients had a follow-up telephone call ≥ 6 days after the last dose of study drug. Since MIs are likely to produce symptoms, this medical officer believes that the safety surveillance was reasonable to detect the majority of MIs (e.g., silent MIs would not be detected).

Table 42: Post-discharge safety surveillance of BR patients in the U.S. POI studies

Had investigator follow-up visit, n (%)	**Anytime**	**1 (0.1)**	**3 (0.2)**
Had a follow-up telephone call, n (%)	**Anytime**	**861 (87)**	**1484 (88)**
	1-5 days after	116 (12)	242 (14)
	6-14 days after	700 (74)	1181 (70)
	≥ 15 days after	45 (5)	61 (4)
Readmission rates, n/N (%)		58/695 (8)	35/1099 (3)

Reference: September 21, 2006 submission (response to our September 6, 2006 information request), Table 3, Page 123.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

All of the six phase 3 POI trials used the Medical Dictionary for Regulatory Activities Terminology (MedDRA) version 4.1 nomenclature to classify AEs. Of the three phase 2 POI trials, two used MedDRA and one (Study 206) used Coding Symbols for a Thesaurus of Adverse Reactions Terms (COSTART) nomenclature to classify AEs. The AEs in Study 206 that were originally coded with COSTART were re-coded using MedDRA version 4.1.

7.1.5.3 Incidence of common adverse events

The sponsor defined the following adverse events:

1) Adverse events (AEs): An AE was defined as any untoward medical occurrence in a subject administered a pharmaceutical product whether or not it had a causal relationship with that treatment. An AE could be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study medication, whether or not considered causally associated with the use of the study medication. Laboratory values deemed clinically significant by the investigator, regardless of causal relationship, were reported as AEs.

2) Treatment-emergent AEs (TEAEs): An AE was defined as treatment-emergent if it had an onset date and time on or after the date and time of the first dose of study medication administration, including up to 7 days after the last dose of study medication, and if it was not present at baseline or was present at baseline but increased in severity after the start of study medication treatment.

3) Treatment-related AE: An AE was considered to be treatment-related if the investigator thought there was a reasonable possibility that the study medication caused the response. A reasonable possibility was meant to convey that there were facts, evidence, or arguments to suggest a causal relationship. These may include, for example, a temporal relationship, a pharmacologically predicted event, or a positive dechallenge or rechallenge. An AE was considered to be unrelated to treatment if the investigator thought there was not a reasonable possibility that the study medication caused the response.

4) An SAE was defined as any event that met the following criteria:

   - Resulted in death or was life-threatening (immediate risk of death from the event as it occurred). This definition was not intended to include an AE that, had it occurred in a more severe form, might have caused death;
   - Resulted in persistent or substantial disability or incapacitation. This definition was not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, diarrhea, or sprained ankle;
   - Resulted in hospital readmission;
   - Resulted in prolongation of an existing hospitalization as determined by the investigator. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline did not meet the definition of an SAE, nor did social or convenience admission to a hospital or prolongation of hospitalization for social or convenience reasons not due to the occurrence of an AE;
   - Was a congenital anomaly or birth defect; or
   - Required medical or surgical intervention to prevent any of the above outcomes.

After the occurrence of an AE or SAE, the investigator was required to follow proactively each subject and provide further information on the subject's condition. All AEs and SAEs

documented at a previous visit or contact and designated as ongoing were reviewed at subsequent visits or contacts. SAEs were followed until resolution, until the condition stabilized, until the event was otherwise explained, or until the subject was lost to follow-up.

7.1.5.4 Common adverse event tables

Table 43 displays the most frequent common TEAEs (≥1%) in the POI population.

Table 43: Common TEAEs (≥1%) in the POI population

	placebo	alvimopan			
		1-3 mg	6 mg	12 mg	total
	(N=1365)	(N=62)	(N=898)	(N=1650)	(N=2610)
Preferred Term (1)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with at least one AE	1172 (85.9)	60 (96.8)*	712 (79.3)	1451 (87.9)*	2223 (85.2)
NAUSEA	699 (51.2)	39 (62.9)*	367 (40.9)	858 (52.0)	1264 (48.4)
VOMITING	299 (21.9)	13 (21.0)	152 (16.9)	305 (18.5)	470 (18.0)
ABDOMINAL DISTENSION	177 (13.0)	12 (19.4)*	79 (8.8)	176 (10.7)	267 (10.2)
PYREXIA	189 (13.8)	6 (9.7)	84 (9.4)	165 (10.0)	255 (9.8)
HYPERTENSION	143 (10.5)	3 (4.8)	100 (11.1)	171 (10.4)	274 (10.5)
PRURITUS	135 (9.9)	4 (6.5)	70 (7.8)	162 (9.8)	236 (9.0)
HYPOTENSION	124 (9.1)	6 (9.7)	79 (8.8)	118 (7.2)	203 (7.8)
HEADACHE	106 (7.8)	6 (9.7)*	68 (7.6)	141 (8.5)	215 (8.2)
FLATULENCE	105 (7.7)	9 (14.5)*	56 (6.2)	143 (8.7)	208 (8.0)
INSOMNIA	106 (7.8)	8 (12.9)*	68 (7.6)	131 (7.9)	207 (7.9)
CONSTIPATION	104 (7.6)	5 (8.1)	37 (4.1)	160 (9.7)*	202 (7.7)
HYPOKALAEMIA	103 (7.5)	1 (1.6)	55 (6.1)	114 (6.9)	170 (6.5)
TACHYCARDIA	103 (7.5)	6 (9.7)*	53 (5.9)	96 (5.8)	155 (5.9)
DIARRHOEA	98 (7.2)	2 (3.2)	66 (7.3)	88 (5.3)	156 (6.0)
POSTOPERATIVE ILEUS	127 (9.3)	1 (1.6)	44 (4.9)	66 (4.0)	111 (4.3)
ANAEMIA	74 (5.4)	5 (8.1)*	40 (4.5)	89 (5.4)	134 (5.1)
DYSPEPSIA	65 (4.8)	11 (17.7)*	33 (3.7)	98 (5.9)*	142 (5.4)
OLIGURIA	78 (5.7)	2 (3.2)	54 (6.0)	67 (4.1)	123 (4.7)
BODY TEMPERATURE INCREASED	82 (6.0)	0	44 (4.9)	73 (4.4)	117 (4.5)
DIZZINESS	61 (4.5)	3 (4.8)	29 (3.2)	87 (5.3)	119 (4.6)
ANXIETY	48 (3.5)	2 (3.2)	29 (3.2)	68 (4.1)	99 (3.8)
URINARY TRACT INFECTION	52 (3.8)	3 (4.8)*	23 (2.6)	68 (4.1)	94 (3.6)
POSTOPERATIVE INFECTION	64 (4.7)	0	27 (3.0)	53 (3.2)	80 (3.1)
HYPOMAGNESAEMIA	48 (3.5)	0	26 (2.9)	53 (3.2)	79 (3.0)
ABDOMINAL PAIN	44 (3.2)	4 (6.5)*	17 (1.9)	59 (3.6)	80 (3.1)
ATELECTASIS	51 (3.7)	0	21 (2.3)	42 (2.5)	63 (2.4)
OEDEMA PERIPHERAL	45 (3.3)	3 (4.8)*	24 (2.7)	42 (2.5)	69 (2.6)
BACK PAIN	36 (2.6)	2 (3.2)	19 (2.1)	56 (3.4)	77 (3.0)
URINARY RETENTION	31 (2.3)	0	23 (2.6)	57 (3.5)*	80 (3.1)
CONFUSIONAL STATE	50 (3.7)	2 (3.2)	23 (2.6)	31 (1.9)	56 (2.1)
POST PROCEDURAL PAIN	34 (2.5)	10 (16.1)*	29 (3.2)	30 (1.8)	69 (2.6)

BREATH SOUNDS DECREASED	42	(3.1)	9	(14.5)*	20	(2.2)	29	(1.8)	58	(2.2)
DYSPNOEA	43	(3.2)	5	(8.1)*	15	(1.7)	30	(1.8)	50	(1.9)
POSTOPERATIVE WOUND COMPLICATION	41	(3.0)	1	(1.6)	21	(2.3)	30	(1.8)	52	(2.0)
URINE OUTPUT DECREASED	43	(3.2)	0		4	(0.4)	39	(2.4)	43	(1.6)
PHARYNGOLARYNGEAL PAIN	31	(2.3)	2	(3.2)	13	(1.4)	37	(2.2)	52	(2.0)
HICCUPS	26	(1.9)	0		18	(2.0)	38	(2.3)	56	(2.1)
BRADYCARDIA	33	(2.4)	1	(1.6)	16	(1.8)	23	(1.4)	40	(1.5)
WHEEZING	31	(2.3)	2	(3.2)	16	(1.8)	19	(1.2)	37	(1.4)
RASH	21	(1.5)	1	(1.6)	11	(1.2)	30	(1.8)	42	(1.6)
ATRIAL FIBRILLATION	29	(2.1)	0		10	(1.1)	23	(1.4)	33	(1.3)
ARTHRALGIA	20	(1.5)	2	(3.2)*	11	(1.2)	25	(1.5)	38	(1.5)
COUGH	23	(1.7)	1	(1.6)	10	(1.1)	22	(1.3)	33	(1.3)
HYPOPHOSPHATAEMIA	23	(1.7)	0		15	(1.7)	18	(1.1)	33	(1.3)
OXYGEN SATURATION DECREASED	27	(2.0)	3	(4.8)*	10	(1.1)	16	(1.0)	29	(1.1)
ERUCTATION	17	(1.2)	0		4	(0.4)	29	(1.8)	33	(1.3)
HYPERGLYCAEMIA	22	(1.6)	0		10	(1.1)	18	(1.1)	28	(1.1)
ASPARTATE AMINOTRANSFERASE INCREASED	19	(1.4)	0		8	(0.9)	22	(1.3)	30	(1.1)
DYSURIA	18	(1.3)	1	(1.6)	7	(0.8)	22	(1.3)	30	(1.1)
CRACKLES LUNG	22	(1.6)	3	(4.8)*	6	(0.7)	16	(1.0)	25	(1.0)
PLEURAL EFFUSION	22	(1.6)	0		8	(0.9)	16	(1.0)	24	(0.9)
ALANINE AMINOTRANSFERASE INCREASED	17	(1.2)	0		6	(0.7)	22	(1.3)	28	(1.1)
ASTHENIA	14	(1.0)	0		9	(1.0)	21	(1.3)	30	(1.1)
BLOOD POTASSIUM DECREASED	17	(1.2)	3	(4.8)*	11	(1.2)	13	(0.8)	27	(1.0)
SINUS TACHYCARDIA	16	(1.2)	0		9	(1.0)	19	(1.2)	28	(1.1)
BLOOD MAGNESIUM DECREASED	14	(1.0)	4	(6.5)*	10	(1.1)	15	(0.9)	29	(1.1)
SMALL INTESTINAL OBSTRUCTION	25	(1.8)	0		7	(0.8)	11	(0.7)	18	(0.7)
HYPOCALCAEMIA	17	(1.2)	0		11	(1.2)	13	(0.8)	24	(0.9)
PROCEDURAL COMPLICATION	10	(0.7)	0		6	(0.7)	25	(1.5)	31	(1.2)
HOT FLUSH (#F)	6	(0.7)	2	(3.9)*	3	(0.6)	15	(1.3)	20	(1.2)
GASTROOESOPHAGEAL REFLUX DISEASE	15	(1.1)	1	(1.6)	10	(1.1)	14	(0.8)	25	(1.0)
WOUND DEHISCENCE	14	(1.0)	0		8	(0.9)	18	(1.1)	26	(1.0)
BLOOD PHOSPHORUS DECREASED	18	(1.3)	2	(3.2)*	7	(0.8)	12	(0.7)	21	(0.8)

Reference: ISS, Table A.2.4.1, Page 800.

Medical Reviewer's Comments: The frequency of the most common TEAEs in the POI population was similar in the alvimopan and placebo groups.

7.1.5.5 Identifying common and drug-related adverse events

Table 44 displays the most frequent treatment-related TEAEs in the POI population.

Table 44: Common treatment-related, TEAEs in the POI population

	placebo	alvimopan			
		1-3 mg	6 mg	12 mg	total
	(N=1365)	(N=62)	(N=898)	(N=1650)	(N=2610)
Preferred Term (1)	n (%)	n (%)	n (%)	n (%)	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.

<u>Medical Reviewer's Comments</u>: The frequency of the most common treatment-related TEAEs in the POI population was similar in the alvimopan and placebo groups.

7.1.5.6 Additional analyses and explorations

Since there were no clear drug-related TEAEs, additional analyses were not performed.

7.1.6 Less Common Adverse Events

Please refer to Table 43 for the common TEAEs.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

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 preformed 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.

Table 45 displays a list of the blood tests performed at baseline and after study drug treatment in Studies 206, 213, 214, 302, 306, 308, and 313 (i.e., studies submitted in the first-cycle NDA). The percentage of patients who did not have blood tests after study drug administration was comparable among patients in the alvimopan and placebo groups. The percentage of patients who did not have the routine laboratory testing at the end of study drug treatment ranged from 13% to 29%.

Table 45: The number and percentage of blood tests performed at baseline and at the end of study drug administration in POI Studies 206, 213, 214, 302, 308, 313, and 306

ALT	Placebo (N=735)	184 (25)	Sodium	Placebo (N=740)	183 (25)
	Alvimopan Groups (N=1670)	363 (22)		Alvimopan Groups (N=1675)	381 (23)
AST	Placebo (N=738)	185 (25)	Potassium	Placebo (N=740)	181 (24)
	Alvimopan Groups (N=1672)	363 (22)		Alvimopan Groups (N=1675)	376 (22)
Alkaline Phosphatase	Placebo (N=739)	181 (25)	BUN	Placebo (N=735)	189 (26)
	Alvimopan Groups (N=1669)	360 (22)		Alvimopan Groups (N=1668)	395 (24)
Direct Bilirubin	Placebo (N=669)	251 (38)	Creatinine	Placebo (N=739)	185 (25)
	Alvimopan Groups (N=1521)	501 (33)		Alvimopan Groups (N=1670)	381 (23)
Total Bilirubin	Placebo (N=737)	183 (25)	Glucose	Placebo (N=736)	195 (27)
	Alvimopan Groups (N=1671)	369 (22)		Alvimopan Groups (N=1673)	397 (24)
Albumin	Placebo (N=734)	211 (29)	Calcium	Placebo (N=728)	205 (28)
	Alvimopan Groups (N=1661)	428 (26)		Alvimopan Groups (N=1643)	404 (25)
GGT[3]	Placebo (N=20)	9 (45)	TSH[4]	Placebo (N=0)	2 (100)
	Alvimopan Groups (N=41)	21 (51)		Alvimopan Groups (N=2)	2 (100)
LDH	Placebo (N=636)	193 (30)	Phosphorus[4]	Placebo (N=2)	2 (100)
	Alvimopan Groups (N=1486)	381 (26)		Alvimopan Groups (N=0)	N/A
WBC	Placebo (N=744)	174 (23)	INR	Placebo (N=21)	19 (90)

Hematocrit	Alvimopan Groups (N=1679)	364 (22)	PTT[4]	Alvimopan Groups (N=30)	29 (97)
	Placebo (N=744)	118 (16)		Placebo (N=20)	18 (90)
Platelets	Alvimopan Groups (N=1681)	225 (13)		Alvimopan Groups (N=30)	29 (97)
	Placebo (N=743)	174 (24)			
	Alvimopan Groups (N=1673)	369 (22)			

1 N is # of patients who had the test at baseline
2 n is # of patients who did not have the test at the end of the study
3 Values for GGT were only collected for one phase 2 study (Study 206);
4 TSH, Phosphorus, INR, and PTT tests were not routinely performed in the POI studies
Reference: ISS, Table 107, Page 256-8; Table 109, Page 260; Table 6.3.1 Pages 17265-99; Table 6.1.1 Pages 16563-75

Medical Reviewer's Comments: Routine coagulation studies including INR and PTT were not routinely performed. These tests should have been measured to assess possible hemorrhagic AEs before and after study drug administration. Additionally, TSH, and phosphorus testing were not routinely performed.

The absence of follow-up blood tests (one week after the last dose of study medication) may impair the assessment of blood test abnormalities AEs. This medical officer believes that follow-up laboratory testing should have been performed in all of the POI studies. Please see Medical Reviewer's Comments under Section 7.1.5.1 of this review.

Table 46 delineates a list of the blood tests performed at baseline and after study drug treatment in Study 314. In Study 314, about 93% to 96% of patients had laboratory tests performed after study drug treatment (on the day of hospital discharge or study termination). Therefore, Study 314 had a higher percentage of blood tests performed after study drug administration compared to the studies submitted in the first-cycle NDA.

Table 46: The number and percentage of blood tests performed at baseline and at the end of study drug administration in POI Study 314

ALT	Placebo (N=325)	18 (6)	Sodium	Placebo (N=325)	18 (6)
	12 mg Alvimopan (N=329)	6 (4)		12 mg Alvimopan (N=329)	6 (4)
AST	Placebo (N=325)	18 (6)	Potassium	Placebo (N=325)	18 (6)
	12 mg Alvimopan (N=329)	6 (4)		12 mg Alvimopan (N=329)	6 (4)
Alkaline Phosphatase	Placebo (N=325)	18 (6)	BUN	Placebo (N=325)	18 (6)
	12 mg Alvimopan (N=329)	6 (4)		12 mg Alvimopan (N=329)	6 (4)
Direct Bilirubin	Placebo (N=325)	18 (6)	Creatinine	Placebo (N=325)	18 (6)
	12 mg Alvimopan (N=329)	6 (4)		12 mg Alvimopan (N=329)	6 (4)
Total Bilirubin	Placebo (N=325)	18 (6)	Glucose	Placebo (N=325)	18 (6)
	12 mg Alvimopan (N=329)	6 (4)		12 mg Alvimopan (N=329)	6 (4)
Albumin	Placebo (N=325)	18 (6)	Hematocrit	Placebo (N=325)	22 (7)
	12 mg Alvimopan (N=329)	6 (4)		12 mg Alvimopan (N=329)	14 (4)
WBC	Placebo (N=325)	22 (7)	Platelets	Placebo (N=325)	22 (7)
	12 mg Alvimopan (N=329)	14 (4)		12 mg Alvimopan (N=329)	14 (4)

1 N is # of patients who had the test at baseline
2 n is # of patients who did not have the test at the end of the study
Reference: ISS, Table 23, Page 50, Table 25, Page 52, and Table 27, Page 54

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

This medical officer selected all of the U.S. POI studies (Studies 206, 213, 214, 302, 306, 308, 313 and 314) to compare laboratory values between the treatment groups because the POI studies were all placebo-controlled, had high doses of alvimopan (up to 24 mg/day), included the proposed patient population (i.e., patients undergoing elective BR surgery), and included the proposed duration of use (up to 7.5 days).

7.1.7.3 Standard analyses and explorations of laboratory data

There were no significant differences in the percentage of outliers or marked outliers of the laboratory values (i.e., CBC, BMP, and hepatic panel tests) among the alvimopan and placebo groups in the U.S. POI studies. Moreover, in the U.S. POI studies there were no significant differences in laboratory values between the 6 mg and 12 mg alvimopan doses.

7.1.7.4 Additional analyses and explorations

There were no significant differences in the percentage of outliers or marked outliers of the laboratory values (i.e., CBC, BMP, and hepatic panel tests) among the 12 mg alvimopan and 6 mg alvimopan treatment groups. Time dependency analyses were not performed in the POI population because the POI studies were of short duration (i.e., the median days of treatment in the POI studies was six).

7.1.7.5 Special assessments

Tables 47 and 48 display patients who had elevated liver tests (≥ 3 times normal) at baseline and after treatment in Study 314 and in the first-cycle U.S. POI studies (i.e., Studies 206, 213, 214, 302, 306, 308, and 313). 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.

Table 47: Patients with elevated liver tests (≥ 3 times normal) in POI Study 314

Lab Parameter	Placebo N=325 n (%)	Alvimopan 12 mg N=329 n (%)
Alanine aminotransferase (ALT)		
N	307	317
Baseline	2 (0.7)	2 (0.6)
Total Post Baseline	6 (2.0)	3 (1.0)
Aspartate aminotransferase (AST)		
N	307	317
Baseline	2 (2.0)	1 (0.3)
Total Post Baseline	4 (1.3)	3 (1.0)
Alkaline phosphatase		
N	307	317
Baseline	0	1 (0.3)
Total Post Baseline	0	1 (0.3)
Bilirubin, direct		
N	306	317
Baseline	0	1 (0.3)
Total Post Baseline	2 (0.7)	0
Bilirubin, total		
N	306	317
Baseline	1 (0.3)	2 (0.6)
Total Post Baseline	2 (0.7)	2 (0.6)

Reference: ISS, Table 29, Page 56

Table 48: Patients with elevated liver tests (≥ 3 times normal) in U.S. POI Studies 206, 213, 214, 302, 306, 308, and 313

Patients with at least one liver test* ≥ 3 times normal in the study (post-baseline)	10 (2.5)	1 (1.6)	11 (1.8)	19 (1.9)	31 (1.8)

* Liver tests included ALT, AST, alkaline phosphatase, direct bilirubin, indirect bilirubin, GGT, and LDH.
Reference: Adapted from first-cycle ISS, Table 6.2.5.2.1, Pages 17068-17069.

Medical Reviewer's Comments: 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.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

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.

Medical Reviewer's Comments: The most important vital signs are the changes in mean systolic and diastolic blood pressure in the alvimopan and placebo treatment groups. Since there may be a CV signal associated with alvimopan use in the long-term OIC studies, it is important to determine if increased blood pressure contributed to the increased CV events in the alvimopan group, compared to the placebo group.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

This medical officer selected all of the U.S. POI studies (Studies 206, 213, 214, 302, 306, 308, 313 and 314) to compare vital signs between the treatment groups because these POI studies were all placebo-controlled, had high doses of alvimopan (up to 24 mg/day), included the proposed patient population (i.e., patients undergoing elective BR surgery), and included the proposed duration of use (up to 7.5 days).

7.1.8.3 Standard analyses and explorations of vital signs data

Tables 49 and 50 present the mean (SD) diastolic and systolic blood pressure and heart rate readings in the POI population (i.e., Studies 206, 213, 214, 302, 306, 308, 313, 314, and 001) and the OIC population (i.e., Studies 217, 304, 11, 12, 13, and the 6-month interim safety analysis of Study 14), respectively.

Table 49: Mean (SD) blood pressure and heart rate in patients in all the POI studies[1]

	Treatment Group	Baseline	Last Observation Carried Forward	Change
Systolic BP in mmHg	**Placebo (N=1365)**	132.2 (20)	131.2 (20)	-1.1 (22)
	Alvimopan (N=2610)	132.3 (20)	130.8 (20)	-1.5 (21)
Diastolic BP in mmHg	**Placebo (N=1365)**	76.2 (11)	73.5 (11)	-2.5 (11)
	Alvimopan (N=2610)	76.4 (11)	74.0 (11)	-2.5 (12)
Pulse in beats/minute	**Placebo (N=1365)**	76.3 (12)	81.3 (13)	5.0 (15)
	Alvimopan (N=2610)	76.1 (12)	80.2 (13)	3.9 (15)

BP is blood pressure
1 The POI studies included Studies 206, 213, 214, 302, 306, 308, 313, 314, and 001
Reference: September 13, 2006 submission (response to our September 6, 2006 information request), Table 2.1, Pages 6-7

Table 50: Mean (SD) blood pressure and heart rate in patients in all the OIC studies (3-52 weeks)[1]

	Treatment Group	Baseline	Last Observation Carried Forward	Change
Systolic BP in mmHg	Placebo (N=790)	125.3 (17)	124.7 (18)	-0.6 (16)
	Alvimopan (N=1728)	125.0 (16)	124.6 (16)	-0.5 (15)
Diastolic BP in mmHg	Placebo (N=790)	77.2 (10)	76.2 (11)	-1.1 (10)
	Alvimopan (N=1728)	76.8 (10)	76.8 (10)	-0.3 (9)
Pulse in beats/minute	Placebo (N=790)	75.4 (11)	76.0 (11)	0.7 (11)
	Alvimopan (N=1728)	75.0 (11)	75.4 (11)	0.4 (11)

BP is blood pressure
1 These results include the results of Studies 217, 304, 11, 12, 13, and the 6-month interim safety analysis of Study 14
2 Alvimopan treatment group includes 0.5 mg q day, 1 mg q day, 0.5 mg BID, and 1 mg BID
Reference: September 21, 2006 submission (response to our September 6, 2006 information request), Table 2, Pages 15-17

Medical Reviewer's Comments: There is no evidence that alvimopan increases blood pressure, compared to the placebo group, in the POI or the OIC population.

7.1.8.4 Additional analyses and explorations

Since there were no significant differences in important vital signs (i.e., systolic and diastolic blood pressure), additional analyses were not performed.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECGs
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) were performed in a subset of study patients. In Study 214, QTc evaluations were performed.

Non-clinical Studies
The following two *in vitro* assays for CV effects of alvimopan and its primary degradant (ADL 08-0011) were completely negative for any significant cardiovascular pharmacologic effect: cloned hERG channels expressed in mammalian cells and isolated dog Purkinje fibers. 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).

Thorough QT/QTc Clinical Study
Study SB-767905/016 was a standard four arm (i.e., placebo, alvimopan 6 mg BID, alvimopan 24 mg BID, and moxifloxacin 400 mg q day) thorough QT/QTc study in healthy subjects (it was randomized, placebo-controlled, and actively-controlled).

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

This medical officer selected all of the POI studies which conducted ECGs (Studies 206, 213, 214, 302, 306, 308, 313, and 001) to compare ECG changes between the treatment groups because these POI studies were all placebo-controlled, had high doses of alvimopan (up to 24 mg/day), included the proposed patient population (i.e., patients undergoing elective BR

surgery), and included the proposed duration of use (up to 7.5 days). Additionally, Study SB-767905/016 was selected for QTc analysis because it was a standard thorough QT/QTc study that was placebo-controlled and active-controlled in healthy subjects.

7.1.9.3 Standard analyses and explorations of ECG data

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. Please see Table 51 for a summary of the ECG changes from baseline in these studies. Only five U.S. POI patients (with normal baseline ECGs) had abnormal ECGs after study drug administration.

Table 51: Summary of ECG changes at the end of the study (compared to the baseline) for the U.S. POI population[1]

Baseline	EOS		
	Normal N (%)	Abnormal but NCS N (%)	Abnormal and CS N (%)
Normal			
Placebo (N=235)	167 (71.1)	67 (28.5)	1 (0.4)
Alvimopan 6 mg (N=166)	108 (65.1)	57 (34.3	1 (0.6)
Alvimopan 12 mg (N=429)	325 (75.8)	101 (23.5)	3 (0.7)
Abnormal but NCS			
Placebo (N=224)	66 (29.5)	157 (70.1)	1 (0.4)
Alvimopan 6 mg (N=179)	47 (26.3)	129 (72.1)	3 (1.7)
Alvimopan 12 mg (N=331)	117 (35.3)	211 (63.7)	3 (0.9)
Abnormal and CS			
Placebo (N=5)	1 (20)	1 (20)	3 (60)
Alvimopan 6 mg (N=4)	0	1 (25)	3 (75)
Alvimopan 12 mg (N=5)	1 (20)	2 (40)	2 (40)

The U.S. POI population included patients from Studies 206, 213, 214, 302, 308, 313 and 306
EOS – end of study; CS – clinically significant; NCS – not clinically significant
Reference: ISS from first-cycle NDA, Table 42, Page 107

Medical Reviewer's Comments: The above clinical data supports the safety of alvimopan in the treatment of POI.

7.1.9.3.1 Analyses focused on measures of central tendency

Table 52 presents the results of mean QTc intervals (by Fridericia's correction) in a subset of patients in Study 001.

Table 52: Mean (SD) QTc intervals (Fridericia's correction) in msec in Study 001*

Treatment Group	Time of ECG	n	Mean (SD)
Placebo (N=40)	Baseline	40	404 (24)
	Day 3 Pre-Dose	32	406 (25)
	Day 3 1.5 hours Post-Dose	38	400 (24)
	Day 7 Pre-Dose	17	407 (27)
	Day 7 1.5 hours Post-Dose	19	397 (20)
Alvimopan 6 mg (N=40)	Baseline	40	403 (22)
	Day 3 Pre-Dose	29	404 (22)
	Day 3 1.5 hours Post-Dose	37	401 (23)
	Day 7 Pre-Dose	14	399 (30)
	Day 7 1.5 hours Post-Dose	20	404 (19)
Alvimopan 12 mg (N=38)	Baseline	38	407 (23)
	Day 3 Pre-Dose	29	401 (27)
	Day 3 1.5 hours Post-Dose	34	400 (23)
	Day 7 Pre-Dose	19	407 (29)
	Day 7 1.5 hours Post-Dose	20	405 (29)

* Only a subset of patients in Study 001 had these four ECGs during the treatment period.
Reference: GSK001 Study Report, Table 14.57, Page 1076.

Medical Reviewer's Comments: In this subset of patients, there is no evidence that alvimopan has a significant effect on the QTc interval.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Table 53 delineates the following responder analyses of the QTc interval in a subset of patients in POI Study 001: the proportion of patients with change from baseline of the QTc interval ≥ 30 msec and ≥ 60 msec; and the proportion of patients with an absolute maximum QTc of ≥ 480 msec.

Table 53: Responder analyses[1] — Number (%) of patients with maximum QTc interval prolongation (Fridericia's correction) in patients in Study 001[2]

Time point	Number (%) of subjects					
	Placebo N=45		Alvimopan 6mg N=50		Alvimopan 12mg N=47	
Change from baseline in QTcF						
Day 3						
N	44	(100)	50	(100)	44	(100)
<30msec	35	(80)	41	(82)	42	(95)
≥30 to ≤60msec	9	(20)	8	(16)	2	(5)
>60msec	0		1	(2)	0	
≥30 to <60msec	9	(20)	8	(16)	2	(5)
≥60msec	0		1	(2)	0	
Day 7						
N	26	(100)	27	(100)	31	(100)
<30msec	20	(77)	20	(74)	27	(87)
≥30 to ≤60msec	6	(23)	7	(26)	4	(13)
>60msec	0		0		0	
≥30 to <60msec	6	(23)	7	(26)	4	(13)
≥60msec	0		0		0	
Maximum QTcF						
Baseline						
N	45	(100)	50	(100)	47	(100)
≤450msec	43	(96)	47	(94)	43	(91)
>450msec	2	(4)	3	(6)	4	(9)
>480msec	0		0		0	
Day 3						
N	44	(100)	50	(100)	44	(100)
≤450msec	43	(98)	49	(98)	42	(95)
>450msec	1	(2)	1	(2)	1	(2)
>480msec	0		0		1	(2)
Day 7						
N	26	(100)	27	(100)	31	(100)
≤450msec	25	(96)	26	(96)	29	(94)
>450msec	1	(4)	1	(4)	1	(3)
>480msec	0		0		1	(3)

1 Responder analyses included the number and proportion of patients with an absolute QTc interval prolongation > 450, > 480, and > 500 msec and the number and proportion of patients with a change from baseline of > 30 and > 60 msec.
2 Only a subset of patients in Study 001 had these four ECGs during the treatment period.
Reference: ISS, Table 30, Page 58.

Medical Reviewer's Comments: In this subset of patients, there is no evidence that alvimopan has a significant effect on the QTc interval.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

See Section 7.1.9.3.2 for the marked outliers for QTc abnormalities.

7.1.9.4 Additional analyses and explorations

There were no significant differences in ECG changes and QTc interval changes between the 12 mg alvimopan and 6 mg alvimopan treatment groups.

7.1.10 Immunogenicity

Alvimopan is not a protein and does demonstrate evidence for immunogenicity.

7.1.11 Human Carcinogenicity

Since the proposed alvimopan dosage regimen is for short-term use — up to 7.5 days of therapy [one dose prior to surgery (POD 0) then BID on POD 1 to POD 7] — human carcinogenicity studies were not required.

Non-clinical genotoxicity studies were negative. Non-clinical carcinogenicity studies were not required because of the proposed short duration of alvimopan use.

7.1.12 Special Safety Studies

Thorough QT/QTc Study: 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.

Results:
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.

According to Dr. Lee, the clinical pharmacology reviewer, the thorough QT/QTc study was negative: the upper bound of the 90% confidence intervals of the change from baseline in the QTc interval using Fridericia's correction was less than 10 msec for all alvimopan groups at the following time points: 2 hours post dosing on Day 1, 2 hours post dosing on Day 7, and 12 hours post dosing on Day 7. Please see Tables 54, 55, and 56).

Table 54: The change from baseline in the QTc interval (Fridericia's correction) at 2 hours post-dose on Day 1

Comparison	Point Estimate	90% Confidence Interval
Alvimopan 6 mg bd – Placebo	0.35	(-3.65, 4.35)
Alvimopan 24 mg bd – Placebo	0.37	(-3.67, 4.41)
Moxifloxacin 400 mg – Placebo	9.77	(5.76, 13.78)

Reference: SB-767905-016 Final Study Report, Table 18, Page 76

Table 55: The change from baseline in the QTc interval (Fridericia's correction) at 2 hours post-dose on Day 7

Comparison	Point Estimate	90% Confidence Interval
Alvimopan 6 mg bd – Placebo	-0.42	(-5.27, 4.44)
Alvimopan 24 mg bd – Placebo	2.84	(-2.14, 7.81)

Reference: SB-767905-016 Final Study Report, Table 19, Page 76

Table 56: The change from baseline in the QTc interval (Fridericia's correction) at 12 hours post-dose on Day 1

Comparison	Point Estimate	90% Confidence Interval
Alvimopan 6 mg bd – Placebo	3.04	(-1.17, 7.25)
Alvimopan 24 mg bd – Placebo	-0.46	(-4.79, 3.87)

Reference: SB-767905-016 Final Study Report, Table 20, Page 77

Medical Reviewer's Comments: The thorough QT/QTc study was negative. This supports the safety of alvimopan in the treatment of POI.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no evidence of withdrawal phenomena of alvimopan administration; however, the POI studies were of short duration and efficacy was not measured after the study treatment was stopped. There is no evidence of abuse potential with alvimopan.

7.1.14 Human Reproduction and Pregnancy Data

There were no pregnant patients in the short-term alvimopan development program.

7.1.15 Assessment of Effect on Growth

Alvimopan was not studied in the pediatric population. Height measurements were not routinely performed in the alvimopan development program.

7.1.16 Overdose Experience

No patient had a clear overdose of alvimopan in the POI studies. Single doses up to 120 mg and multiple doses up to 48 mg per day for 7 days have been administered to healthy subjects with significant AEs.

7.1.17 Postmarketing Experience

Alvimopan has never been approved in the United States or any foreign country; therefore, no post-marketing data is available.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The most important POI trials for this review include **five** POI phase 3 trials of BR surgery patients [**one** U.S. safety/efficacy trial submitted to this second-cycle NDA (314), **three** U.S. safety/efficacy trials originally submitted to the first-cycle NDA (302, 308, and 313), and **one** European trial safety/efficacy trial originally submitted to the first-cycle NDA (001)]. Please see Table 57 for a tabular listing of these important trials.

Table 57: Completed alvimopan studies: the treatment of POI

STUDY	TITLE	OBJECTIVES	N	TREATMENT GROUPS	DURATION
1) 13C206	A Phase II , DB, PC, Parallel Study of Efficacy for Shortening the Duration of POI	Determine if Alvimopan shortened the duration of POI after partial colectomy or TAH in patients receiving IV opioids for postoperative pain.	79	Placebo Alvimopan 1 mg Alvimopan 6 mg	Up to 8 days
2) 13C213	A MC Phase II/III, DB, Dose Ranging, PC, Parallel Study of Alvimopan in Opioid-Induced Postoperative Bowel Dysfunction/POI	Determine the clinically optimal dose of alvimopan	153	Placebo Alvimopan 3 mg Alvimopan 6 mg Alvimopan 12 mg	Up to 8 days
3) 13C214	A MC, Phase II, DB, PC Study Assessing Efficacy of Alvimopan for Speeding Recovery from Postoperative Opioid-Induced Bowel Dysfunction	Determine if alvimopan would shorten the duration of POI as assessed by faster recovery of bowel function following intra-abdominal surgery (excluding planned BRs). Determine whether 12 mg of alvimopan was safe for use in a population of patients who had undergone intra-abdominal surgery	65	Placebo Alvimopan 12 mg	Up to 8 days
4) 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
5) 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
6) 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
7) 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
8) SB-767905/001 (001)[2]	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
9) 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	654	Placebo Alvimopan 12 mg	Up to 8 days

		GI function in patients undergoing partial small or large BR with primary anastomosis			

N = number of patients
1 For the original 8 POI studies, the first dose was administered at least 2 hours prior to surgery, and the next doses BID for up to 7 days or until hospital discharge (which ever is sooner) and for Study 314 the first dose was administered 0.5 to 1.5 hours prior to surgery, and the next doses BID for up to 7 days or until hospital discharge (which ever is sooner)
2 Study SB-767905/001 (001) was conducted in Europe, Australia, and New Zealand
3 Study 13CL314, which is shaded, was submitted in this second-cycle
Reference: Final Study Report Study 314, ISS, Table 74, Pages 154-158

See section 4.2 for a description of the **49** alvimopan clinical studies (**10 bolded studies submitted in this second-cycle,** 36 studies submitted in the first-cycle, 2 studies completed during the second-cycle NDA review, and 1 ongoing study with six-month interim safety data):

1) Table 2 lists the 9 single-dose studies in healthy subjects (14C114, 14CL115, RC99-CP006, 13C111, 14CL124, 14CL127, **14CL130**, **SB-767905/019**, and **17CL133**);
2) Table 3 lists the 11 multiple-dose studies in healthy subjects (H3G-LC-BGGA, 14CL118, 14CL119, RC99-CP007, 13C109, RC98-CP001, H3G-LC-BGGC and SB-767905/016, **14CL128**, **14CL201**, and **SB-767905/018**);
3) Table 4 lists the 5 studies in special populations (14CL116, 14CL117, 14CL123, 14CL125, 14CL126);
4) Table 5 lists the 9 POI studies in surgery patients in Europe and the United States (13C206, 13C213, 13C214, 302 , 306, 308, 313, 001, and **314**)
5) Table 6 lists the 8 OIC studies in chronic (non-cancer) pain patients (RC99-CT001, RC99-CT002, 13C210, 13C208, 13C209, 13C217, 13C304, and **SB-767905/011**);
6) Table 7 lists the 2 OIC studies in chronic cancer pain patients (13CL223 and 13CL224);
7) Table 8 lists the 2 idiopathic chronic constipation studies (**SB-767905/004** and **SB-767905/007**); and
8) Table 9 lists the 2 OIC studies in chronic (non-cancer) pain patients that were completed during the second-cycle NDA review period [SB-767905/012 (Study 12) and SB-767905/013 (Study 13),] and the 1 one-year OIC study in chronic, non-cancer pain patients that is ongoing [SB-767905/014 (Study 14)].

In addition, Table 9 shows two additional ongoing alvimopan OIC trials in chronic cancer pain patients (SB-767905/008 and SB-767905/ABD101684).

7.2.1.2 Demographics

Table 58 lists the demographics (including age, race, and gender) of the surgery patients in the nine POI studies (i.e., Studies 206, 213, 214, 302, 306, 308, 313, 314, and 001) and Table 59 lists the demographics of the BR subpopulation in the POI population (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.

Table 58: Demographics in the POI population*

Demographic Factor Statistics	Placebo (N=1365) n (%)	Alvimopan 6 mg (N=898) n (%)	Alvimopan 12 mg (N=1650) n (%)	Alvimopan Total[a] (N=2610) 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

Table 59: Demographics in the BR surgery subpopulation*

Demographic Factor Statistics	Placebo (N=986) n (%)	Alvimopan 6 mg (N=663) n (%)	Alvimopan 12 mg (N=999) n (%)	Alvimopan Total[a] (N=1681) 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

<u>Medial Reviewer's Comments</u>: **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.**

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.

7.2.1.3 Extent of exposure (dose/duration)

Table 60 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 60: Extent of exposure in the overall POI population*

Parameter / Statistics	Placebo (N=1365) n (%)	Alvimopan 6 mg (N=898) n (%)	Alvimopan 12 mg (N=1650) n (%)	Alvimopan Total[a] (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, Page 36.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

This NDA does not contain secondary clinical data sources.

7.2.2.1 Other studies

This review includes CV safety data from the OIC studies (i.e., Studies 13C217, 13C304, 11, 12, 13, and the six-month interim safety analysis of Study 14).

7.2.2.2 Postmarketing experience

Alvimopan has never been approved in the United States or any foreign country; therefore, no post-marketing data is available.

7.2.2.3 Literature

The most relevant studies found in the literature were studies performed by the sponsor that are part of the primary data source containing 46 studies.

7.2.3 Adequacy of Overall Clinical Experience

Medial Reviewer's Comments: This medical officer believes that the safety database of 3975 patients (nearly 4000 patients) including 2610 patients who received alvimopan is acceptable for the proposed short-term indication (i.e., ≤ 7.5 days of therapy). Furthermore, the well-designed POI studies were adequate to answer critical questions in this NDA.

Patients who were excluded from the major phase 3 efficacy BR trials (such as patients who were scheduled for a total colectomy, colostomy, and ileostomy) should not limit the relevance of the safety database. However, physicians should be informed about the lack of demonstrated efficacy in this subgroup of surgery patients.

Patients on significant baseline opioid analgesics should be contraindicated to use alvimopan because these patients were excluded from the major phase 3 efficacy BR trials. Chronic opioid users may be at higher risk of opioid withdrawal and should not use alvimopan in the treatment of POI.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

According to Dr. Tamal Chakraborti, the pharmacology/toxicology reviewer, the non-clinical testing was adequate to explore possible AEs from an opioid antagonist. Please see his November 4, 2004 review for more details.

The following two *in vitro* assays for CV effects of alvimopan and its primary degradant (ADL 08-0011) were completely negative for any significant cardiovascular pharmacologic effect: cloned hERG channels expressed in mammalian cells and isolated dog Purkinje fibers. 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).

7.2.5 Adequacy of Routine Clinical Testing

Medial Reviewer's Comments: The alvimopan POI development program included adequate types of clinical testing including blood tests, vital signs, ECGs. The clinical safety tests performed at baseline and at the end of study drug administration were acceptable. One minor deficiency in the laboratory testing was that only a few coagulation tests (i.e., INR and PTT) were performed; however, frequent platelet measurements were obtained.

All of the BR studies did not have optimal follow-up periods. It was possible for hospitalized patients in one of the POI clinical trials to achieve the primary efficacy endpoint (e.g., GI2 or GI3) in the morning and be send home later that day. In this example, the discharge procedures (including physical exam, laboratory testing, and ECG testing) 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, these patients may have had suboptimal post-treatment follow-up. A follow-up telephone call five to seven days after hospital discharge may not have elicited all AEs.

The essential question is whether the follow safety evaluations were adequate to detect all MIs in the POI population given the possible CV signal seen in the longer-term OIC studies. This medical officer believes that the telephone calls (i.e., about 88% of patients had a follow-up telephone call and about 75% of patients had a follow-up telephone call ≥ 6 days after the last dose of study drug) were adequate to detect symptomatic MIs and these telephone calls represented reasonable safety surveillance for MI in the POI database. However, as noted above, a follow-up telephone call after hospital discharge may not have elicited all of the alvimopan-associated AEs.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Please see Dr. Sue Chih Lee's review for details regarding drug-drug interaction assessments, the effects of alvimopan on CYP450 enzymes, and identification of enzymatic pathways responsible for alvimopan clearance.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The sponsor adequately assessed the hepatic safety of alvimopan (see Section 7.1.7.5) and the effects of alvimopan on the QTc interval (see a review of the thorough QT/QTc study in Section 7.1.12).

7.2.8 Assessment of Quality and Completeness of Data

The overall quality of the data in the POI population was excellent.

7.2.9 Additional Submissions, Including Safety Update

The DGP sent the sponsor information requests on the following days: August 1, 2006; August 23, 2006; September 6, 2006; and September 13, 2006.

August 1, 2006 Information Requests:

1) Provide narratives for all the serious cardiovascular (CV) events (including myocardial infarctions (MIs) and unstable angina) that occurred in Study 767905/007 (the phase II, chronic constipation trial);
2) Provide narratives of the two "cardiac arrests" (Patients 1347 and 1349) that occurred in Study SB-767905/008 (Study 8);
3) Provide more details regarding the death of Patient 2077 in Study 8 and the serious adverse events (SAEs) of Patient 2474 in Study 8;
4) Provide more details regarding the MI that occurred in Patient 1650 in Study SB-767905/11 (Study 11);
5) Provide the troponin-I levels of patient 807 in Study SB-767905/14 (Study 14) and the hospital laboratory reference range for troponin-I levels;
6) Provide more details regarding the adverse events of Patient 13689 in Study 14 and provide the identity of the study treatment received by Patient 13689;
7) Provide the incidence rate of each of the following SAEs in the alvimopan and placebo treatment groups in the controlled alvimopan trials 2: two weeks duration: MIs, unstable angina, and all serious CV events;
8) Provide the incidence rate of each of the following SAEs in the alvimopan and placebo treatment groups in controlled alvimopan noncancer trials 2: two weeks duration: MIs, unstable angina, and all serious CV events;
9) Did your May 16, 2006 briefing package include all of the patients in the controlled, alvimopan trials of ≥ 2 weeks duration that had unstable angina? Please clarify;
10) Calculate the incidence rate per 100 patient years and the incidence density risk (IDR) of the alvimopan and placebo treatment groups with 95% confidence intervals of the following:

    - CV SAEs in the post-operative ileus (POI) studies;
    - MIs in the POI studies;
    - CV SAEs in the OIC studies;
    - MIs in the OIC studies;
    - CV SAEs in the controlled, alvimopan studies ≥ 2 weeks duration; and
    - MIs in the controlled, alvimopan studies ≥ 2 weeks duration.

August 23, 2006 Information Requests:

1) Given the increased incidence of serious cardiovascular events associated with the alvimopan groups in the OIC trials, compared to the placebo groups, please propose new labeling for Entereg (alvimopan) for the post-operative ileus indication.
2) Please refer to our August 1, 2006 information request to GlaxoSmithKline. In this request, for all questions relating to serious cardiovascular events please include serious arrhythmias and serious cerebral vascular events (i.e., strokes).

September 6, 2006 Information Requests:

We are reviewing the Clinical section of your submission and have the following information requests for the postoperative ileus (POI) population (Studies 13C206, 13C213, 13C214, 13CL302, 13CL308, 13CL313, 13CL314, SB-767905/001, and 13CL306); the noncancer OIC population* (Studies SB-767905/011, SB-767905/012, SB-767905/013, SB-767905/014, 13CL217, and 13C304); and the Study SB-767905/014 population:

1) Provide the percentage of patients in each treatment group in each population that had the following baseline cardiovascular risk factors (prior to study entry): diabetes, hypertension, current or recent smoking history, and obesity (BMI ~ 30). Provide the mean age in each treatment group in each population.
2) Provide the change in mean systolic and diastolic blood pressure and change in mean heart rate (baseline to last reading during the treatment period) for each treatment group in each population.
3) Provide the incidences of each of the following events in each treatment group in each population: all cause death, cardiovascular death, nonfatal myocardial infarction (MI), congestive heart failure, stroke, unstable angina, and serious arrhythmia. Provide the relative risks (RRs) with 95% confidence intervals of these seven events in each population.
4) Provide the incidences in each treatment group in each population of the Antiplatelet Trialist Collaboration composite endpoint (non-fatal MI, nonfatal stroke, vascular death, and death from an unknown cause). Vascular death is defined as a cardiac, cerebrovascular, venous thromboembolic, hemorrhagic, or other vascular death. Provide the RRs with 95% confidence intervals for this composite endpoint in each population.

* We did not include the two single dose OIC studies (Studies 13C208 and 13C209) in the OIC population.

September 13, 2006 Information Request:

1) What proportion of patients in the pooled nine POI studies (i.e., Studies 206, 214, 213, 302, 306, 308, 313, GSK001, and 314) had a follow telephone call within 5 days, 7 days, 14 days, and 30 days of their last study dose?; and
2) What proportion of patients in the pooled nine POI studies had a follow-up safety visit within 5 days, 7 days, 14 days, and 30 days of their last study dose?

Data from the Information Requests:

Tables 49 and 50 in Section 7.1.8.3 display the mean systolic blood pressure (BP), diastolic BP, and heart rate (at baseline and at the last reading during the treatment period) of patients in the treatment groups in the POI and OIC populations, respectively.

Tables 36 and 39 in Section 7.1.4 show the incidence and relative risk of the following CV events in the POI and OIC trials, respectively: all cause death, cardiovascular death, CHF (fatal and nonfatal), nonfatal unstable angina, fatal and nonfatal serious arrhythmia and the composite APTC endpoint (which includes nonfatal MI, nonfatal CVA, vascular death, and death due to unknown cause).

Tables 37 and 40 in Section 7.1.8.3 display the narratives of the MIs in the POI and OIC populations, respectively.

Table 42 in Section 7.1.5.1 displays the post-discharge safety surveillance of the U.S. BR patients. In addition, Table 61 shows the U.S. BR patients who remained in the hospital on POD 7 and POD 10.

Table 61: U.S. BR patients[1] who remained in the hospital on POD 7 and POD 10

POD 7	283 (26)	114 (19)	153 (11)	272 (14)
POD 10	103 (10)	25 (4)	48 (4)	75 (4)

1 BR patients in Studies 206, 213, 214, 302, 308, 313, and 314. Study 306 did not have any BR patients. Study 001 was the European study with different discharge practices.
Reference: September 21, 2006 submission (response to our September 6, 2006 information request), Table 1, Page 124

Medial Reviewer's Comments: Therefore, about 20% of the BR patients in the U.S. were observed in the hospital on POD 7. This provides additional safety surveillance data to assess CV events in the short-term POI studies.

Tables 62, 63, and 64 delineate CV risk factors (i.e., mean age, obesity, diabetes, HTN, and smoking history) of the treatment groups in the POI studies, 3-12 week OIC studies, and the six-month interim safety analysis of Study 14, respectively.

Table 62: CV risk factors in the POI population[1]

CV risk factor	Placebo N=[illegible]	Alvimopan [illegible] N=[illegible]	Alvimopan 6 mg N=[illegible]	Alvimopan 12 mg N=[illegible]	Alvimopan Total N=[illegible]
Mean (SD) age in years	58 (14)	54 (12)	59 (15)	56 (15)	57 (15)
Mean (SD) BMI in kg/m²	28 (6)	31 (8)	28 (6)	28 (6)	28 (6)
Percentage of patients BMI ≥ 30	32	44	26	30	29
Percentage of Diabetics	10	11	13	11	12
Percentage of Hypertensives	43	42	39	38	39
Percentage of Smokers	10	8	8	9	8

1 The POI population included Studies 206, 213, 214, 302, 306, 308, 313, 314, and 001.
Reference: September 21, 2006 submission (response to our September 6, 2006 information request), Table 1, Page 8.

Table 63: CV risk factors in the 3-12 week OIC studies[1]

CV risk factor	Placebo N=[illegible]	Alvimopan 0.5 mg QD N=[illegible]	Alvimopan 1 mg QD N=[illegible]	Alvimopan 0.5 mg BID N=[illegible]	Alvimopan 1 mg BID N=[illegible]	Alvimopan Total N=[illegible]
Mean (SD) age in years	52 (11)	52 (12)	51 (10)	51 (11)	49 (11)	51 (11)
Mean (SD) BMI in kg/m²	30 (7)	30 (7)	30 (7)	29 (7)	30 (8)	29 (7)
Percentage of patients BMI ≥ 30	40	39	41	37	39	39
Percentage of Diabetics	4	0	14	2	9	4
Percentage of Hypertensives	12	6	31	7	25	13
Percentage of Smokers	42	33	26	42	42	36

1 The 3-12 week OIC population included patients in Studies 13C217, 13C304, 11, 12, and 13. This population did not include results from Study 14.
Reference: September 21, 2006 submission (response to our September 6, 2006 information request), Table 2, Page 9.

Table 64: CV risk factors[1] in the 6-month interim analysis of Study 14

CV risk factor	Placebo N=[illegible]	Alvimopan 0.5 mg BID N=[illegible]
Mean (SD) age in years	52 (12)	54 (13)
Mean (SD) BMI in kg/m2	30 (8)	30 (8)
Percentage of patients BMI ≥ 30	38	41
Percentage of Diabetics	12	11
Percentage of Hypertensives	36	39
Percentage of Smokers	40	38

1 These CV risk factors were obtained retrospectively (medication lists helped generate diagnoses for DM and HTN)
Reference: September 21, 2006 submission (response to our September 6, 2006 information request), Table 3, Page 10

Medial Reviewer's Comments: Within all three populations (i.e., the POI studies, the 3-12 week OIC studies, and the six-month interim analysis of Study 14), there were no differences in CV risk factors among the treatment groups. Thus, the baseline CV risk profile in Study 14 does not explain the imbalance of MIs seen in the alvimopan group compared to placebo.

The patients in Study 14 appear to be at greater CV risk then the patients in the shorter-term 3-12 week OIC studies because a higher percentage of patients in Study 14 had diabetes and had HTN. This would explain the higher rate of MIs seen in Study 14 compared to the 3-12 week studies. But, this would not explain the imbalance of MIs seen in the alvimopan group compared to placebo.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Medial Reviewer's Comments: There were no clear alvimopan-related adverse events in the short-term POI studies. The proportion of deaths, nonfatal SAEs, discontinuations due to AEs were not higher in the alvimopan groups compared to the placebo group.

This medical officer believes that there is no CV signal in the short-term POI population because of the following reasons:

- **There is no overall CV signal for all cause death, CV death, CHF, nonfatal CVA, nonfatal MI, serious arrhythmia, and unstable angina (i.e., there is no difference in these combined CV events between the alvimopan and placebo groups);**
- **Unblinded adjudication of MIs by this medical officer and Dr. Nhi Beasley, a medical officer in the Division of Cardiovascular and Renal Products demonstrated that the proportion of treatment-related MIs in the alvimopan and placebo groups were similar;**
- **Blinded adjudication by Dr. Karen Hicks, an interventional cardiologist in the Division of Cardiovascular and Renal Products demonstrated that the proportion of possible or likely MIs in the two treatment groups were similar; and**
- **The POI safety database of nearly 4000 patients (3975 patients) in which 2610 and 1365 received alvimopan and placebo was large and safety surveillance was adequate to detect MIs (by telephone calls post-discharge).**

This medical officer cannot rule out a longer term alvimopan-associated CV signal (i.e., MI and/or unstable angina) given the imbalance of MIs seen in the alvimopan group compared to the placebo group from the available data in Study 14 (i.e., about a 3.5 MIs in the alvimopan group to 0 MIs in the placebo group, accounting for the 2:1 randomization). Thus, the major limitation of the present data is incomplete information on alvimopan-associated MIs and unstable angina in ongoing Study 14.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Medial Reviewer's Comments: **This medical officer believes that the following 12 mg of alvimopan dose regimen demonstrated efficacy in the treatment of POI in partial small BR and partial large BR adult surgery patients:**

- **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; then**
- **Following surgery, 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 hospital discharge (whichever is earlier).**

This medical officer believes that that short-term 12 mg alvimopan regimen (i.e., ≤ 7.5 days duration) demonstrated adequate safety (including CV safety) in the short-term treatment of POI. However, longer-term use of 0.5 mg of alvimopan BID, compared to placebo, in OIC patients was associated with a higher incidence of MI and unstable angina. This medical officer recommends a full assessment of this longer-term risk prior to approval of the 12 mg alvimopan regimen for short-term treatment of POI.

8.2 Drug-Drug Interactions

According to Dr. Sue Chih Lee, alvimopan has no significant drug-drug interactions.

8.3 Special Populations

Gender: From the safety perspective, males and females had similar percentages of treatment-related AEs, SAEs, and discontinuations from AEs in the U.S. POI population.

Race: From the safety perspective, Caucasians and African-Americans had similar percentages of treatment-related AEs, SAEs, and discontinuations from AEs in the U.S. POI population.

Geriatrics: From the safety perspective, geriatric patients (compared to patients under 65 years old) were more likely to have slightly higher treatment-related AEs, SAEs, and discontinuations from AEs in the U.S. POI population. However, the death rate was similar in the two groups.

Hepatic insufficiency: In Study 14C126, out of the three severe hepatic insufficiency patients who received alvimopan, one patient developed very high alvimopan blood levels and two patients had only slightly higher alvimopan levels (compared to patients without hepatic disease). Patients with mild to moderate hepatic insufficiency had similar alvimopan pharmacokinetics compared to patients without hepatic disease.

Renal insufficiency: In Study 14CL116, out of the six patients with severe renal insufficiency who received alvimopan, two patients developed high ADL 08-0011 blood levels (alvimopan's metabolite). Mild and moderate renal insufficiency patients did not have significant differences in alvimopan or ADL 08-0011 blood levels compared to patients without renal insufficiency. Alvimopan was not studied in end-stage renal disease patients or dialysis patients.

Medical Reviewer's Comments:
Gender, Race, and Geriatrics: This medical officer believes that the differences in AE rates between geriatric patients and patients less than 65 years old are likely to higher surgery morbidity associated with increased age and not due to alvimopan effects on geriatric patients.

In summary, there are no special dosing considerations for gender, race, or age.

Hepatic and renal insufficiency: Since the exposure of alvimopan in severe hepatic insufficiency patients is limited, these patients should not receive alvimopan. Patients with mild to moderate hepatic impairment should be closely monitored for AEs (e.g. diarrhea, abdominal pain). Dosage adjustments based solely on mild to moderate hepatic insufficiency are not required.

Patients with severe renal disease should be closely monitored for AEs that could indicate higher metabolite levels. Dosage adjustments based solely on mild to moderate renal insufficiency are not required.

8.4 Pediatrics

[redacted]

8.5 Advisory Committee Meeting

No Advisory Committee Meetings occurred during this second cycle or the first cycle. An Advisory Committee Meeting may be necessary after submission of the full results of Study 14.

8.6 Literature Review

Literature was referenced throughout this review.

8.7 Postmarketing Risk Management Plan

Since this medical officer recommends an approvable action, no post-marketing risk management plan is needed at this time.

If the complete results of Study 14 demonstrate a CV signal in long-term use, this medical officer will recommend a post-marketing risk management plan prior to approval for the short-term POI indication; to reduce long-term alvimopan use.

8.8 Other Relevant Materials

There are no additional relevant materials.

9 OVERALL ASSESSMENT

9.1 Conclusions

This medical officer has the following conclusions regarding the use of alvimopan for the short-term POI indication:

1) Efficacy was demonstrated; and
2) With short-term use, there was no evidence of a significant safety signal — including a cardiovascular (CV) signal — in a large safety database.

However, there may be CV toxicity associated with the long-term use of alvimopan. Thus, this medical officer recommends submission of CV data from ongoing Study 14 prior to approval of alvimopan for the short-term POI indication for adequate labeling (i.e., the need for CV WARNINGS) and to determine if a risk management plan is necessary.

9.2 Recommendation on Regulatory Action

This medical officer recommends an **approvable** action for the 12 mg dose of ENTEREG® (alvimopan) Capsules to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis. To obtain approval of the 12 mg dose of alvimopan for this post-operative ileus (POI) indication, the sponsor must provide the results of their one-year, ongoing, alvimopan phase 3 trial in opioid-induced constipation patients [i.e., SB-767905/014 (Study 14)] including detailed analyses of myocardial infarction, unstable angina, and other serious cardiovascular events.

9.3 Recommendation on Postmarketing Actions

Because this medical officer recommends an approvable action during this cycle, no post-marketing actions are recommended at this time.

9.3.1 Risk Management Activity

Risk management activities are not indicated.

9.3.2 Required Phase 4 Commitments

Phase 4 commitments are not indicated.

9.3.3 Other Phase 4 Requests

Other phase 4 requests are not indicated.

9.4 Labeling Review

Since this medical officer does not recommend approval a complete labeling review was not performed.

9.5 Comments to Applicant

This medical officer has no additional comments to the sponsor.

10 APPENDICES

10.1 Review of Individual Study Reports

Please see Sections 6.1.2, 6.1.3, and 6.1.4 for this medical officer's review of the individual study reports.

10.2 Line-by-Line Labeling Review

Since this medical officer recommends an approvable action, a line-by-line labeling review was not included.

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/s/

Eric Brodsky
10/31/2006 10:19:01 AM
MEDICAL OFFICER

Ruyi He
10/31/2006 11:59:06 AM
MEDICAL OFFICER

Karen A. Hicks, M.D.
Division of Cardiovascular and Renal Products, HFD-110

Food and Drug Administration
10903 New Hampshire Avenue, Building 22, Room 4182
Silver Spring, MD 20993-0002
Tel: (301) 796-1089
FAX: (301) 796-9841

Memorandum

FROM: *Karen A. Hicks, M.D., Medical Officer*
Division of Cardiovascular and Renal Products

THROUGH: *Norman L. Stockbridge, M.D., Ph.D., Director*
Division of Cardiovascular and Renal Products

TO: *Tanya Clayton*
Division of GI Products
White Oak, Building 22
Room 5103

Ruyi He, M.D., Team Leader
Division of GI Products

Brian E. Harvey, M.D., Ph.D., Director
Division of GI Products

SUBJECT: *Review of 24 narratives from NDA 21-775 for Alvimopan, an investigational opioid antagonist for postoperative ileus*

DATE RECEIVED: *October 11, 2006*

DATE COMPLETED: *October 24, 2006*

Background:
Alvimopan (ADL 8-2698), an investigational opioid antagonist, is currently undergoing a second cycle NDA review for postoperative ileus (POI) with a PDUFA goal date of November 9, 2006. In Study 14, an opioid-induced constipation trial, Alvimopan was associated with 8 serious cardiovascular events, including 7 myocardial infarctions (MIs) and 1 event of unstable angina.

The GI Division now submits 24 narratives for blind adjudication regarding myocardial infarction and unstable angina that occurred in the POI population with short-term (< 8 days) Alvimopan or placebo therapy.

Conclusions:
A total of 24 narratives were submitted. One patient had two identical narratives submitted (Case reference number 14CL308.13.01235; Study 14CL308), so there were only 23 unique subject narratives submitted for blind adjudication. Table 1 displays the FDA-adjudicated events. Based on limited information, I was unable to adjudicate 6 out of the 23 cases. There were 11 myocardial infarctions, 2 presumed myocardial infarctions, 1 myocardial ischemia and possible myocardial infarction, and 3 possible myocardial infarctions.

Some patients experienced multiple cardiac events. Case Reference Number 14CL308.13.01235 experienced a myocardial infarction during the initial hospitalization and got readmitted after discharge with unstable angina. Case Reference Number B0323216A experienced 2 events, a non-ST-segment elevation myocardial infarction as well as a subsequent ST-segment elevation myocardial infarction. Case Reference Number 14CL314.032.00586 also experienced two events, including a presumed non-ST-segment-elevation myocardial infarction on Day 1 and a "small demand myocardial infarction" on Study Day 22.

There were 2 deaths, including Case Reference Number 14CL313.13.13015, a 64 year old Caucasian male who experienced a myocardial infarction and cardiogenic shock and Case Reference Number 14CL314.036.00240, a 78 year old Caucasian woman who experienced respiratory failure, myocardial infarction, congestive heart failure, and multisystem organ failure.

Should 12-lead ECGs and cardiac enzyme results become available for the possible myocardial infarctions and the 6 subjects I was unable to adjudicate, I would be happy to review this information.

Table 1. FDA Adjudicated Events

#	Case Reference Number	Study	Adjudicated Event
1	14CL302.53.01306	14CL302	I cannot adjudicate this case due to incomplete information. I need to review all of the 12-lead Electrocardiograms (ECGs) to determine if this patient had a myocardial infarction. Information regarding cardiac enzymes would also be helpful to adjudicate this case.
2	14CL313.04.04031	14CL313	I cannot adjudicate this case due to incomplete information. I need to review all of the ECGs to determine if this patient had a myocardial infarction. Information regarding cardiac enzymes would also be helpful to adjudicate this case.
3	14CL313.03.03014	14CL313	Presumed myocardial infarction. This narrative did not provide cardiac enzyme results prior to coronary artery bypass grafting (CABG), did not specify the duration of this subject's chest discomfort on readmission to the hospital, and did not describe any ECG changes. Cardiac catheterization reportedly demonstrated several occluded vessels, for which this patient was referred for CABG.

#	Case Reference Number	Study	Adjudicated Event
4	14CL313.13.13015	14CL313	Myocardial infarction, cardiogenic shock, and **death.** This patient experienced an acute inferior wall myocardial infarction with possible right ventricular extension. He underwent unsuccessful percutaneous coronary intervention. He subsequently developed cardiogenic shock and despite endotracheal intubation and intraaortic balloon pump placement, this patient died.
5	14CL314.001.00702	14CL314	Myocardial infarction and congestive heart failure. The patient also developed multisystem organ dysfunction, requiring endotracheal intubation, surgical wound dehiscence, and prolonged hospitalization.
6	14CL314.025.00025	14CL314	Myocardial infarction, with cardiac catheterization demonstrating a totally occluded proximal left anterior descending artery (LAD). The patient underwent percutaneous transluminal coronary angioplasty (PTCA) of the LAD and placement of an intraaortic balloon pump (IABP). The fact that the IABP was placed suggests a large anterior infarct with hemodynamic compromise and possible cardiogenic shock. The patient also developed congestive heart failure and atrial fibrillation.
7	14CL314.032.00586	14CL314	Acute respiratory failure requiring endotracheal intubation, alcohol withdrawal, and presumed non-ST-segment-elevation myocardial infarction on Study Day 1 (mildly elevated troponin T and elevated CPK. It would have been helpful to have CK-MB results to better adjudicate this case). This patient also reportedly experienced a second myocardial infarction ("small demand myocardial infarction") on Study Day 22.
8	14CL314.036.00240	14CL314	Acute respiratory failure requiring endotracheal intubation, myocardial infarction, congestive heart failure, multisystem organ failure, and **death.**
9	B0309139B	767905 001	Myocardial infarction and congestive heart failure (secondary to demand ischemia from the atrial fibrillation with rapid ventricular response)
10	B0336389A	767905 001	Myocardial ischemia (and possible myocardial infarction) in the setting of profound anemia, requiring transfusion. No cardiac enzymes results were reported in the narrative. If the cardiac enzymes were abnormal, these findings would be consistent with myocardial infarction.

#	Case Reference Number	Study	Adjudicated Event
11	B0308629A	767905 001	Cardiac dysrhythmia leading to a reportedly life-threatening myocardial infarction (reportedly confirmed by an echocardiogram and cardiac catheterization). Surgery was aborted. The particular "cardiac dysrhythmia" which developed 2 ½ hours after the first dose of investigational product was not further described. It is unclear if this patient experienced an "anesthesia accident" due to inappropriate administration of medications.
12	B0323216A	767905 001	Two myocardial infarctions (1 non-ST-segment elevation myocardial infarction on Day 1, one day after initiation of study drug, and 1 ST-segment-elevation myocardial infarction with AV escape rhythm on Day 6). The patient underwent percutaneous transluminal coronary angioplasty of a 90% right coronary artery lesion on Day 6. On Day 7, the patient developed atrial fibrillation. Following cardioversion of the atrial fibrillation, the patient developed a bradyarrhythmia, which required pacemaker placement on Day 8. Study drug was discontinued on Day 5.
13	B0304647A	767905 001	Myocardial infarction, one day following thrombectomy and stent placement in a severe "femoral artery occlusion."
14	13CL213.05.00006	13CL213	Myocardial infarction, congestive heart failure, upper gastrointestinal bleed, surgical wound dehiscence, intestinal perforation, and esophagitis.
15	14CL308.13.01235	14CL308	Myocardial infarction and congestive heart failure. This patient also had atrial fibrillation with a rapid ventricular response. This patient was later readmitted for unstable angina and cardiac catheterization reportedly demonstrated obstructive 1 vessel disease with "probable resolving thrombus in the posterolateral branch" of the left circumflex coronary artery.
16	14CL313.04.04013	14CL313	I cannot adjudicate this case due to incomplete information. I need to review the ECGs to determine whether or not this patient experienced an anterior infarct. It is possible the anterior infarct may not have been an anterior infarct at all, but rather an artifact related to lead placement. Information regarding cardiac enzymes would have been very helpful in adjudicating the adverse event in this patient.
17	14CL314.008.00733	14CL314	Myocardial infarction (acute ST-segment elevation myocardial infarction manifested by a totally occluded right coronary artery, requiring stent placement.)
18	B0318700B	767905 001	I cannot adjudicate this case due to incomplete information. I need to review the ECGs to determine whether or not this patient had a non-ST-segment elevation myocardial infarction. It would also be helpful to know the results of the cardiac enzyme results.
19	GSK001/15-1139	-	I cannot adjudicate this case due to incomplete information. I need to review the ECGs to determine whether or not this patient experienced myocardial ischemia. It would also be helpful to know the results of the cardiac enzymes.
20	GSK001/69-1064	1064	I cannot adjudicate this case due to incomplete information. I need to review the ECGs to determine whether or not this patient experienced myocardial ischemia. It would also be helpful to know the results of the cardiac enzymes.

#	Case Reference Number	Study	Adjudicated Event
21	14CL314.008.0646	14CL314	This patient had prolonged chest discomfort at rest, lasting > 20 minutes, which could have been consistent with a myocardial infarction. Although the initial 12-lead electrocardiogram (ECG) and cardiac enzymes were negative, it is unclear if the patient underwent repeat ECGs and serial cardiac enzymes. The chest discomfort did not resolve until the following morning. Even if the ECG was unremarkable, the patient could have significant left circumflex disease; which is often electrically silent. Based on the limited information from the narrative, I describe this adverse event as **possible myocardial infarction**. This patient also developed a postoperative wound infection.
22	14CL314.50.0615	14CL314	This patient experienced 45 minutes of "mild heart pain" on postoperative Day #2. Any time a patient experiences ≥ 20 minutes of chest discomfort, the patient could be having a myocardial infarction. No ECG or cardiac enzyme results are reported in the narrative. Based on the limited information from the narrative, I describe this adverse event as **possible myocardial infarction.**
23	14CL314.065.0672	14CL314	This patient reportedly experienced 9 hours of "mild cardiac chest pain associated with shortness of breath" on postoperative day 4. No ECG or cardiac enzyme results are reported in the narrative. Based on the limited information from the narrative, I describe this adverse event as **possible myocardial infarction.**

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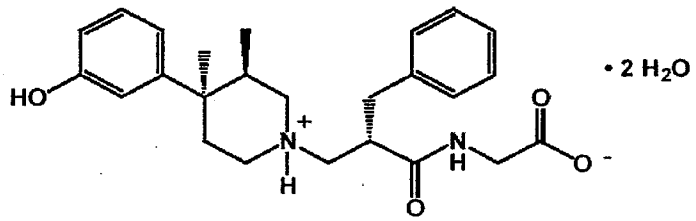
/s/

Karen Hicks
10/27/2006 04:40:58 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISON OF GASTROENTEROLOGY PRODUCTS

Medical Officer's Review of Alvimopan-Associated Serious Cardiovascular Adverse Events

DRUG NAME: **Alvimopan**



PROPOSED LONG TERM GOAL: Treatment of opioid-induced constipation (OIC)

IND#: [redacted]

RECEIPT DATE BY CDR: May 16, 2006

PDUFA GOAL DATE: Not applicable

DRUG TYPE: μ-opioid receptor antagonist

SPONSOR: GlaxoSmithKline (GSK)

ROUTE OF ADMINISTRATION: Oral

FROM: Eric Brodsky, M.D., Medical Officer

1.0 BACKGROUND:

GlaxoSmithKline (GSK) and Adolor Corporation are investigating the use of alvimopan, an opioid receptor antagonist, for the treatment of the following disorders: opioid-induced constipation (OIC) in noncancer and cancer patients, post-operative ileus (POI), and chronic idiopathic constipation. The sponsors have submitted a second cycle NDA (under NDA 21-775) for alvimopan for the treatment of POI in patients with bowel resection surgery.

On May 15, 2006, GlaxoSmithKline (GSK) requested an urgent teleconference with the Division of Gastroenterology Products (DGP) regarding alvimopan-associated serious cardiovascular (CV) events that occurred in noncancer patients in one of their OIC studies (Study 14). Study 14 is an ongoing, randomized, double-blinded, placebo-controlled, parallel-group, multi-centered (230 sites), phase III, one-year, safety study of alvimopan in noncancer patients with OIC. Patients were randomized 2:1 into the following two treatment groups: alvimopan 0.5 mg BID and placebo. According to GSK, ongoing Study 14 is fully enrolled with 805 patients (537 and 268 patients have received alvimopan and placebo, respectively) and the last patient will be finished with the last visit in February 2007. During the May 15, 2006 teleconference between GSK and the DGP, GSK informed the DGP of the following:

1) Due to an apparent numerical increase in the proportion of patients in Study 14 who developed an acute myocardial infarction (MI) relative to their other alvimopan studies, the alvimopan development team referred this issue to the GSK Global Safety Board (GSB). According to GSK, the GSK GSB operates independently from the alvimopan development team;
2) After the GSK GSB determined the need to un-blind Study 14, they discovered eight cases of serious CV events [seven patients who developed an acute MI and one patient who developed unstable angina] in the alvimopan arm and no cases of serious CV events in the placebo arm. Since there was no prior defined increased risk of MI or other serious CV events with alvimopan, no pre-specified analyses of CV events or prospective collection of coronary artery disease (CAD) risk factors were performed in Study 14. Therefore, GSK GSB collected serious CV events by evaluating medical records (including hospital discharge summaries);
3) There were no differences in CAD risk factors between the alvimopan and placebo treatment groups in Study 14;
4) The overwhelming majority of patients who had MIs in Study 14 had typical symptoms, EKG changes, and elevated troponins;
5) Since there was a 2:1 randomization in Study 14, the actual ratio of serious CV events in the alvimopan arm relative to the placebo arm was 4:0;
6) The GSK GSB assessed if the design of Study 14 produced a higher rate of CV serious adverse events (SAEs) than the other alvimopan trials; and evaluated the possible background rate of CV SAEs in a chronic noncancer pain population;
7) Of the eight serious CV events in Study 14, three occurred at one site in Scotland and two occurred in one site in the United States; and
8) GSK GSB stated that there were no differences in the baseline CAD risk factors in patients in Study 14 compared to the patients in the other alvimopan studies.

In addition to the information presented in the teleconference, the GSK May 16, 2006 submission [redacted] included the following:

1) The incidence of MI in a historical chronic pain population taking opioids (who had similar CV risk as the patients in Study 14);
2) The biologic plausibility of a clinical effect of opioid receptor antagonists on CV function based on the literature, and nonclinical and clinical databases; and
3) The narratives of the CV SAEs associated with study treatments in the alvimopan studies.

In the May 16, 2006 submission, GSK provided the following CV safety data:

1) In the phase 2 and phase 3 pooled, short-term POI studies (9 studies), the incidences of MI and angina were 0.81% (11/1365), 0.78% (7/898), and 0.42% (7/1650) in the placebo, 6 mg (12 mg daily) alvimopan, and 12 mg (24 mg daily) alvimopan treatment groups, respectively;
2) In the phase 2 and phase 3 pooled, short-term POI studies (9 studies), the incidences of MI were 0.29% (4/1365), 0.22% (2/898), and 0.36% (6/1650) in the placebo, 6 mg (12 mg daily) alvimopan, and 12 mg (24 mg daily) alvimopan treatment groups, respectively;
3) In the phase 2 and phase 3 pooled OIC studies in cancer (Study 8) and noncancer (Studies 11, 12, 13, and 14), the cumulative risks of MI were 0.63% (11/1760) and 0.37% (3/813) in the alvimopan and placebo treatment groups, respectively. The 95% confidence intervals for the alvimopan and placebo groups were 0.31%-1.12% and 0.08%-1.07%, respectively. The relative risk of MI for the alvimopan groups, compared to the placebo group, was 1.69; and
4) In the phase 2 and phase 3 pooled OIC studies in cancer and noncancer, the incidence rates per 100 patient-years were 3.6 and 2.1 in the alvimopan and placebo treatment groups, respectively. The 95% confidence intervals for the alvimopan and placebo groups were 1.8 to 6.5 and 0.4 to 6.1, respectively. The incidence density risk (IDR) for the alvimopan groups, compared to the placebo group, was 1.71.

After their CV safety evaluation of their alvimopan clinical development program, GSK concluded the following:

1) The increased rate of MI in the alvimopan-treated patients in Study 14, compared to the other alvimopan studies, was unprecedented, inconsistent with the totality of the data, and most likely due to chance;
2) There was no overall change in the risk/benefit ratio of continuing or significantly modifying the ongoing alvimopan studies;
3) There should be additional CV safety monitoring in the ongoing alvimopan studies;
4) All the relevant regulatory authorities and investigators will be notified about the serious CV events; and
5) An independent Data Monitoring Committee (DMC) will establish stopping rules in the ongoing alvimopan studies.

2.0 REVIEW:

2.1 Serious cardiovascular events in alvimopan studies ≥ 2 weeks duration:

GSK evaluated the CV SAEs by grouping alvimopan studies by proposed indication. This medical officer decided to assess the CV SAEs by duration of alvimopan exposure. Since the largest imbalance of MIs in the alvimopan treatment groups, compared to the placebo groups, occurred in the long-term safety study (Study 14), the duration of alvimopan treatment may be a factor in the development of CV SAEs. Thus, this medical officer evaluated the number of CV SAEs that occurred in controlled alvimopan studies ≥ 2 weeks duration (see Table 1). Controlled alvimopan studies ≥ 2 weeks duration included all the OIC trials in cancer patients (Study 8 and Study ABD101684), the OIC trials in noncancer patients (Studies 11, 12, 13, 14, 13C217, and 13C304), and the one chronic constipation trial (Study 7).

All of the POI alvimopan trials were less than 2 weeks duration and were not included in Table 1. Furthermore, in the nine phase 2 and phase 3 POI studies, the incidences of MI and angina were 0.81% (11/1365), 0.78% (7/898), and 0.42% (7/1650) in the placebo, 6 mg (12 mg daily) alvimopan, and 12 mg (24 mg daily) alvimopan treatment groups, respectively. Therefore, the incidence of CV SAEs in the short-term POI trials was lower in the alvimopan groups then the placebo group.

The incidence of CV SAEs in the alvimopan and placebo groups in the pooled controlled alvimopan trials ≥ 2 weeks duration was 0.54% (11/2054) and 0.43% (4/924), respectively. Thus, the relative risk of CV SAEs in the alvimopan and placebo groups in the pooled controlled alvimopan trials ≥ 2 weeks duration was 1.26. This medical officer will request the sponsor perform additional analyses of the incidence and incidence density risk of CV SAEs over various durations of alvimopan exposure.

Table 1: Cardiovascular SAEs in controlled alvimopan studies ≥ 2 weeks duration

Study	Design	Treatment Groups	Patients with CV SAE (study treatment)
14	R, DB, MC, PC, safety study in chronic pain patients for **one year**	N=805* Alvimopan 0.5 mg BID (n=537) Placebo (n=268)	➢ 6 MIs (alvimopan) ➢ 1 unstable angina (alvimopan) ➢ 1 SOB, possibly CHF (alvimopan) ➢ 1 positive ETT (N/A)
12	R, DB, MC, PC, phase 3 study in chronic pain patients for **12 weeks**	N=519*; 2 alvimopan groups (n=346) Alvimopan 0.5 mg BID Alvimopan 0.5 mg q day Placebo (n=173)	1 MI (placebo)
13	R, DB, MC, PC, phase 3 study in chronic pain patients for **12 weeks**	N=491*; 2 alvimopan groups (n=327) Alvimopan 0.5 mg BID Alvimopan 0.5 mg q day Placebo (n=164)	1 MI (placebo)
7	R, DB, MC, PC, phase 2 study in chronic constipation patients for **8 weeks**	N=217* Alvimopan 1 mg BID (n=55) Alvimopan 3 mg BID (n=55) Alvimopan 8 mg BID (n=54) Placebo BID (n=53)	1 MI (placebo)
11	R, DB, MC, PC, phase 2 study in chronic pain patients for **6 weeks**	N=522* Alvimopan 0.5 mg BID (n=130) Alvimopan 1 mg QD (n=133) Alvimopan 1 mg BID (n=130) Placebo (n=129)	2 MI (alvimopan)
8**	R, DB, MC, PC, phase 2 study in cancer pain patients for **3 to 6 weeks**	N=236*; 2 alvimopan groups (n=157) Alvimopan 0.5 mg BID Alvimopan 1 mg BID Placebo (n=79)	1 cardiac arrest (alvimopan) 1 cardiac arrest (placebo)
ABD 101684	DB, MC, PC, phase 2 extension study in cancer patients	N=1* Alvimopan 0.5 mg BID Alvimopan 1 mg BID Placebo	0 MI
13C217	R, DB, MC, PC, phase 2 study in chronic pain patients for **3 weeks**	N=20* Alvimopan 0.5 mg (n=8) Alvimopan 1 mg (n=8) Placebo (n=4)	0 MI
13C304	R, DB, MC, PC, phase 2 study in chronic pain patients for **3 weeks**	N=168* Alvimopan 0.5 mg (n=58) Alvimopan 1 mg (n=56) Placebo (n=54)	0 MI

R (randomized), DB (double-blind), MC (multi-center), PC, (placebo-controlled)

* Number enrolled at the time of the May 16, 2006 briefing package

** Study 8 was amended (the duration changed from 6 to 3 weeks and the 1 mg/day alvimopan dose regimen was discontinued)

2.2 Narratives of serious cardiovascular adverse events

Table 2 summarizes the patient narratives of CV SAEs in the alvimopan controlled trials ≥ 2 weeks duration. In Study 14, there were 6 patients (Patient #'s 759, 805, 18322, 18321, 1818, and 17641) who received alvimopan who developed a MI and no patients who received placebo who developed an MI. In addition, one patient who received alvimopan (Patient # 3202) developed unstable angina.

In Study 14, Patient # 807 — with a significant history of congestive heart failure (CHF), atrial fibrillation (AF), and valvular heart disease — was treated with alvimopan and developed shortness of breath (SOB) and edema. Patient # 807 may have had a recurrence of CHF due to her underlying valvular heart disease and AF; she may not have ruled in for a MI (her reported troponin level was only 0.08); and her SAE may not be related to her study drug. This medical officer recommends obtaining more information about her case. Because it is not clear if this patient had a MI and it is possible that this patient had a recurrence of her underlying CHF, this medical officer will perform another analysis of alvimopan-associated CV SAEs, while excluding this CV SAE.

There is limited information regarding the adverse event (AE) that occurred with Patient # 13689 and the identity of the study drug in Study 14; thus, this medical officer will request more information about this case.

In their May 16, 2006 submission, GSK reported that Patient # 2077 and Patient # 2474 in Study 8 (the OIC study in cancer patients) developed SAEs. Patient # 2077 (received placebo) with ovarian cancer developed acute delirium and subsequently died. Patient # 2474 (received alvimopan) with metastatic breast cancer developed severe vomiting, diarrhea, and abdominal pain and had an EKG performed that showed ischemic changes with negative enzymes. Both of these patients had SAEs; however, both of these patients may not have had primary CV SAEs; they may have had secondary CV SAEs. Since cancer patients have increased morbidity and mortality, it is difficult to ascribe a causal relationship between the study drug and the CV SAEs. Patient # 2077 may have had delirium from many factors including, but not limited to, the following: hypoxia, hypercarbia, electrolyte problems, concomitant medications, and/or infections. There is no clear evidence that this patient had a primary CV event. Patient # 2474 may have had unstable angina (ischemic EKG changes and negative enzyme levels). It is not clear if the patient was having classic angina symptoms including exertional CP and/or SOB. It appears that this patient did not have a MI. It is possible that this patient had false positive EKG changes. This medical officer recommends obtaining more information about these two cases and this medical officer will perform another analysis of alvimopan-associated CV SAEs, while excluding these two SAEs.

This medical officer recommends requesting additional information on Patient # 1650 in Study 11 because the narrative does not detail the presence or absence of symptoms, EKG findings, and cardiac enzyme abnormalities.

Patient # 17641 in Study 14 had recurrent CV symptoms after he ruled in for a MI and was found to have 5-vessel CAD. It is likely that this patient had post-infarct angina. This patient's diabetes most likely contributed to his extensive CAD, his initial infarct, and his probable post-infarct angina. It is possible that alvimopan contributed to his MI and contributed to his possible post-infarct angina. This may represent a positive re-challenge test.

Table 2: Narratives of cardiovascular SAEs in the alvimopan controlled trials ≥ 2 weeks duration[1]

Patient # (Study)	Days on study treatment (Site)	Narrative
759 (Study 14)	38 days (Glasgow)	71 year old male with COPD and with stable angina and the following CV risk factors: hyperlipidemia, increased age, obesity (BMI=38.2), glucose intolerance, family history of CV disease. He received **alvimopan**. He had severe chest pain (CP), ST depression, and positive troponin-I. Catheterization showed diffuse, triple vessel disease.
807 (Study 14)	30 days (Glasgow)	75 year old female with osteoarthritis (OA) with a history of AF, CHF, hypertension (HTN), transient ischemic attack (TIA), hyperlipidemia, obesity, smoker, and aortic valve regurgitation. She received **alvimopan**. She had SOB and edema and was hospitalized. Troponin positive (0.08) and echo showed severe mitral regurgitation (MR), moderate to severe tricuspid regurgitation (TR) and severe hypokinesis of the left ventricle.
805 (Study 14)	85 days (Glasgow)	75 year old female with OA and COPD with the following CV risk factors: HTN, smoker, obesity, hyperlipidemia received **alvimopan** and later developed CP, ST elevation, and positive troponin-I.
18322 (Study 14)	65 days (Tampa, FL)	62 year old female with reflex sympathetic dystrophy (RSD) and OA and peripheral vascular disease (PVD), HTN, hyperlipidemia, and smoker and received **alvimopan**. She had CP, q waves and ST elevations on EKG, and positive troponin. The catheterization showed critical LAD artery disease and got stented.
18321 (Study 14)	111 days (Tampa, FL)	48 year old male with chronic back pain with history of CV disease, HTN and obesity and received **alvimopan**. He felt weak and had arm pain and developed syncope, ST segment elevation, and positive troponin. During hospitalization had AF and cardiogenic shock requiring intraaortic balloon pump (IABP) and vasopressors. Catheterization showed severe two-vessel disease and he had two stents placed.
3202 (Study 14)	83 days	47 year old female with history of cerebral vascular accident (CVA) CV disease (coronary stent placed), HTN, hyperlipidemia and received **alvimopan**. Developed unstable angina and was hospitalized
1818 (Study 14)	58 days	93 year old female with OA with ischemic heart disease and received **alvimopan**. She had SOB for one week and hospitalized. In hospital had cardiac arrest and intubated. ST wave elevation and positive troponin consistent with a MI. She died within 12 hours of admission.
17641 (Study 14)	106 days	68 year old male, with chronic shoulder pain and DM, who received **alvimopan**. Had CP at rest, EKG showed inferior T wave inversions, positive troponin, and echocardiogram showed apical left ventricle hypokinesis with normal ejection fraction. Catheterization showed 5-vessel disease and he had a stent of the RCA placed and returned two weeks later for two additional stents. Patient resumed alvimopan

		treatment and 2 weeks later he was readmitted with CV symptoms for 3 days. The alvimopan was discontinued during the hospitalization. He was discharged from the hospital. Short after discharge, on the same day, he had more symptoms and was readmitted and had an angioplasty.
13689 (Study 14)	140 days	53 year old male with OA, obesity received study drug[2]. After 140 days developed CP and subsequently had a positive stress test then placed on Zocor, atenolol, and isosorbide.
973 (Study 11)	4 days	55 year old male with history of MI, PTCA, CABG twice, PVD, COPD, hyperlipidemia, HTN, smoker, received 4 days of **alvimopan** then had SOB and CP. He presented to the hospital 2 days later, CP relieved with NTG, EKG showed ST depression, and had positive troponin-I. Had evidence of CHF on X-ray. He had CABG of his RCA.
1650 (Study 11)	33 days	57 year old female with history of CABG and PTCA, renal artery bypass received **alvimopan** for 33 days then had a MI.
6053 (Study 12)	78 days	91 year old female with chronic neck pain, HTN, got **placebo** and had SOB, CP, nausea, vomiting, diaphoresis and she was diagnosed with CHF and a subendocardial MI (positive troponin I but EKG showed no acute changes).
9983 (Study 13)	66 days	47 year old male with multiple sclerosis with a history of three coronary stents in 1991 and two stents in 2005, HTN, hyperlipidemia, diabetes, obesity, and a smoker. He received **placebo** and after 66 days had a cardiac arrest and was found to have an occluded RCA.
2077 (Study 8)	12 days	72 year old female with ovarian cancer, who received **placebo**, developed acute delirium 12 days later. Patient died and no autopsy was performed.
2474 (Study 8)	1 day	43 year old female with metastatic breast cancer to the bones, who was receiving chemotherapy (5-Florouracil, cyclophosphamide, doxorubicin, and docetaxel) received one dose of **alvimopan** 0.5 mg BID and one hour later developed severe vomiting, diarrhea, abdominal pain, and shivering. She was hospitalized. EKG showed sinus arrhythmia and ischemic changes which resolved the next day. Her CKMB levels were negative. Her adverse events resolved.
(Study 7)[3]	N/A	Patient who received **placebo** had a myocardial infarction.

1 The controlled alvimopan studies ≥ 2 weeks duration included the OIC cancer studies (Study 8 and ABD101684), the OIC noncancer GSK studies (Studies 11, 12, 13, and 14), the OIC noncancer Adolor studies (204 and 217), and the GSK chronic constipation study (Study 7). Studies ABD101684, 204, and 217 did not have any CV SAEs in any of the treatment groups.

2 The GSK briefing document did not detail the study drug.

3 The most recent alvimopan annual report (January 18, 2006) reported one MI that occurred in a patient who received placebo in Study 7, the chronic constipation study. No more information was available.

The incidence of CV SAEs in the alvimopan and placebo groups in the pooled controlled alvimopan trials ≥ 2 weeks duration (excluding the equivocal cases) was 0.44% (9/2054) and 0.32% (3/924), respectively. Thus, the relative risk of CV SAEs in the alvimopan treatment groups, compared to the placebo group, in the pooled controlled alvimopan trials ≥ 2 weeks duration (excluding the equivocal cases) was 1.38. The incidence of MIs in the alvimopan and placebo groups in the pooled controlled alvimopan trials ≥ 2 weeks duration (excluding the equivocal cases and excluding unstable angina

cases) was 0.39% (8/2054) and 0.32% (3/924), respectively. Thus, the relative risk of MIs in the alvimopan and placebo groups in the pooled controlled alvimopan trials ≥ 2 weeks duration (excluding the equivocal cases and excluding unstable angina cases) was 1.22. This medical officer will request the sponsor perform analyses of the incidence and IDR of all CV SAEs (including MI, unstable angina, arrhythmias, and CHF) and the incidence of only MIs in the alvimopan and placebo groups in the alvimopan trials ≥ 2 weeks duration.

2.3 Characteristics of patients who had alvimopan-associated CV SAEs in the alvimopan trials

All of the eight patients, who had a MI (who received alvimopan), in alvimopan controlled trials ≥ 2 weeks duration were at very high risk of having a MI. Of these eight patients, four had known CAD, one had known CVD, one had known PVD, one had diabetes, and one had at least five CAD risk factors. Patients with vascular disease (including CAD, CVD, and PVD) and patients with diabetes are at much higher risk of having a MI.

2.4 Relative risks of CV SAEs

Table 3 displays the incidences and relative risks MIs and CV SAEs of alvimopan, compared to placebo, in the alvimopan trials. The first three analyses are from the sponsor and the last three analyses are from this medical officer.

Short-term exposure to alvimopan in POI studies was not associated with an increased risk of CV SAEs or MIs, compared to placebo exposure. The overwhelming majority of patients, who received alvimopan in these short-term POI studies, received 12 mg or 24 mg of alvimopan daily for about 7 days. In contrast, patients who received alvimopan in the OIC studies received 0.5 mg to 2 mg of alvimopan daily from 3 weeks to about 9 months [at the time of the sponsor's May 2006 submission regarding these CV SAEs, patients in the 12 month, safety study (Study 14) received at most 9 months of study treatment].

The relative risks of CV SAEs and MIs in the alvimopan groups, compared to the placebo groups, change depending on which CV SAEs are included in the analyses. The relative risks of unequivocal CV SAEs and unequivocal MIs in controlled alvimopan studies ≥ 2 weeks duration in the alvimopan groups, compared to the placebo groups, were 1.38 and 1.22, respectively. This medical officer will ask the sponsor to estimate 95% confidence intervals of these relative risks and estimate the incidence density ratios for these analyses.

Table 3: Incidence and relative risk of CV SAEs in alvimopan studies

	Treatment Groups	Cumulative Risk
Incidence of CV SAEs in POI studies[1,2]	Alvimopan	0.55% (14/2548)
	Placebo	0.81% (11/1365)
	Alvimopan/Placebo	**RR=0.68**
Incidence of MIs in POI studies[1,2]	Alvimopan	0.31% (8/2548)
	Placebo	0.29% (4/1365)
	Alvimopan/Placebo	**RR=1.07**
Incidence of CV SAEs in OIC studies[1,3]	Alvimopan	0.63% (11/1760)
	Placebo	0.37% (3/813)
	Alvimopan/Placebo	**RR=1.69**
Incidence of CV SAEs in controlled alvimopan trials ≥ 2 weeks duration[4, 5]	Alvimopan	0.54% (11/2054)
	Placebo	0.43% (4/924)
	Alvimopan/Placebo	**RR=1.26**
Incidence of CV SAEs (excluding equivocal cases) in controlled alvimopan trials ≥ 2 weeks duration[4, 5]	Alvimopan	0.44% (9/2054)
	Placebo	0.32% (3/924)
	Alvimopan/Placebo	**RR=1.38**
Incidence of MIs (excluding equivocal cases) in controlled alvimopan trials ≥ 2 weeks duration[4, 5]	Alvimopan	0.39% (8/2054)
	Placebo	0.32% (3/924)
	Alvimopan/Placebo	**RR=1.22**

1 Sponsor's analyses
2 POI studies included Studies 302, 308, 313, 301, 001, 306, 206, 214, and 213. In these POI studies, alvimopan daily doses were mostly 12 mg/day or 24 mg/day for about 7 days.
3 OIC GSK studies in cancer (Study 7 and ABD101684) and noncancer patients (Studies 11, 12, 13, and 14)
4 This medical officer's analyses
5 Controlled alvimopan trials ≥ 2 weeks duration include Studies 7, 11, 12, 13, and 14 and Studies 217 and 304 (Adolor OIC studies) and Study 7 (chronic constipation study)

3.0 RECOMMENDATIONS FOR REGULATORY ACTION:

This medical officer believes that a causal association of alvimopan and serious cardiovascular events has not clearly been established at this time. However, this medical officer will request additional information from the sponsor to elucidate if a causal cardiovascular safety signal exists with alvimopan use. This medical officer agrees with the sponsor's decision to continue the ongoing alvimopan trials, to increase cardiovascular safety monitoring in the ongoing alvimopan trials, to notify the relevant regulatory authorities and investigators about the serious cardiovascular events, and to establish an independent Data Monitoring Committee (to establish stopping rules in the ongoing alvimopan trials).

This medical officer has the following information requests/questions:

1) Provide narratives for all the serious cardiovascular (CV) events [including myocardial infarctions (MIs) and unstable angina] that occurred in Study 767905/007 (the phase II, chronic constipation trial);
2) Provide narratives of the two "cardiac arrests" (Patients 1347 and 1349) that occurred in Study SB-767905/008 (Study 8);

3) Provide more details regarding the death of Patient 2077 in Study 8 and the serious adverse events (SAEs) of Patient 2474 in Study 8;
4) Provide more details regarding the MI that occurred in Patient 1650 in Study SB-767905/11 (Study 11);
5) Provide the troponin-I levels of patient 807 in Study SB-767905/14 (Study 14) and the hospital laboratory reference range for troponin-I levels;
6) Provide more details regarding the adverse events of Patient 13689 in Study 14 and provide the identity of the study treatment received by Patient 13689;
7) Provide the incidence rate of each of the following SAEs in the alvimopan and placebo treatment groups in the controlled alvimopan trials ≥ two weeks duration: MIs, unstable angina, and all serious CV events;
8) Provide the incidence rate of each of the following SAEs in the alvimopan and placebo treatment groups in controlled alvimopan noncancer trials ≥ two weeks duration: MIs, unstable angina, and all serious CV events;
9) Did your May 16, 2006 briefing package include all of the patients in the controlled, alvimopan trials of ≥ 2 weeks duration that had unstable angina?;
10) Calculate the incidence rate per 100 patient years and the incidence density risk (IDR) of the alvimopan and placebo treatment groups with 95% confidence intervals of the following:

- CV SAEs in the post-operative ileus (POI) studies;
- MIs in the POI studies;
- CV SAEs in the opioid-induced constipation (OIC) studies;
- MIs in the OIC studies;
- CV SAEs in the controlled, alvimopan studies ≥ 2 weeks duration;
- MIs in the controlled, alvimopan studies ≥ 2 weeks duration;

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/s/

Eric Brodsky
7/27/2006 05:49:13 PM
MEDICAL OFFICER

Ruyi He
7/28/2006 09:12:38 AM
MEDICAL OFFICER

MEMORANDUM

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

DATE: July 15, 2005

FROM: Julie Beitz, MD

SUBJECT: Deputy Office Director Memo

TO: NDA 21-775 Alvimopan Capsules; Adolor Corporation

Alvimopan is a μ-opioid receptor antagonist that has been evaluated in the postoperative setting for the management of ileus, a common cause of prolonged hospitalization. It has received Fast Track designation and has been selected for inclusion in the Continuous Marketing Application Pilot 1. This memo documents my concurrence with the Division of Gastrointestinal and Coagulation Product's approvable action for alvimopan capsules to accelerate time to recovery of gastrointestinal function following bowel resection surgery.

On August 24, 2004, Adolor Corporation submitted NDA 21-775 containing three randomized, double-blind, placebo-controlled studies in support of an indication to *accelerate time to recovery of gastrointestinal function following abdominal or pelvic surgery.* In February 2005, post hoc subgroup analyses in 346 complex hysterectomy patients were performed by the sponsor and lead to a modification of the proposed indication to *accelerate time to recovery of gastrointestinal function following major abdominal or complex pelvic surgery.* At a March 16, 2005 meeting, the Division advised Adolor that their submitted studies did not support an indication in pelvic surgery and that their post hoc analysis in a select group of complex hysterectomy patients, a population not previously specified, was exploratory and would need to be further evaluated in prospective clinical trials. At a teleconference on July 14, 2005, Adolor proposed to revise its indication yet again to *accelerate time to recovery of gastrointestinal function following bowel resection surgery.* The proposed regimen is alvimopan 12 mg (two 6 mg capsules) administered orally within 30 minutes and no more than 5 hours prior to surgery, then 12 mg bid daily beginning the day after surgery for up to 7 days.

In January 2005, results of a fourth randomized, double-blind, placebo-controlled study in bowel resection patients conducted in Europe, Australia and New Zealand (sponsored by Adolor's partner, GlaxoSmithKline) became available. The Division requested a full study report which was submitted in April 2005. The magnitude of this submission necessitated extension of the review clock.

All four studies randomized patients 1:1:1 to receive 6 mg, 12 mg or placebo orally prior to surgery, then bid daily beginning the day after surgery for up to 7 days. The primary efficacy endpoint was GI^3 or the time (in hours) to recovery of both upper GI tract motility (defined as the time from the end of surgery to the time of first tolerated solid food) and lower GI tract motility (defined as the time from the end of surgery to the first flatus or the first bowel movement). FDA statistical reviewers re-calculated the median time to recovery of gastrointestinal tract motility derived from Kaplan-Meyer survival curves as described in the *Draft Guidance for Industry: Clinical Studies Section of Labeling for Prescription Drugs and Biologics – Content and Format.* Hazard ratios of alvimopan to placebo were calculated by the sponsor and FDA from a Cox proportional hazards model that included treatment.

In FDA's analysis of the bowel surgery patient subgroup, Study 14CL302 demonstrated a significant hazard ratio of 1.48 (95% CI: 1.10, 1.98) for the 6 mg dose of alvimopan compared to placebo (p=0.009). Study 14CL313 demonstrated a significant hazard ratio of 1.49 (95% CI: 1.17, 1.91) for the 12 mg dose of alvimopan compared to placebo (p=0.002). In addition, there were positive trends favoring the 6 mg dose compared to placebo in Study SB767905/001 (hazard ratio 1.22), and favoring the 12 mg dose compared to placebo in Study 14CL308 (hazard ratio 1.32). In both instances, the lower bound of the 95% CI of the

hazard ratio excluded 1.0 but the p value was too large (> 0.025). When both doses are considered together, time to gastrointestinal recovery, when assessed at 108 hours post-surgery, ranged from one hour longer to 17 hours shorter relative to placebo suggesting that an earlier hospital discharge would be possible for some alvimopan-treated patients. The Division has concluded and I agree that these results do not show substantial evidence of efficacy for either the 6 mg or the 12 mg dose of alvimopan, and that a statistically significant positive finding for the 12 mg dose in the ongoing US bowel surgery study (14CL314) would be needed for approval.

In FDA's analysis of the pelvic surgery patient subgroup, Study 14CL313 demonstrated a significant hazard ratio of 12.97 (95% CI: 2.36, 71.39) for the 12 mg dose of alvimopan compared to placebo (p=0.003). This finding was not confirmed in any other study, including Study 14CL306 that enrolled only hysterectomy patients. No significant findings or positive trends (i.e., comparisons for which the hazard ratio excluded 1.0) were observed for the alvimopan 6 mg dose. The Division has concluded and I agree that both the 6 mg and 12 mg dose of alvimopan are not effective in this patient subgroup.

A randomized, double-blind controlled trial in bowel resection patients in the US is ongoing (Study 14CL314) and is expected to complete in 2006. This study compares 12 mg alvimopan to placebo using a similar composite endpoint representing recovery of upper and lower GI tract motility. Before this application may be approved, it will be necessary for the sponsor to submit the final study report of the ongoing US study in an effort to replicate the efficacy findings for alvimopan 12 mg in bowel resection patients that have been observed to date. An FDA Advisory Committee Meeting may need to be convened during the next review cycle to discuss the strength of the findings and their clinical relevance.

The safety profile of alvimopan 6 mg and 12 mg is acceptable. The most common treatment-emergent side effects reported were gastrointestinal in nature, including nausea and vomiting, abdominal distention, flatulence, diarrhea, constipation, and dyspepsia. These events occurred with similar frequency in the alvimopan and placebo treatment arms. As might be expected, the frequency of postoperative ileus was lower on alvimopan (6.8% on 6 mg, 4.1% on 12 mg) as compared to placebo treatment (9.5%). The frequency of opioid withdrawal symptoms in alvimopan-treated patients was similar to that of placebo-treated patients.

Tradename Review
The tradename "Entereg" is acceptable.

Labeling
Product labeling remains unresolved at this time.

Phase 4 Studies
No phase 4 studies are requested at this time.

Julie Beitz, MD
Deputy Director,
Office of Drug Evaluation III
CDER, FDA

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/s/

Julie Beitz
7/21/05 10:13:58 AM
DIRECTOR

07/14/05

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: 07/14/2005

FROM: Joyce A Korvick, MD, MPH

DGCDP/ODE III

SUBJECT: Deputy Division Director Approvable Comments
NDA 21-775

APPLICANT: **Adolor Corporation**

DRUG: **Entereg® (Alvimopan capsules)**

DIVISION RECOMMENDATION:
I am in agreement with the Division's recommendation that this application be made approvable.

In the original application, Adolor proposed that "Alvimopan is indicated to accelerate time to recovery of GI function following abdominal or pelvic surgery". During a March 16, 2005 meeting (mid-cycle) between Adolor Corporation and the Division of Gastrointestinal and Coagulation Drug Products, Adolor Corporation proposed to revise the indication to the following: Alvimopan is "indicated to accelerate time to recovery of gastrointestinal function following major abdominal or complex pelvic surgery". However, in the March 2005 meeting, the Division of Gastrointestinal and Coagulation Drug Products stated that the efficacy data did not support modification of the original indication and therefore the revised indication was unacceptable. On July 14, 2005 Adolor proposed dropping the pelvic surgery from the indication.

The proposed dosing regimen is 12 mg of alvimopan 0.5 to 5 hours prior to the surgery. Then, 12 mg of alvimopan BID for a maximum of 7 days (POD 1 to POD 7) while the patient is hospitalized or until discharge from the hospital.

DEFICIENCIES:

1. **Inadequate proof of efficacy in:**
    a. **Recovery of GI function after abdominal surgery:** This deficiency should be placed in the approvable letter.
    b. **Recovery of GI function after gynecologic surgery:** the medical reviewer outlines the data upon which this judgment is based (this deficiency does not need to be placed in the letter since the sponsor has proposed withdrawing it from the proposed indication).

Recommendations for resolution of deficiencies:

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 statistical significance and clinical meaningfulness of the proposed dosing regimen.
2. Justify you conclusion that the results of the time-to analyses are clinically meaningful.

ADDITIONAL REQUESTS: The biopharmaceutics comments should be added to the action letter as requests, they are not meant as deficiencies. See biopharmaceutics section below.

BACKGROUND:

Alvimopan was given Fast Track Status and participated in the Pilot-1 CMA program. CMC and pharm/tox reviewable units were submitted on May 27, 2004. The complete NDA was filed August 24, 2004. It was designated a standard review because of significant review issues which were identified in the 74-day memo. They included the following:

> 1) "It appears that 12 mg of Entereg demonstrated statistical significance over placebo in the primary efficacy endpoint [the time to tolerate the first solid meal and (the time to the first bowel movement or first flatus)] in only one (313) of the four Phase III efficacy trials (302, 308, 313, and 306).
> 2) It appears that 12 mg of Entereg demonstrated statistical significance over placebo in a secondary endpoint (time to discharge written) in only two (313 and 308) of the four Phase III efficacy trials.
> 3) In Trial 313, the demonstration of a positive primary efficacy endpoint may have been due to the poor placebo response."

The division was preparing to take this application to an Advisory Committee Hearing when the results from a European study (001) were made public. It was reported that this study was a negative study. This study was similar in design to those which were submitted in the original NDA and conducted by Aldolor. The Division met with the sponsor and agreed that it would be premature to hold an AC and we requested the study report for this study. Adolor responded with a substantial amendment in the final month of the review cycle and the clock was extended by 3 months. Results from the analyses of these studies are well described in the statistical and clinical reviews and are discussed below.

Alvimopan (ADL 8-2698) is a μ-opioid receptor antagonist with no agonist activity. The inhibitory effects of opioids on gastrointestinal (GI) motility are considered to be primarily mediated through μ -opioid receptors located within the enteric nervous system. Alvimopan is intended to act peripherally without producing reversal of the desired, centrally mediated, analgesic effects of opioids.

Following oral administration of Entereg capsules, another compound, identified as ADL 08-0011, was found to be present in the plasma. ADL 08-0011 is an amide hydrolysis

product of Alvimopan and an antagonist at the μ -receptor and is approximately equipotent to Alvimopan in nonclinical models. In contrast to the relative NDA 21-775 CPB Review 3 inability of alvimopan to antagonize the CNS effects of morphine, ADL 08-0011 has been demonstrated to antagonize morphine-induced analgesia in animal studies. This did not occur, however, until doses were 5-8-fold higher than those to reverse GI effects in the rat with intravenous (IV) administration. In addition, autoradiographs in rats do not demonstrate the presence of alvimopan or its metabolites in the brain tissue. The metabolite (ADL 08-0011) is produced by the action of intestinal bacteria on the parent compound.

I. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

A. OPDRA/DDMAC/DMETS:

The original review by DMETS of the proposed name, Entereg, concluded that it was acceptable. DDMAC consult recommended labeling wording, however, the labeling is not being acted upon this review cycle. An additional consult to DDMAC will be made during the next cycle.

B. Chemistry and Manufacturing:

Based upon the CMC review, the NDA is recommended for approval. The overall EES recommendation is acceptable as of April 25, 2005.

C. Pre-Clinical Pharmacology/Toxicology:

There were no significant pharmacologic or toxicological concerns raised by the reviewers. Overall, they recommend that the preclinical data were adequate to support the approval of Alvimopan for the proposed use in post-operative patients.

D. Biopharmaceutics:

The biopharmaceutics team had the following comments regarding the submission.

"Pharmacokinetics and Biopharmaceutics section of the NDA is acceptable provided that (i) a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert and (ii) the sponsor satisfactorily addresses the comments listed below." (These comments should be included in the action letter as requests to the sponsor which can be answered in the future and not deficiencies).

Comments

1. "The potential of alvimopan and ADL 08-0011 as CYP inducers should be evaluated with hepatocytes from at least 3 donors. (The studies conducted for alvimopan were inadequate and no studies were conducted for ADL 08-0011.)"
2. "The following comments pertain to the population PK analysis:

a. Vss/F was estimated to be 1949 L from the population PK analysis, which is much higher than expected from a Vss estimate of 30 L following IV administration and a F of <10%. The model does not seem to describe well the alvimopan pharmacokinetics.
b. Some covariates were found to impact on the fraction of drug absorbed (F). It is unclear whether the covariates were tested for their impact on CL (or CL/F).
c. Analysis on creatinine clearance may be inaccurate. It is noted that, in the population PK dataset, creatinine clearance (CLcr) ranged up to >300 mL/min. In the calculation of CLcr, adjustment may be made for subjects with high BMI. Alternatively, a maximum limit in CLcr may be imposed in the population PK analysis. This, however, does not seem to have been done based on the control codes provided.
d. For analysis pertaining to drug-drug interactions, separate analysis should be performed for each drug. In addition, a table should be provided listing the number of patients on each dose.
e. It is noted that some covariates are concentrated in certain studies. For the information to be included in the label, the covariates should be further examined/tested to verify that samples size was adequate and that the impact of the covariate was not driven by one particular study."

Thorough evaluation of QT effects of alvimopan revealed a slight dose response; however, this was not meaningful when compared to Moxifloxacin, the active control.

II. Clinical/Statistical:

A. Efficacy: The four phase 3 trials (302, 308, 313, and 001) were randomized, double-blind, placebo-controlled, parallel-group, multi-center trials in patients who were scheduled to have elective GI or gynecologic surgery. In these trials for GI surgery, only partial large bowel resection (BR) and partial small BR were allowed. Additionally, in these trials for pelvic surgery, only open simple Total Abdominal Hysterectomy (sTAH) and open radical Total Abdominal Hysterectomy (rTAH) were allowed. All four trials randomly assigned patients to receive 6 mg of alvimopan, 12 mg of alvimopan or placebo at least two hours prior to the scheduled surgery and then bid beginning postoperative day 1 until postoperative day 7 or discharge from the hospital.

The primary outcome variable was designated as GI3 which included recovery of upper and lower GI tract function. This composite endpoint consisted of the time from the end of surgery to the time of the patient's ability to tolerate solid food, of first flatus or first bowel movement (whichever occurred first). Dr. Brodsky's and Dr. Castillo's reviews discuss the sub-analysis of results by type of surgery which does have a

significant impact on post-operative bowel function. It appears from these analyses and also from the sponsor's point of view, that the pelvic surgery patients did not appear to derive significant benefit from the treatment with Alvimopan.

The sponsor provided analysis for time to recovery of GI function (GI3) in the GI surgery subgroup in Studies 302, 308, 313, and 001. The results of the median time to GI3 were inconsistent across treatment groups within and between studies. The 12 mg dose was statistically significant in study 313 (93 hrs vs 103 hrs, respectively) only, while the 6 mg dose was statistically significant in study 302 (94 hrs vs 104 hrs, respectively). The clinical meaningfulness of these differences is not clear, but it may be supported by several pre-specified secondary analyses: READY and DISCHARGE. READY was statistically significant for the 12mg dose in study 313 as well as 302 and 308. DISCHARGE was statistically significant for study 313 as well as 308. However, there remains this overall inconsistency.

The results of Study 001 did not demonstrate and clinically statistical differences among the treatment groups.The sponsor considered regional differences in patient management following surgery to be the main reason for the failure of Study 001 which was conducted in Europe, Australia and New Zealand. Another study (14CL314) is currently ongoing in the U.S. which will enroll about 660 GI patients (no gynecologic patients) to compare the 12 mg alvimopan group and the placebo group for the time to recovery of GI functions following abdominal surgery. This large study may support the approval of this indication if the data are robust enough. This study will be completed by the end of 2005.

B. **Safety:** Safety database included 2902 patients who received alvimopan. No serious safety signals have be seen in the alvimopan treatment groups compared to placebo.

III. **Pediatric Use:** This will be addressed in the next cycle

IV. **Labeling:** This will be addressed in the next cycle after the findings of efficacy and safety are approved.

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/s/

Joyce Korvick
7/14/05 06:38:21 PM
MEDICAL OFFICER

07/14/05

MEMORANDUM

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

Date: July 14, 2005

From: Ruyi He, M.D.
Medical Team Leader, GI Team II
Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Subject: Medical Team Leader Review for NDA 21-775, Entereg (Alvimopan) capsules, submitted 6/25/04

The proposed indication: Accelerate time to recover of GI function following abdominal or pelvic surgery

Proposed Dosing Regimen: 12 mg of alvimopan 0.5 to 5 hours prior to the surgery. Then, 12 mg of alvimopan BID for a maximum of 7 days (POD 1 to POD 7) while the patient is hospitalized or until discharge from the hospital.

Applicant: Adolor Corporation

Priority Designation: Standard

To: NDA 21-775

RECOMMENDATIONS:

I have following recommendations on regulatory action for NDA 21-775 (alvimopan):

- an approvable action for the 12 mg dose of Entereg (alvimopan) Capsules to accelerate the time to recovery of gastrointestinal (GI) function following abdominal surgery (partial large or partial small bowel resection).
- [redacted]
- [redacted]

To obtain approval of the 12 mg dose of alvimopan in GI surgery patients, the sponsor should provide one additional adequate and well-controlled study to confirm statistical significance and clinical meaningfulness of the 12 mg alvimopan dose. An Advisory Committee Meeting may be useful to discuss the clinical meaningfulness of these results.

BACKGROUND:

Postoperative ileus (POI) commonly follows abdominal or pelvic surgery. It is associated with frequent and unpleasant symptoms including nausea, vomiting, abdominal distension/bloating and pain. The duration and severity of POI cannot be reliably predicted. Passage of flatus, stool and the ability to tolerate solid food are the clinical events that represent resolution of POI.

Opioid-based regimens remain the "gold standard" for postoperative pain management. Despite providing effective pain control, morphine and other μ-opioid receptor agonists prolong the duration of POI through a variety of mechanisms including delayed gastric emptying, reduced GI motility and disrupted colonic myoelectric activity.

Current approaches for the management of POI yield inconsistent results, often limiting treatment to supportive measures only. There are no currently approved drugs indicated for the management of POI.

Alvimopan is a novel, selective, peripherally-acting μ-opioid receptor antagonist. The potent effects of opioids on GI motility are primarily mediated through μ-opioid receptors within the enteric nervous system. Following oral administration, alvimopan antagonizes the peripheral effects of opioids on GI motility and secretion by competitively binding to GI tract μ-opioid receptors. Alvimopan achieves this selective GI opioid antagonism without reversing the central analgesic effects of μ-opioid agonists.

In the original NDA submission, the sponsor submitted three Phase 3 studies (14CL302, 14CL308, and 14CL313) conducted in the U.S. to support alvimopan reduces the duration of POI by accelerating recovery of GI function following abdominal or pelvic surgery. On April 8, 2005, per the Division's request, the sponsor provided dataset and summaries on the GlaxoSmithKline Study 001 which was finished in December 2004 and was conducted in Europe and Asia-Pacific. Because of this major amendment, the review goal date was extended for three additional months.

EFFICACY

The four phase 3 trials (302, 308, 313, and 001) were randomized, double-blind, placebo-controlled, parallel-group, multi-center trials in patients who were scheduled to have elective GI or gynecologic surgery. In these trials for GI surgery, only partial large bowel resection (BR) and partial small BR were allowed. Additionally, in these trials for pelvic surgery, only open simple Total Abdominal Hysterectomy (sTAH) and open radical Total Abdominal Hysterectomy (rTAH) were allowed.

In all four trials, patients were randomly assigned (1:1:1) to receive 6 mg of alvimopan, 12 mg of alvimopan, or placebo, given by mouth at least two hours prior to the scheduled start of surgery and then twice daily beginning postoperative day 1 until postoperative day 7 (or until hospital discharge).

In the four studies, the primary efficacy endpoint was the time to recovery of both upper and lower GI tract function following GI or gynecologic surgery. The time to recovery of upper GI tract function was defined as the time from the end of surgery to the time to first tolerate solid food. The time to recovery of lower GI tract function was defined as the time from the end of surgery to the time to first flatus or first bowel movement (whichever occurred first). This 3-component, composite endpoint (solid food, flatus or bowel movement) was identified as GI^3.

Efficacy in the GI surgery subgroup

Table 1 summaries the GI subgroup results of the primary efficacy endpoint — the time to recovery of upper and lower GI function following surgery.

Table 1: Time to recovery of GI function (the primary efficacy endpoint, GI^3) for the GI surgery subgroup in Studies 302, 308, 313, and 001

Study	Treatment Group	N	Median Time analysis [a] (Hour)	Difference (Hour)	Hazard Ratio	p-value
302	Placebo	99	104.3			
	6 mg	99	94.5	9.8	1.48	0.009*
	12 mg	98	96.7	7.6	1.30	0.086
308	Placebo	142	113.0			
	6 mg	137	101.0	12	1.23	0.106
	12 mg	139	99.6	13.4	1.32	0.029
313	Placebo	142	103.0			
	6 mg	149	96.5	6.5	1.25	0.084
	12 mg	160	92.5	10.5	1.49	0.002*
001	Placebo	229	81.3			
	6 mg	237	74.6	6.7	1.22	0.042
	12 mg	238	76.9	4.4	1.13	0.20

[a] Sponsor's median analysis: Estimate time in hours was calculated from a Cox proportional hazards model.
* Statistically significant after adjustment for multiple comparisons using the Hochberg method.

For the primary efficacy endpoint (GI^3) in the GI surgery subpopulation, the 6 mg alvimopan dose showed statistical significance compared to placebo in only one (302) of the four phase 3 trials. In Study 302, the 6 mg alvimopan group and the placebo group achieved GI^3 in 94.5 and 104.3 hours, respectively (9.8 hours median difference). The 9.8 hours difference in time to GI recovery may not be clinically meaningful. In addition, the 12 alvimopan dose in the same study did not demonstrate statistical and clinical significance compared to placebo (7.6 hours difference, p=0.086). The statistical and clinical failures at the higher alvimopan dose (12 mg) in Study 302 make the positive statistical results of the 6 mg alvimopan dose in this study unreliable.

In the GI surgery subgroup, the 12 mg dose demonstrated statistical significance compared to placebo in the primary efficacy endpoint (GI^3) in Study 313 only. In Study 313, the 12 mg alvimopan group and the placebo group achieved GI^3 in 92.5 and 103 hours, respectively (10.5 hours median difference, p=0.002). In Study 308, the 12 mg alvimopan group and the placebo group achieved GI^3 in 99.6 and 113 hours, respectively (13.4 hours median difference, p=0.029). These 2 studies showed that 12 mg alvimopan may have potential efficacy (GI^3) to accelerate the time to recovery of GI function following abdominal surgery. The sponsor considered that regional difference (the Europe vs. the U.S.) in patient management following surgery was the main reason for the failure of Study 001 which was conducted in Europe, Australia and New Zealand. Another study (14CL314) is currently ongoing in the U.S. which will enroll about 660 GI patients (no gynecologic patients) to compare the 12 mg alvimopan group and the placebo group for the time to recovery of GI functions following abdominal surgery. This study will provide very useful information about efficacy of alvimopan and the result from this study will be essential for final regulatory decision.

Table 2 summaries the responder analysis at the 108 hours cut-off point. A small BR or large BR patient was considered a responder if he/she achieved recovery of GI function (GI^3) within 108 hours after surgery.

Table 2: Responder analysis for GI Subgroup Population at 108 hours Point

Studies	Treatment Group	Number of patient N	Responders (%)	Difference %
302	Placebo	99	47.5	
	6 mg	99	64.6	17.1
	12 mg	98	63.3	15.8
308	Placebo	142	50.0	
	6 mg	137	53.3	3.3
	12 mg	139	60.4	10.4
313	Placebo	142	53.3	
	6 mg	149	59.1	5.6
	12 mg	160	64.4	10.9
001	Placebo	229	70.7	
	6 mg	237	74.3	3.6
	12 mg	238	69.9	-0.8

Source: Statistical review by Dr. Castillo, Table B.1.
* p-value for difference is statistically significant based on chi-square test and after adjustment for multiple comparisons using Hochberg's procedure. In Study 302, the p-values for 6 mg and 12 mg at Day 4.5 (108 hrs) are 0.0149 and 0.0258, respectively.

All 3 studies conducted in the U.S. showed that there were more responders (10% to 16% more) in the 12 mg group than in the placebo group. These results further support that 12 mg alvimopan may have potential efficacy to accelerate the time to recovery of GI function following GI surgery.

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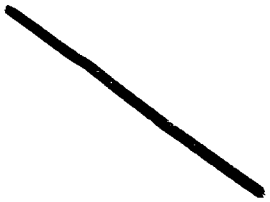
✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 2



In conclusion, 12 mg alvimopan may have potential efficacy (GI^3) to accelerate the time to recovery of GI function following abdominal surgery. Additional study is needed to confirm this result. The studies demonstrated that 6 mg alvimopan does not have efficacy to accelerate the time to recovery of GI function following abdominal surgery. Both alvimopan doses (6 mg and 12 mg) did not demonstrate efficacy in the treatment of POI in the gynecologic subpopulation.

SAFETY

The entire alvimopan safety data base contained 4181 subjects/patients in which 2902 received alvimopan (doses ranging from 0.125 mg/day to 120 mg/day) and 1233 received placebo. The postoperative ileus subpopulation contained 3326 patients (of which 2285 received alvimopan and 1041 received placebo). Of the 2285 patients who received alvimopan in the eight postoperative ileus trials, 66, 898, and 1321 patients received 1 mg or 3 mg, 6 mg, and 12 mg of alvimopan, respectively. In the eight postoperative ileus trials, the median duration of alvimopan exposure was five to six days and the total median alvimopan exposure for the entire trial duration was 0, 48, and 125 mg of alvimopan for the placebo group, the 6 mg alvimopan group, and the 12 mg alvimopan group, respectively.

In the entire safety database, there were 18 deaths. All 18 deaths occurred in the POI subpopulation. Of the 18 deaths, 7 occurred in patients taking placebo (7/1041, 0.67%), 5 occurred in patients taking 6 mg of alvimopan (6/898, 0.67%), and 6 occurred in patients taking 12 mg of alvimopan (6/1321, 0.45%). No death was directly related to the study drug. Majority of death were due to underline diseases and infection/sepsis.

A summary of Treatment-Emergent Serious Adverse Events (TESAEs) reported in $\geq$ 0.5% of total overall POI population in the U.S subjects is presented in Table 4. The proportion of subjects who reported TESAEs was lower in the alvimopan groups compared to placebo (placebo 17.0%, alvimopan 6 mg 10.8%, and alvimopan 12 mg 8.2 %). The incidence of POI reported as a TESAE was lower in the alvimopan 6 mg or 12 mg group compared to placebo.

Table 4: Treatment-Emergent Serious Adverse Events (≥ 0.5% in Either the Total Alvimopan or Placebo Groups) - Overall POI Population in the U.S

SOC/ Preferred Term*	Placebo (N=748) N (%)	Alvimopan 6 mg (N=604) N (%)	Alvimopan 12 mg (N=1024) N (%)	Alvimopan Total[a] (N=1690) N (%)
Subjects with at least one AE				
Total	127 (17.0)	65 (10.8)	84 (8.2)	154 (9.1)
Mild	12 (1.6)	6 (1.0)	11 (1.1)	17 (1.0)
Moderate	58 (7.8)	33 (5.5)	33 (3.2)	69 (4.1)
Severe	57 (7.6)	26 (4.3)	40 (3.9)	68 (4.0)
Injury, Poisoning and Procedural Complications	67 (9.0)	33 (5.5)	38 (3.7)	71 (4.2)
GI disorder NOS, postoperative	20 (2.7)	13 (2.2)	10 (1.0)	23 (1.4)
Postoperative ileus	35 (4.7)	10 (1.7)	9 (0.9)	19 (1.1)
Therapeutic procedural complication	3 (0.4)	2 (0.3)	8 (0.8)	10 (0.6)
Infections and Infestations	31 (4.1)	16 (2.6)	20 (2.0)	37 (2.2)
Postoperative abscess	5 (0.7)	7 (1.2)	3 (0.3)	10 (0.6)
Postoperative wound infection	10 (1.3)	3 (0.5)	7 (0.7)	10 (0.6)
Urinary tract infection NOS	4 (0.5)	0	0	1 (0.1)
Gastrointestinal Disorders	17 (2.3)	8 (1.3)	4 (0.4)	14 (0.8)
Vomiting NOS	4 (0.5)	0	1 (0.1)	2 (0.1)
Vascular Disorders	9 (1.2)	6 (1.0)	11 (1.1)	18 (1.1)
Pulmonary embolism	3 (0.4)	3 (0.5)	7 (0.7)	11 (0.7)
Cardiac Disorders	12 (1.6)	5 (0.8)	7 (0.7)	12 (0.7)
Atrial fibrillation	5 (0.7)	1 (0.2)	2 (0.2)	3 (0.2)

Source: ISS Section 18.2; Table 5.4.2.2.1

NOS=not otherwise specified. [a] Total includes 62 subjects who received alvimopan 1-3 mg.

Note: A subject who had more than one AE in the same category was counted only once.

A summary of Treatment-Emergent Adverse Events (TEAEs) for the POI population in the U.S. is presented in Table 5. The TEAEs were most commonly associated with the GI system, and nausea was the most frequently reported TEAE. The incidence of nausea was comparable among treatment groups (placebo 61.6%, alvimopan 6 mg 56.3%, and alvimopan 12 mg 62.4%). Other GI-related TEAEs including vomiting, abdominal distension, flatulence, diarrhea, and dyspepsia were also reported at comparable rates among treatment groups. Postoperative ileus reported as a TEAE was lower in the alvimopan groups compared to placebo (placebo 9.5%, alvimopan 6 mg 6.8%, and alvimopan 12 mg 4.1%).

Table 5: Treatment-Emergent Adverse Events by Frequency (≥ 5% in Any Treatment Group) - Overall POI Population in the U.S.

		Alvimopan		
	Placebo (N=748)	6 mg (N=604)	12 mg (N=1024)	Total · (N=1690)
Preferred Term	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Subjects with one or more TEAEs	**703 (94.0)**	**566 (93.7)**	**975 (95.2)**	**1601 (94.7)**
Nausea	461 (61.6)	340 (56.3)	639 (62.4)	1017 (60.2)
Vomiting NOS	198 (26.5)	135 (22.4)	246 (24.0)	394 (23.3)
Abdominal distension	109 (14.6)	76 (12.6)	115 (11.2)	203 (12.0)
Pyrexia	103 (13.8)	73 (12.1)	108 (10.5)	187 (11.1)
Flatulence	89 (11.9)	56 (9.3)	130 (12.7)	195 (11.5)
Pruritus NOS	94 (12.6)	70 (11.6)	116 (11.3)	190 (11.2)
Constipation	84 (11.2)	35 (5.8)	138 (13.5)	178 (10.5)
Headache NOS	71 (9.5)	64 (10.6)	112 (10.9)	182 (10.8)
Hypotension NOS	85 (11.4)	70 (11.6)	83 (8.1)	159 (9.4)
Insomnia	67 (9.0)	64 (10.6)	90 (8.8)	162 (9.6)
Hypertension NOS	67 (9.0)	65 (10.8)	90 (8.8)	157 (9.3)
Tachycardia NOS	63 (8.4)	51 (8.4)	65 (6.3)	122 (7.2)
Oliguria	75 (10.0)	47 (7.8)	59 (5.8)	108 (6.4)
Diarrhea NOS	57 (7.6)	47 (7.8)	66 (6.4)	115 (6.8)
Hypokalemia	63 (8.4)	50 (8.3)	57 (5.6)	108 (6.4)
Postoperative ileus	71 (9.5)	41 (6.8)	42 (4.1)	84 (5.0)
Dyspepsia	44 (5.9)	27 (4.5)	64 (6.3)	102 (6.0)
Body temperature increased	52 (7.0)	41 (6.8)	50 (4.9)	91 (5.4)
Dizziness	41 (5.5)	27 (4.5)	66 (6.4)	96 (5.7)
Urinary tract infection NOS	39 (5.2)	17 (2.8)	55 (5.4)	75 (4.4)

Source: ISS Section 18.2; Table 5.9.1.2.1

NOS=not otherwise specified. ·Total includes 62 subjects who received alvimopan 1-3 mg.

Note: A subject who had more than one AE in the same category was counted only once.

In summary, both doses of alvimopan (6 mg or 12 mg) demonstrated no significant safety signals from those clinical studies.

CONCLUSIONS AND RECOMMENDATIONS:

In conclusion, 12 mg alvimopan may have potential efficacy (GI^3) to accelerate the time to recovery of GI function following abdominal surgery. Additional study is needed to confirm this result for final approval. [redacted]

[redacted] Both alvimopan doses (6 mg and 12 mg) did not demonstrate efficacy in the treatment of POI in the gynecologic subpopulation. No significant safety signals have been identified for either alvimopan dose (6 mg or 12 mg).

I concur with Dr. Eric Brodsky's recommendations on regulatory action (see his Medical Officer Review dated 7/12/05 for details):

- an approvable action for the 12 mg dose of Entereg (alvimopan) Capsules to accelerate the time to recovery of GI function following abdominal surgery (partial large or partial small bowel resection).
- [redacted]
- [redacted]

To obtain approval of the 12 mg dose of alvimopan to accelerate the time to recovery of GI function following abdominal surgery, the sponsor should provide an additional adequate and well-controlled study to confirm statistical significance and clinical meaningfulness of the 12 mg alvimopan dose. An Advisory Committee Meeting may be useful to discuss the clinical meaningfulness of these results.

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/s/

Ruyi He
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MEDICAL OFFICER

07/12/05

CLINICAL REVIEW TEMPLATE

Application Type	NDA
Submission Number	21-775
Submission Code	000
Letter Date	6/25/04
Stamp Date	6/25/04
PDUFA Goal Date	7/25/05
Reviewer Name	Eric Brodsky, MD
Review Completion Date	7/1/05
Established Name	Alvimopan
(Proposed) Trade Name	Entereg™
Therapeutic Class	μ-opioid receptor antagonist
Applicant	Adolor Corporation
Priority Designation	Standard
Formulation	Oral capsule
Proposed Dosing Regimen	Initial dose: 12 mg of alvimopan 0.5 to 5 hours prior to the scheduled start of the surgery on postoperative day (POD) 0. Next doses: 12 mg of alvimopan BID for a maximum of 7 days (POD 1 to POD 7) while the patient is hospitalized or until discharge from the hospital.
Original Proposed Indication	Acceleration of the time to recovery of GI function following abdominal or pelvic surgery.
Intended Population	Patients undergoing abdominal or pelvic surgery not taking chronic opioids

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This medical officer recommends an **approvable** action for the 12 mg dose of Entereg™ (alvimopan) Capsules to accelerate the time to recovery of upper and lower gastrointestinal tract motility following partial large or partial small bowel resection surgery with anastomosis.

[redacted]

To obtain approval of the 12 mg dose of alvimopan in gastrointestinal surgery patients for this postoperative ileus indication, the sponsor must:

1) Provide at least one additional adequate and well-controlled study (in patients scheduled to have partial large or partial small bowel resection surgery with anastomosis) that demonstrates statistical significance and clinical meaningfulness of the 12 mg alvimopan dose.
2) Demonstrate the clinical meaningfulness of the results of the 12 mg alvimopan dose in Studies 313 and 308. This medical officer believes that an Advisory Committee Meeting will be required to recommend the clinical meaningfulness of these results.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Risk management activities are not indicated.

1.2.2 Required Phase 4 Commitments

Required phase 4 commitments are not indicated.

1.2.3 Other Phase 4 Requests

Other phase 4 requests are not indicated.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Adolor Corporation submitted this new drug application to support the approval of oral Entereg™ (alvimopan) Capsules in the treatment of post-operative ileus. Post-operative ileus is a disorder characterized by temporary impairment of gastrointestinal (GI) tract motility (without complete blockage of the GI tract) following surgery. Adolor Corporation

originally requested the following post-operative ileus indication: Alvimopan is indicated "to accelerate time to recovery of GI function following abdominal or pelvic surgery". During a March 16, 2005 meeting (in the middle of the NDA review cycle) between Adolor Corporation and the Division of Gastrointestinal and Coagulation Drug Products, Adolor Corporation proposed to revise the indication to the following: Alvimopan is "indicated to accelerate time to recovery of gastrointestinal function following major abdominal or complex pelvic surgery". However, in the March 2005 meeting, the Division of Gastrointestinal and Coagulation Drug Products stated that the efficacy data did not support modification of the original indication and therefore the revised indication was unacceptable.

Adolor Corporation submitted a total of **36 completed clinical trials** to support the approval of their application. In the 36 trials, the entire safety database had a total population of 4181 subjects/patients. Of the 4181 subjects/patients, 2902 received alvimopan and 1233 received a control.

The most important clinical trials — to support the **efficacy** of alvimopan in the treatment of postoperative ileus — included four postoperative ileus trials. Three trials [14CL302 (identified as 302), 14CL308 (identified as 308), and 14CL313 (identified as 313)] were conducted in the United States and Canada and the final reports were submitted in the original NDA. The fourth study [Study SB-767905/001 (identified as 001)] was conducted in Europe, Australia, and New Zealand. During the NDA review cycle, the Division of Gastrointestinal and Coagulation Drug Products became aware of Study 001 and requested its submission. Subsequently, Adolor Corporation submitted the final study report of Study 001 on April 8, 2005 (during the NDA review cycle). Because of this major amendment, the review goal date was extended for three additional months (from April 25, 2005 to July 25, 2005). The four important phase 3 efficacy trials in POI had a subpopulation of 2507 patients (of which 1673 received alvimopan and 834 received placebo).

The most important clinical trials — to support the **safety** of alvimopan in the treatment of postoperative ileus — included eight postoperative ileus trials [three phase 2 trials in the United States (13C206, 13C214, and 13C213); one phase 3 trial in the United States with primary safety endpoints (14CL306 — identified as 306); and the four safety/efficacy trials (302, 308, 313, and 001)]. The eight important safety trials in POI patients had a subpopulation of 3326 patients (of which 2285 received alvimopan and 1041 received placebo).

1.3.2 Efficacy

The four most important efficacy trials (302, 308, 313, and 001) were randomized, double-blind, placebo-controlled, parallel-group, multi-center trials in patients who were scheduled to have particular elective GI or gynecologic surgery. In these trials, only the following two types of scheduled GI surgery were allowed: partial large bowel resection (BR) with anastomosis (surgical connection of two severed parts of the bowel to form a continuous channel) and partial small BR with anastomosis. Additionally, in these trials, only the following two types of scheduled gynecologic surgery were allowed: open simple Total Abdominal Hysterectomy (sTAH; removal of the entire uterus including the cervix through a large, open abdominal incision) and open radical Total Abdominal Hysterectomy (rTAH;

removal of the entire uterus including the cervix, the supporting ligaments and tissues, the upper portion of the vagina, and the pelvic lymph nodes through a large, open abdominal incision).

All four efficacy trials had the following identical design features: 1) all the trials included patients scheduled to receive large BR or rTAH surgery and 2) patients were randomly assigned (1:1:1) to receive 6 mg of alvimopan capsules, 12 mg of alvimopan capsules, or identical placebo capsules, given by mouth at least two hours prior to the scheduled start of surgery and then twice daily beginning postoperative day 1 until postoperative day 7 (or until hospital discharge). Studies 302, 308, and 313 were all conducted in the United States and Canada; whereas, Study 001 was conducted in Europe, Australia, and New Zealand.

In the four important efficacy studies, the original, pre-specified, **primary efficacy endpoint** was the time to recovery of **both upper and lower GI tract function** following GI or gynecologic surgery. The time to recovery of upper GI tract function was defined as the time from the end of surgery to the time to first tolerate solid food. The time to recovery of lower GI tract function was defined as the time from the end of surgery to the time to first flatus or first bowel movement (whichever occurred first). The primary efficacy endpoint was the time when both the upper and the lower GI tracts recovered after surgery (which ever occurred last). This 3-component, composite endpoint was identified as **GI^3** and was mathematically expressed as follows: **GI^3** = max [upper GI tract, lower GI tract] = max [solid food, min (flatus, BM)].

The four important efficacy studies had six identical secondary endpoints. The one European study had 19 additional endpoints. In the four efficacy trials, this medical officer believes that the two most important (identical), pre-specified, **secondary efficacy endpoints** were the following:

#1) The time from the end of surgery to the time that the hospital discharge order was written (identified as **DISCHARGE**).
#2) 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 (identified as **READY**).

This medical officer believes that the primary efficacy endpoint was adequate because it accounted for both upper and lower GI track motility following surgery. This medical officer believes that **DISCHARGE** 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.

Since the efficacy results were highly dependant on the surgical type, patients were divided into two subgroups: patients scheduled to have 1) GI surgery (large and small BR) or 2) Gynecologic surgery (sTAH and rTAH).

GI surgery subgroup

Primary Efficacy Endpoint (GI^3): Table I delineates the GI subgroup results of the primary efficacy endpoint – the time to recovery of upper and lower GI tract motility following surgery. In Table I, the sponsor's median analyses were derived from the Cox proportion

hazards model; whereas, the FDA's median analyses were derived from the Kaplan-Meier survival curve. Despite differences in their approach in calculating the median analyses, the sponsor and the FDA used the same method in the calculation of hazard ratios and p-values. Additionally, the sponsor and the FDA agreed on the results of the hazard ratios and the p-values.

Table I: Time to recovery of GI tract motility (the primary efficacy endpoint, GI^3) for the GI surgery subgroup (large and small BR) in Studies 302, 308, 313, and 001

Study	Treatment Group	N	Median Time in Hours Sponsor's analysis[a]	Median Time in Hours FDA's analysis[b]	Hazard Ratio[c]	p-value[c]
302	**Placebo**	99	104.3	108.3		
	Alvimopan 6 mg	99	94.5	93.3	1.48	**0.009***
	Alvimopan 12 mg	98	96.7	97.5	1.30	0.086
308	**Placebo**	142	113.0	109.8		
	Alvimopan 6 mg	137	101.0	104.5	1.23	0.106
	Alvimopan 12 mg	139	99.6	98.0	1.32	0.029
313	**Placebo**	142	103.0	98.9		
	Alvimopan 6 mg	149	96.5	96.5	1.25	0.084
	Alvimopan 12 mg	160	92.5	94.1	1.49	**0.002***
001	**Placebo**	229	81.3	81.3		
	Alvimopan 6 mg	237	74.6	74.6	1.22	0.042
	Alvimopan 12 mg	238	76.9	76.9	1.13	0.20

a Sponsor's median analysis: Estimate time in hours was calculated from a Cox proportional hazards model.
b FDA median analysis: Estimated time in hours was derived from the Kaplan-Meier survival curve.
c The FDA and the sponsor agreed on the results of the hazard ratios and the p-values.
***Statistically significant after adjustment for multiple comparisons using the Hochberg method.**
Please see Table 26 for complete references and for more details.

In the GI surgery subpopulation, the **6 mg alvimopan dose** demonstrated statistical significance compared to placebo in the primary efficacy endpoint (GI^3) in only one (302) of the four important phase 3 trials (302, 308, 313, and 001). In Study 302, the 6 mg alvimopan group and the placebo group achieved GI^3 in 94.5 and 104.3 hours, respectively, according to the sponsor's median analysis of the GI subpopulation. The sponsor calculated a 9.8 hour median difference in GI recovery between the 6 mg alvimopan group and the placebo group. This medical officer believes that the clinical meaningfulness of 9.8 hour difference in time to GI recovery is questionable and that the validity of the sponsor's methods for calculating this difference is debatable. See Table I for these results or Table 26 for more detailed results.

In the GI surgery subgroup, the **12 alvimopan dose** did not demonstrate statistical significance compared to placebo in the primary efficacy endpoint in Study 302. The statistical failure of the higher alvimopan dose (12 mg) in Study 302 diminishes the positive statistical results of the 6 mg alvimopan dose in this study.

In the GI surgery subgroup, the **12 alvimopan dose** demonstrated statistical significance compared to placebo in the primary efficacy endpoint (GI^3) in only one (313) of the four phase 3 trials. In Study 313, the 12 mg alvimopan group and the placebo group achieved GI^3 in 92.5 and 103 hours, respectively, according to the sponsor's median analysis of the GI subpopulation. The sponsor calculated a 10.5 hour median difference in GI recovery between the 12 mg alvimopan group and the placebo group. This medical officer believes that the clinical meaningfulness of 10.5 hour difference in time to GI recovery is questionable and that the validity of the sponsor's methods for calculating this difference is debatable. See Table I or Table 26.

Secondary Efficacy Endpoints (READY and DISCHARGE): In the GI surgery subpopulation, the 6 mg alvimopan dose demonstrated statistical significance compared to placebo in **READY**, an important secondary endpoint, in three (302, 308, and 313) out of the four efficacy trials and the 6 mg alvimopan dose demonstrated statistical significance compared to placebo in **DISCHARGE**, another important secondary endpoint, in two (302 and 308) out of the four efficacy trials. In the GI surgery subpopulation, the 12 mg alvimopan dose demonstrated statistical significance compared to placebo in **READY** in three (302, 308, and 313) out of the four efficacy trials and the 12 mg alvimopan dose demonstrated statistical significance compared to placebo in **DISCHARGE** in two (308 and 313) out of the four efficacy trials.

FDA Post-hoc Responder Analyses: To help elucidate the clinical meaningfulness of the efficacy results, the FDA conducted 40 post-hoc responder analyses on the primary efficacy endpoint — recovery of both upper and lower GI tract motility following surgery. A responder was defined as a GI surgery patient who achieved GI^3 within the following five cut-off points: 72 hours (3 days), 96 hours (4 days), 108 hours (5 days), 120 hours (6 days), and 144 hours (7 days). Out of the 40 responder analyses, only 4 demonstrated statistical significance. The four positive analyses were the following: the 6 mg dose compared to placebo at 108 hours in Study 302 (64.6% versus 47.5%); the 12 mg dose compared to placebo at 108 hours in Study 302 (63.3% versus 47.5%); the 12 mg dose compared to placebo at 120 hours in Study 313 (73.8% versus 59.2%); and the 12 mg dose compared to placebo at 144 hours in Study 313 (83.8% versus 70.4%). These results were consistent with the primary efficacy results for the GI subpopulation. For more details, see Table 31.

[redacted] In the GI subpopulation, the 12 mg alvimopan dose demonstrated some efficacy in the treatment of postoperative ileus; however, the following major deficiencies remain:

1) Only one out of four adequate and well-controlled trials demonstrated statistical significance of the 12 mg dose compared to placebo in the primary efficacy endpoint.
2) The clinical meaningfulness of the one positive statistical result — the 12 mg alvimopan dose in the primary efficacy endpoint in Study 313 — is questionable.

1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 3

In summary, both alvimopan doses did not demonstrate efficacy in the treatment of POI in the gynecologic subpopulation.

1.3.3 Safety

The entire alvimopan safety data base contained **36 completed clinical trials** with 4181 subjects/patients [of which 2902 received alvimopan (doses ranging from 0.125 mg/day to 120 mg/day) and 1233 received a control]. The most important subpopulation in the entire safety database included the eight postoperative ileus trials [three phase 2 studies (13C206, 13C214, and 13C213) and five phase 3 studies (302, 308, 313, 306, and 001)]. The postoperative ileus subpopulation contained 3326 patients (of which 2285 received alvimopan and 1041 received placebo). Of the 2285 patients who received alvimopan in the eight postoperative ileus trials, 66, 898, and 1321 patients received 1 mg or 3 mg, 6 mg, and 12 mg of alvimopan, respectively.

In the eight postoperative ileus trials, the median duration of alvimopan exposure was five, five, and six days for the placebo group, the 6 mg alvimopan group, and the 12 mg alvimopan group, respectively. In the eight postoperative ileus trials, the total median alvimopan exposure for the entire trial duration was 0, 48, and 125 mg of alvimopan for the placebo group, the 6 mg alvimopan group, and the 12 mg alvimopan group, respectively.

In the entire safety database, the percentages of deaths (0.38% in the alvimopan group compared to 0.57% in the placebo group), serious adverse events, discontinuations of study medication, common adverse events, vital sign abnormalities, and laboratory abnormalities were similar in the placebo and alvimopan groups. Similarly, the percentages of **treatment-related** deaths (there were no treatment-related deaths in the placebo and alvimopan groups), serious adverse events, discontinuations of study medication, and common adverse events were similar in the placebo and alvimopan groups.

Additionally, there were similar percentages of serious adverse events, discontinuations of study medication, and common adverse events among the 6 mg and 12 mg alvimopan groups.

One minor limitation of the available safety data in the postoperative ileus subgroup was the lack of adequate follow-up safety data. Of 3326 patients in the eight postoperative ileus trials, only 519 (16%) patients received a follow-up safety visit with a physical exam and laboratory testing (7-10 days after the last administration of study drug). In contrast, most of the remaining 2807 patients had their last safety visit on their hospital discharge day and had several follow-up telephone calls. Since alvimopan's metabolite has a long-half life — it takes at least five days after the last alvimopan dose for 95% of the metabolite to be cleared from the body — follow-up safety testing at least five days after the last alvimopan dose would be useful. However, there were no safety concerns in the 519 patients with adequate safety follow-up visits.

In summary, both doses of alvimopan demonstrated no safety signals.

1.3.4 Dosing Regimen and Administration

Since the efficacy of alvimopan has not been demonstrated in the treatment of postoperative ileus, this medical officer can not recommend an appropriate dosing regimen.

1.3.5 Drug-Drug Interactions

There are no important drug-drug interactions.

1.3.6 Special Populations

There are no special alvimopan dosing considerations for age, gender, and race.

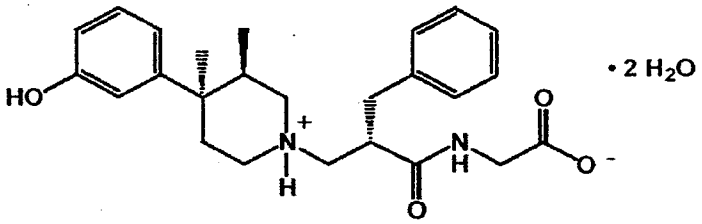
There are no special alvimopan dosing considerations for patients with mild to moderate hepatic insufficiency. However, one out of the three patients with severe hepatic insufficiency who received alvimopan had alvimopan levels ten times higher than patients with no hepatic disease.

Although there were no studies in patients with severe renal insufficiency or patients on dialysis, there are no special alvimopan dosing considerations for patients with mild to severe renal insufficiency.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Proposed Trade Name (established name): Entereg™ (alvimopan)



Original Proposed Indication: To accelerate time to recovery of GI function following abdominal or pelvic surgery.

Revised Proposed Indication: To accelerate time to recovery of GI function following major abdominal or complex pelvic surgery. However, in a March 16, 2005 meeting (in the middle of the NDA review cycle), the Division of Gastrointestinal and Coagulation Drug Products stated that the efficacy data did not support modification of the original indication and therefore was unacceptable.

Proposed Age Group: Adults

Pharmacologic Class: μ-opioid receptor antagonist

Route of Administration, Description, and Formulation: Oral hard gelatin capsules that are blue [redacted]

Chemical Class: New molecular entity (NME)

Proposed Treatment Regimen:
Initial dose: Administer 12 mg of alvimopan [redacted] , 0.5 to 5 hours prior to the scheduled start of the surgery on postoperative day (POD) 0.
Next doses: Administer 12 mg [redacted] of alvimopan BID for a maximum of 7 days (POD 1 to POD 7) while the patient is hospitalized or until discharge from the hospital.

Molecular Formula: $C_{25}H_{32}N_2O_4 \cdot 2H_2O$

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

2.2 Currently Available Treatment for Indications

Currently, there are no drug 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, bethanechol chloride (urecholine®, duvoid®)

2.3 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.

2.4 Important Issues With Pharmacologically Related Products

Three pure opioid antagonists [Naloxone hydrochloride (Narcan®), Naltrexone hydrochloride (ReVia®, Depade®), and Nalmefene hydrochloride (Revex®)] are approved in the United States. Methylnaltrexone (N-methylnaltrexone bromide, MNTX), a pure opioid antagonist, is being developed (in phase 3 trials) for the treatment of opioid-induced constipation in patients with advanced medical illness. Please see Table 1.

There have not been recent labeling changes or recent safety and/or effectiveness concerns regarding the pure opioid antagonists. The pure opioid antagonists are not addictive and do not have abuse potential.

Table 1: Pure opioid antagonists

	NDA/IND	APPROVAL YEAR	ROA[a]	INDICATION(S)
Naloxone hydrochloride (Narcan®)	NDA 16-636	1971	IV, IM, SC	1) Complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids opiate agonist-induced respiratory depression 2) Diagnosis of suspected or known acute opioid overdosage
Naltrexone hydrochloride (ReVia®, Depade®)	NDA 18-932	1984	PO	1) Adjuvant treatment of opiate agonist dependence 2) Adjuvant treatment of alcoholism
Nalmefene hydrochloride (Revex®)	NDA 20-459	1995	IV, IM, SC	1) Complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids 2) Management of known or suspected opioid overdose
Alvimopan[b] (Entereg™)	**NDA 21-775**	**Not approved**	**PO**	**Acceleration of the time to recovery of GI function following abdominal or pelvic surgery (original indication).**
Methylnaltrexone[b] (N-methylnaltrexone bromide, MNTX)	IND 64,583	Not approved	SC	Opioid-induced constipation (by induction of laxation) in patients with advanced medical illness

a ROA = routes of administration (SC=subcutaneously; IM=intramuscularly, IV=intravenously, and PO=orally)
b Alvimopan and N-methylnaltrexone bromide are not approved, thus these are proposed indications
Reference: Adapted from the current drug product labels

2.5 Presubmission Regulatory Activity

Alvimopan is not approved in the United States (or any other country). The highlights of the regulatory activity in the United States include the following:

- In November 1993, Eli Lilly and Company established an IND ([redacted]) for LY246736 Dihydrate, a μ-opioid receptor antagonist, for the treatment of [redacted]
- In February 1997, Eli Lilly and Company transferred IND [redacted] to Roberts Pharmaceutical Corporation (Roberts).
- In June 1998, Roberts licensed IND [redacted] to Adolor Corporation (Adolor) and subsequently transferred all rights to IND [redacted] to Adolor.
- In August 1998, Adolor submitted IND# 56,553 for LY246736 Dihydrate, which was renamed to ADL 8-2698, for the [redacted]
- In December 1999, Roberts withdrew IND [redacted] for "administrative reasons".

- In October 2000, the Division of GI and Coagulation Drug Products (DGICDP) and Adolor met to discuss proposed phase 2 and phase 3 studies for the treatment of POI with ADL 8-2698 (under IND# 56,553). During this meeting the DGICDP stated the following:

  - Rapid recovery from POI needs to be clinically meaningful and defined prospectively. "A clinically meaningful difference in recovery time will be one that is on the order of a day or so, not just a few hours."
  - The "primary endpoint should be assessed as success vs. failure. Effectiveness should be measured by comparing proportions of patients who experience success among treated vs. placebo patients."
  - The DGICDP and Adolor agreed that the primary efficacy endpoint should be a composite variable assessing the recovery of upper (gastric) and lower (colonic) GI motility.
  - The DGICDP and Adolor agreed that appropriate secondary endpoints include the following: the severity of GI symptoms (including nausea, vomiting, abdominal bloating/distention), daily pain, time until hospital discharge, time to achieve adequate oral hydration, and need for reinsertion of nasogastric tube.
  - Approximately 1000 patients exposed to ADL 8-2698 would probably a reasonable safety database for the short-term indication of treatment of POI.

- In March 2001, the DGICDP and Adolor met for an end-of-phase 2 meeting for the treatment of POI with ADL 8-2698 (under IND# 56,553). During this meeting, the DGICDP and Adolor "agreed that the achievement of both time to recovery of upper GI function and time to recovery of lower GI function are necessary to demonstrate efficacy."
- In March 2002, the DGICDP and Adolor met to discuss Adolor's revised clinical development plans for ADL 8-2698 (renamed alvimopan). During this meeting, the following occurred:

  - Adolor agreed with the DGICDP to conduct an additional single dose, phase 1 bioavailability study of alvimopan.
  - Adolor stated that they uncovered an active metabolite of alvimopan.
  - The DGICDP stated that Adolor needed to provide the following biopharmaceutical data to support a future NDA: plasma protein binding, pharmacological activity of the major metabolite, absolute bioavailability, dose proportionality, food effect, a severe hepatic impairment subgroup.
  - Adolor agreed to perform an additional phase 1 study of 12 mg of alvimopan in Crohn's disease patients to assess bioavailability in this population.

- In February 2004, the DGICDP granted the alvimopan development program (for the treatment of POI) fast tract status because POI "is a serious condition for which no drugs have been approved" and alvimopan "appears to be a safe and effective treatment for this medical need."

- In February 2004, the DGICDP and Adolor met for a pre-NDA meeting. During this meeting, the following occurred:

  - The DGICDP stated that given the "highly variable data on PK in patients with severe hepatic impairment, the label may contraindicate the use of alvimopan in this group of patients.
  - The DGICDP stated that they would allow the QT study to be submitted in the 120-day safety update.
  - The DGICDP stated that the clinical and non-clinical data appeared sufficient to support submission of an NDA for alvimopan for the treatment of POI.
  - The DGICDP stated that pediatric trials will be deferred until a regulatory decision on the NDA has been made.
  - The DGICDP confirmed that "carcinogenicity studies are not needed for" the short-term POI indication.

- In May 2004, the DGICDP accepted Adolor's proposed plan for the "Pilot 1 Continuous Marketing Application Reviewable Units for Fast Track Products". Adolor agreed to submit the non-clinical pharmacology and toxicology unit on May 5, 2004; the chemistry, manufacturing, and controls unit on May 30, 2004; and the complete NDA on June 30, 2004.

2.6 Post-submission Regulatory Activity

During the NDA review process (after NDA submission and before the review goal date) the DGICDP met with Adolor two times.

- In November 2004, the DGICDP and Adolor met to discuss several issues during the NDA review. The DGICDP explained to the sponsor their rationale for denying alvimopan a priority review. The DGICDP stated the need for an Advisory Committee Meeting to evaluate the efficacy of alvimopan in the treatment of POI. The DGICDP stated that there were two main reasons to seek recommendations from an Advisory Committee Meeting: 1) the FDA never approved a drug product in this new indication and 2) the equivocal nature of the efficacy results. The DGICDP confirmed that a general surgeon and a gynecologic surgeon will be on the Advisory Committee. Additionally, The DGICDP asked the sponsor to clarify several design features in the important trials. Adolor explained that Study 306 was a primary safety study (with primary safety endpoints and secondary efficacy endpoints).
- In the March 2005 meeting between the DGICDP and Adolor the following was discussed:

  - The DGICDP stated that 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."
  - The sponsor asked to modify the gastrointestinal surgery population to "major abdominal surgery".

- The sponsor asked to modify the gynecologic surgery population to "complex pelvic surgery".

[redacted]

- The DGICDP stated that "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 (GI[3]) and 6 identical secondary endpoints, and the same prohibited medications. -The DGICDP asked the sponsor to "provide sufficient evidence to demonstrate that differences in regional practices explain the dissimilar results in the trials."
- The DGIDCP informed the sponsor that an Advisory Committee Meeting will not be necessary at this time.
- The DGIDCP told the sponsor that the results from the ongoing trial (Study 14CL314) will be needed to complete the evaluation of alvimopan in the treatment of POI.
- The DGICDP restated to Adolor that Study 001 (the European POI Study) will be needed for the current NDA review. 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. The sponsor told the DGICDP that the final study report for Study 001 would be submitted shortly.

Adolor submitted the final study report for Study 001 on April 8, 2005.

2.7 Other Relevant Background Information

There have been no marketing applications filed in any country. This NDA is the first marketing application for alvimopan.

3 Significant Findings from Other Review Disciplines

3.1 CMC (and Product Microbiology, if Applicable)

According to Dr. Ramesh Raghavachari, the chemistry reviewer, "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 (please see his April 26, 2005 review for more details).

3.2 Animal Pharmacology/Toxicology

According to Dr. Tamal Chakraborti, the pharmacology/toxicology reviewer, based on the pharmacology/toxicology perspective "this NDA may be approved." Dr. Chakraborti did not recommend additional phase 4 commitments. (please see his November 4, 2004 review for more details).

According to Dr. Chakraborti, alvimopan "exhibited no significant target organs of toxicity when administered at sufficiently high oral doses up to 13 weeks in mice and up to 6 months in rats

and dogs." "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 (24 mg/day or 17.8 mg/m^2), respectively, based on body surface area. Alvimopan and its active metabolite ADL 08-0011 did not show any potential for genotoxicity. In fertility and reproductive performance study in rats, alvimopan did not cause any adverse effect. It was not teratogenic in rats or rabbits."

The in vitro assays for cardiovascular effects including the effect of alvimopan and its metabolite (ADL 08-0011) on cloned hERG channels expressed in mammalian cells and isolated dog Purkinje fibers were completely negative for any significant cardiovascular pharmacologic effect.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Five randomized, double-blind, placebo-controlled, parallel-group, multi-center phase 3 trials and three phase 2 trials of alvimopan in the treatment of POI were evaluated by this medical officer during this review. The five phase 3 trials consisted of three U.S. safety/efficacy trials (14CL302, 14CL308, 14CL313), one European safety/efficacy trial (SB-767905/001), and one U.S. safety trial (14CL306). In this review, the five phase 3 trials, Studies 14CL302, 14CL308, 14CL 313, 14CL 306, and SB-767905/001 will be identified as Studies 302, 308, 313, 306 and 001, respectively. All of the study reports were submitted electronically.

Since this investigational product is not marketed anywhere in the world, foreign post-marketing reports are not part of the sources of information for this review.

4.2 Tables of Clinical Studies

The most important trials for this review include the five POI phase 3 trials [three U.S. safety/efficacy trials (302, 308, and 313), one European trial safety/efficacy trial (001), and one U.S. safety trial (306).] Please see Table 7 for a tabular listing of these important trials.

Thirty-six completed alvimopan clinical trials are listed in the following tables:

1) Table 2 lists the 6 single-dose studies in healthy subjects (14C114, 14CL115, RC99-CP006, 13C111, 14CL124, and 14CL127)
2) Table 3 lists the 8 multiple-dose studies in healthy subjects (H3G-LC-BGGA, 14CL118, 14CL119, RC99-CP007, 13C109, RC98-CP001, H3G-LC-BGGC and SB-767905/016)
3) Table 4 lists the 5 studies in special populations (14CL116, 14CL117, 14CL123, 14CL125, 14CL126)
4) Table 5 lists the 7 opioid bowel dysfunction (OBD) studies in chronic (non-cancer) pain patients (RC99-CT001, RC99-CT002, 13C210, 13C208, 13C209, 13C217, and 13C304)
5) Table 6 lists the 2 OBD studies in chronic cancer pain patients (13CL223 and 13CL224)
6) Table 7 lists the 8 POI studies in surgery patients in Europe and the United States (13C206, 13C213, 13C214, 302 , 306, 308, 313, and 001)

Table 2: Completed single-dose alvimopan studies in healthy subjects

STUDY	TITLE	OBJECTIVES	N[a]	TREATMENT ARM(S)	DAY(S)
1) 14C114	A single center, open-label study to evaluate the absorption, metabolism, and excretion following oral administration of [^{14}C] alvimopan in normal healthy male subjects	To evaluate absorption, metabolism, and excretion following oral dose of radio-labeled alvimopan	6	Alvimopan 12 mg	1
2) 14CL115	A phase I, single-blind, placebo-controlled study of the temporal safety and tolerability of alvimopan on opioid withdrawal in normal healthy volunteers	Temporal safety and tolerability of alvimopan on opioid withdrawal in subjects taking MS Contin for 7 or 10 days	18	Placebo Alvimopan 12 mg	1
3) RC99-CP006 (CP006)	A phase I study assessing use of a peripherally selective μ opioid antagonist to prevent opioid-induced delayed GI transit in normal subjects	Determine if alvimopan would prevent delay of GI transit that occurred with administration of therapeutic dose of morphine sulfate	6[d] 14[e]	Phase 1: Alvimopan 2 mg Phase 2: (crossover) Placebo and Alvimopan 2 mg	1 in each period
4) 13C111	A phase I, randomized, double-blind, placebo-controlled, crossover, dose-ranging, multi-center study to assess the use of alvimopan in reducing the frequency and severity of opioid-induced nausea in subjects with a prior history of opioid-induced nausea	Effect of alvimopan on morphine induced nausea in subjects with confirmed history of opioid induced nausea	42[c]	(Crossover) Alvimopan 1 mg Alvimopan 3 mg Alvimopan 9 mg	1 in each period
14CL124	Pharmacokinetics of alvimopan and its metabolite (ADL 08-0011) in the fed and fasted states	PK of alvimopan 12 mg and its metabolite in the fed and fasted states	24	Alvimopan 12 mg	1 in each period
6) 14CL127	A study of the bioavailability of alvimopan from oral capsule relative to that from oral solution and the absolute bioavailability of alvimopan in normal healthy volunteers	Bioavailability of alvimopan 12 mg from oral capsules (2 x 6 mg) relative to that from an oral solution (12 mg total) and an IV formulation (12 mg total) in normal healthy volunteers	36	Crossover of 12 mg of Alvimopan Oral capsule Oral solution IV	1 in each period

Reference: Volume 133, Table 1, Pages 1-6
a N = number of subjects/patients randomized:
b healthy subjects undergoing third molar extraction;
c healthy subjects with confirmed history of opioid-induced nausea;
d phase I; and
e phase II

Table 3: Completed multiple-dose alvimopan studies in healthy subjects

STUDY	TITLE	OBJECTIVES	N	TREATMENT ARM(S)	DAY(S)
1) H3G-LC-BGGA	Alvimopan: Dose-escalation safety trial	Evaluate the safety and tolerability, and the PK profile of alvimopan after a single dose and after single doses for three consecutive days. To evaluate GI physiology during administration of alvimopan for three consecutive days.	8	Placebo Alvimopan doses ranged from 1.2 mg/day to 120 mg/day	Periods 1, 2, & 3 = 1 day Periods 4 & 5 = 3 days
2) 14CL118	A single-blind, PC study of the plasma PK of intravenous morphine after single and repeat doses of alvimopan in normal healthy volunteers	Effect of single and repeated doses of alvimopan on IV morphine PK.	10	(Crossover) Placebo BID Alvimopan 12 mg BID	4.5
3) 14CL119	A DB, PC study of the pharmacokinetics of repeat doses of alvimopan in normal healthy volunteers	PK of alvimopan and metabolite following repeated doses of alvimopan in healthy subjects	40	Placebo BID Alvimopan 6 mg, 12 mg, 18 mg, and 24 mg BID	4.5
4) RC99-CP007 (CP007)	A phase I, double-blind, placebo-controlled, dose ranging study of the reversal of opioid-induced delay in GI transit in normal subjects	Determine if alvimopan would prevent delayed GI transit that occurs with administration of therapeutic dose of MS Contin without reversing morphine-induced analgesia in healthy subjects	13	(Crossover) Placebo TID Alvimopan 3 mg TID	4
5) 13C109	A double-blind, randomized, placebo-controlled study of the effect of alvimopan on opioid-induced side effects and analgesia in patients after third molar extraction	Determine if alvimopan would reduce subjective opioid GI symptoms without reversing opioid-induced analgesia or pupillary constriction	63	Placebo Alvimopan 2 mg First does 60 minutes before surgery and second dose 60 minutes after surgery	1
6) RC98-CP001 (CP001)	An ascending dose safety study of Alvimopan in man	Evaluate the safety of oral alvimopan by determining if there was a dose-related toxicity with the drug in the proposed dose range (0.25 mg to 36 mg TID) and to estimate the tolerated dose	44	Placebo TID Alvimopan doses ranging from 0.25 mg to 36 mg TID	4
7) H3G-LC-BGGC	Alvimopan: multiple-dose trial in subjects with loperamide-induced constipation	Evaluate the safety and tolerability, the PK profile and the pharmacology and duration of activity of multiple-dose alvimopan compared with placebo in subjects with loperamide-induced constipation.	8	(Crossover) Placebo; Loperamide BID & Alvimopan 24 mg TID; Loperamide BID & Alvimopan 2.4 mg TID; and Loperamide BID	4 to 5
8) *SB-767905/016	A R, PC study to evaluate the effect of single and multiple oral doses of alvimopan on cardiac conduction as assessed by 12-lead ECG in healthy male and female subjects	Exclude a greater than 10 msec effect of single and multiple oral doses of alvimopan 6 mg BID and 24 mg BID on the QTc interval, compared to placebo, as measured by the change from baseline at specified times post-dose	162	Placebo Alvimopan 6 mg and 24 mg BID Moxifloxacin 400 mg per day	7

Reference: Volume 133, Table 1, Pages 5-8

* Study SB-767905/016 is the QT study that was submitted in 10/04 in the Safety Update (it was not submitted in the original NDA).

Table 4: Completed single-dose alvimopan studies in special populations

STUDY	TITLE	OBJECTIVES	N	TREATMENT ARM(S)	DAY(S)
1) 14CL116	Pharmacokinetics of alvimopan in subjects with renal impairment.	Characterize 1) the PK of alvimopan and its primary metabolite (ADL 08-0011) in plasma, following a single oral capsule administration of a dose of 12 mg in subjects with mild, moderate, or severe renal impairment; 2) the urinary excretion of alvimopan and ADL 08-0011 in subjects with mild, moderate, or severe renal impairment.	24	Alvimopan 12 mg	1
2) 14CL117	Pharmacokinetics of alvimopan in subjects with hepatic impairment	Characterize 1) the PK of alvimopan and its primary metabolite in plasma, following a single oral dose of alvimopan 12 mg in normal healthy subjects and subjects with mild or moderate hepatic impairment, as defined by Child-Pugh classification and 2) the urinary excretion of alvimopan and ADL 08-0011 after a single oral dose of alvimopan 12 mg in healthy subjects and subjects with mild or moderate hepatic impairment. This study also evaluated the safety of a single 12 mg dose of alvimopan in normal healthy volunteers and subjects with mild and moderate hepatic impairment.	20	Alvimopan 12 mg	1
3) 14CL123	Pharmacokinetics of oral alvimopan and its metabolite (ADL 08-0011) in elderly subjects 65 years of age or older	Characterize the PK of alvimopan and its metabolite in the elderly after a single 12 mg alvimopan dose.	18	Alvimopan 12 mg	1
) 14CL125	A phase I study of the plasma levels of alvimopan and presence of Its metabolite in patients with Crohn's disease	Describe the pharmacokinetics of alvimopan and ADL 08-0011 in patients with Crohn's disease. Evaluate whether the PK of alvimopan and ADL 08-0011 in patients with active or quiescent Crohn's disease are similar to those observed in previous studies of healthy volunteers after a single dose of 12 mg of alvimopan.	12	Alvimopan 12 mg	1
5) 14CL126	Pharmacokinetics of alvimopan in subjects with severe hepatic impairment	Characterize the PK of alvimopan and its metabolite in plasma, following a single oral capsule administration of a dose of 12 mg in healthy subjects and subjects with severe hepatic impairment. Evaluate the safety of alvimopan in subjects with severe hepatic impairment compared to controls.	10	Alvimopan 12 mg	1

Reference: Volume 133, Table 1, Pages 9-13

Table 5: Completed alvimopan studies: the treatment of opioid bowel dysfunction (OBD) in chronic (non-cancer) pain patients

TUDY	TITLE	OBJECTIVES	N	TREATMENT ARM(S)	DAY(S)
			7	Alvimopan 0.125 mg on visit 1 0.25 mg on visit 2 1 mg on visit 3 3 mg on visit 4	4
			8	Placebo or Alvimopan day 1: 0.125 (or 0.25) mg day 2: 0.25 (or 1) mg day 3: 1 mg day 4 & 5: 3 mg	5
			26	Placebo or Alvimopan day 1: 0.5 mg day 2: 1.5 mg day 3: 3 mg day 4: 4.5 mg	4
			62	Placebo Alvimopan 0.5 mg Alvimopan 1.5 mg Alvimopan 3 mg	1
			13	Placebo Alvimopan 0.5 mg Alvimopan 1.5 mg Alvimopan 3 mg	1
			20	Placebo Alvimopan 0.5 mg Alvimopan 1 mg	21
			168	Placebo Alvimopan 0.5 mg Alvimopan 1 mg	21

Reference: Volume 133, Table 1, Pages 25-31

Table 6: Completed alvimopan studies: the treatment of opioid induced bowel dysfunction in chronic cancer pain patients

STUDY	TITLE	OBJECTIVES	N	TREATMENT ARM(S)	DAY(S)
			16	Alvimopan 0.25 mg to 1 mg prn achievement of satisfactory BM	Up to 21 days
			7	Alvimopan 0.25 mg to 1 mg prn achievement of satisfactory BM	Up to 21 days

Reference: Volume 133, Table 1, Page 32

Table 7: Completed alvimopan studies: the treatment of POI

STUDY	TITLE	OBJECTIVES	N	TREATMENT ARM(S)*	DAY(S)
1) 13C206	A Phase II , DB, PC, Parallel Study of Efficacy for Shortening the Duration of POI	Determine if the peripherally selective μ-opioid antagonist Alvimopan shortened the duration of POI after partial colectomy or TAH in patients receiving IV opioids for postoperative pain.	79	Placebo Alvimopan 1 mg Alvimopan 6 mg	Up to 8 days
2) 13C213	A MC Phase II/III, DB, Dose Ranging, PC, Parallel Study of Alvimopan in Opioid-Induced Postoperative Bowel Dysfunction/POI	Determine the clinically optimal dose of alvimopan	153	Placebo Alvimopan 3 mg Alvimopan 6 mg Alvimopan 12 mg	Up to 8 days
3) 13C214	A MC, Phase II, DB, PC Study Assessing Efficacy of Alvimopan for Speeding Recovery from Postoperative Opioid-Induced Bowel Dysfunction	Determine if the peripherally restricted selective opioid antagonist alvimopan would shorten the duration of POI as assessed by faster recovery of bowel function following intra-abdominal surgery (excluding planned BRs). Determine whether 12 mg of alvimopan was safe for use in a population of subjects who had undergone intra-abdominal surgery	65	Placebo Alvimopan 12 mg	Up to 8 days
4) 13C302 (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 subjects undergoing partial colectomy or to TAH (radical or simple).	451	Placebo Alvimopan 6 mg Alvimopan 12 mg	Up to 8 days
5) 13C306 (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
13C308 (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 subjects undergoing partial small or large BR with primary anastomosis, rTAH, or sTAH.	666	Placebo Alvimopan 6 mg Alvimopan 12 mg	Up to 8 days
7) 13C313 (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 subjects undergoing partial small or large BR with primary anastomosis or rTAH.	510	Placebo Alvimopan 6 mg Alvimopan 12 mg	Up to 8 days
8) 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 subjects 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

Reference: Volume 133, Table 1, Pages 18-24
N = number of planned subjects/patients
* First dose 2 hours prior to surgery, and next doses BID for up to 7 days or until hospital discharge (which ever is sooner)
** Study SB-767905/001 (001) was conducted in Europe, Australia, and New Zealand

The **ongoing** alvimopan clinical trials are listed in the following tables:

1) Table 8 lists ongoing studies in healthy subjects 14CL128, 14CL 201, 14CL 130).
2) Table 9 lists ongoing functional constipation studies (SB-767905/004, SB-767905/007).
3) Table 10 lists ongoing opioid bowel dysfunction (OBD) studies in chronic (non-cancer) pain patients (SB-767905/008, SB-767905/011).
4) Table 11 lists an ongoing POI study (14CL314).

Table 8: Ongoing alvimopan studies in healthy subjects

STUDY	TITLE	OBJECTIVES	N	TREATMENT GROUP	DAY(S)
1) 14CL128	A Phase I, randomized, double-blind, placebo-controlled study of the effect of alvimopan on gastric, small bowel, and colonic transit in healthy subjects	Assess the ability of alvimopan 12 mg PO BID to reverse the effect of codeine sulfate 30 mg PO QID on gastric, small bowel, and colonic transit time. Assess the effect of alvimopan 12 mg PO BID alone on gastric, small bowel, and colonic transit time. Determine the concentrations of alvimopan and its metabolite in plasma in correlation with PD measures of gastric, small bowel, and colonic transit time.	74	Placebo BID Alvimopan 12 mg BID	1
2) 14CL201	A phase I/II study in healthy human subjects of the safety of repeat dosing with intravenous alvimopan and its effect on opioid-induced changes in GI transit	Part A: Assess the effect of oral alvimopan on opioid-induced changes in the GI transit of radiopaque markers. Part B: Assess the tolerability of IV infusion rates >1mg/min for alvimopan 12 mg (1 mg/mL) up to a maximum infusion rate of 12 mg/min. Part C: Determine the safety of repeat doses of alvimopan 6 mg IV administered BID for 7 days at the infusion rate determined in Part B. Assess the GI transit of radiopaque markers in the presence and absence of alvimopan 6 mg IV BID. Assess the PK of alvimopan and ADL 08-0011 after repeat dosing of alvimopan 6 mg IV BID for 7 days. Part D: Determine the safety of repeat dosing of alvimopan IV at various doses administered for 4 days. Study the effect of a range of doses (0.1 to 6 mg BID) of alvimopan IV on opioid-induced changes in GI motility. Assess the PK of alvimopan and ADL 08-0011 after repeat dosing at varying doses of alvimopan IV BID. Establish a dose-response relationship (and concentration-response relationship, if possible) for the effect of alvimopan on opioid-induced changes in GI motility.	129	Part A: Alvimopan 6 mg PO BID Part B: Alvimopan 12 mg IV q day Part C: Alvimopan 6 mg IV BID Part D: Alvimopan 0.1 to 6 mg IV BID	Part A: 4 Part B: 1 Part C: 4 Part D: 4
3) 14CL130	A phase I, open-label, single-dose, two-sequence crossover study to determine the bioequivalence of one alvimopan 12 mg capsule relative to two alvimopan 6 mg capsules in healthy male subjects.	Assess the bioequivalence of one alvimopan 12 mg capsule relative to two 6 mg capsules as measured by the rate and extent of absorption of alvimopan in healthy male subjects.	88	Alvimopan 6 mg Alvimopan 12 mg	1

Reference: 120-Day Safety Update Report, Table 1, Pages 1-5

Table 9: Ongoing alvimopan studies in patients with functional constipation

STUDY	TITLE	OBJECTIVES	N	TREATMENT GROUP	DAY(S)
[redacted]			24	Placebo BID Alvimopan 3mg BID	1
			200	Placebo BID Alvimopan 1 mg BID 3 mg BID 8 mg BID	8 weeks

N = number of planned subjects/patients
Reference: 120-Day Safety Update Report, Table 1, Pages 1-5

Table 10: Ongoing alvimopan studies: the treatment of OBD

STUDY	TITLE	OBJECTIVES	N	TREATMENT GROUP	DAY(S)
[redacted]			500	Placebo Alvimopan 0.5 mg BID 1 mg QD 1 mg BID	6 weeks
			500	Placebo Alvimopan 0.5 mg BID 1 mg QD 1 mg BID	6 weeks

* Study SB-767905/011 was just completed; however, final report was not submitted
N = number of planned subjects/patients
Reference: 120-Day Safety Update Report, Table 1, Pages 1-5

Table 11: The ongoing alvimopan POI study

STUDY	TITLE	OBJECTIVES	N	TREATMENT GROUP	DAY(S)
14CL 314	A phase 3b, MC, DB, PC, parallel study of alvimopan for the management of postoperative ileus.	Demonstrate that 12 mg of alvimopan, administered 30 to 90 minutes prior to the scheduled start of surgery and then BID until hospital discharge (for a maximum of 7 days), accelerates recovery of GI function (GI^2) in subjects undergoing partial small/large BR. Evaluate the safety of alvimopan 12 mg and to assess the postoperative effects of alvimopan on subjects' quality of life.	660	Placebo BID Alvimopan 12 mg BID First dose 2 hours prior to surgery, then BID	Up to 8 days

N = number of planned subjects/patients
Reference: 120-Day Safety Update Report, Table 1, Pages 1-5

4.3 Review Strategy

This medical officer is responsible for the entire safety and efficacy reviews for the POI indication.

Since the efficacy results were highly dependant on the surgical type, patients were divided into two subgroups: patients scheduled to have 1) GI surgery (large and small BR) or 2) gynecologic surgery (sTAH and rTAH).

For the efficacy review of the POI indication for the **GI surgery subgroup**, this medical officer believes that there are four important alvimopan phase 3 trials (302, 308, 313, and 001). These similar trials are equally important because:

- They all had the same complex dosing regimen for up to eight days in the hospital (the first dose two hours prior to surgery, and the next doses BID for 7 postoperative days or until hospital discharge).
- They all had the same three doses (placebo, 6 and 12 mg of alvimopan)
- They all included the same two surgical types (BR and TAH)
- They all had the same primary endpoint (GI^3), six identical secondary endpoints, and one similar secondary endpoint (the responder analysis). Studies 302, 308, and 313 totaled seven pre-specified secondary endpoints and Study 001 had a total of 23 pre-specified secondary endpoints.
- They all had the same prohibited medications.
- They all were large (between 451 to 911 patients), adequate, and well-controlled studies (they were all randomized, double-blinded, placebo-controlled, multi-center, parallel group phase 3 studies.

For the efficacy review of the POI indication for the **gynecologic surgery subgroup**, this medical officer believes that there are five important alvimopan phase 3 trials (302, 308, 313, 001, and 306). Study 306 differs from the four important phase 3 efficacy trials in the following ways:

- Study 306 is primarily a safety study and secondarily an efficacy study (the primary efficacy endpoint are safety variables and the secondary endpoints are efficacy variables). In contrast, the primary and secondary endpoints in the phase 3 efficacy studies are all efficacy variables.
- The major efficacy assessments in Study 306 are based on inpatient and outpatient evaluations. In contrast, the major efficacy assessments in the phase 3 efficacy studies are all based on inpatient evaluations.
- Study 306 includes only one type of surgery (sTAH patients). In contrast, the phase 3 efficacy studies have four types of surgeries (sTAH, rTAH, large BR, and small BR).

Despite the above differences in trial design from the other four efficacy studies, Study 306 had the largest subpopulation of gynecologic surgery patients in any POI study. In Study 306, a total of 408 gynecologic patients received alvimopan; whereas, in all four efficacy studies (302, 308, 313, and 001), a total of 303 gynecologic patients received alvimopan. Given the large

gynecologic population, this medical officer considered Study 306 as one of five important efficacy trials for the gynecologic subpopulation.

For the integrated safety review of the POI indication, this medical officer believes that all 36 completed alvimopan trials should be evaluated. The most important trials for the safety of alvimopan in the proposed indication are the eight POI trials including the three phase 2 POI trials (13C206, 13C213, and 13C214) and five phase 3 POI trials (302, 308, 313, 001, and 306). These eight trials are the most important because these trials are in the proposed population (hysterectomy surgery and bowel resection patients) and they contain the proposed doses (first dose two hours prior to surgery and then BID for a maximum of [redacted]

4.4 Data Quality and Integrity

Three sites in Study 313 (site 04 in Atlanta, GA; site 09 in Grand Rapids, MI; and site 06 in Salt Lake City, Utah) and two sites in Study 308 (site 33 in San Diego, CA and site 10 in Denver, CO) were selected for Division of Scientific Investigations (DSI) audits. The three sites in Study 313 and the two sites in Study 308 had the largest number of patients per site in the respectively trials. In Study 313, sites 04, 09, and 06 treated 38, 35, and 32 patients, respectively, and in study 308, sites 33 and 10 treated 70 and 59 patients, respectively. On initial review before the filing meeting, the proposed alvimopan dose (12 mg) appeared to demonstrate the best efficacy (compared to placebo) in the primary efficacy endpoint in Study 313 and the 12 mg dose appeared to demonstrate the second best efficacy (compared to placebo) in the primary efficacy endpoint in Study 308.

Dr. Khairy W. Malek, the medical reviewer for the Division of Scientific Investigations, reviewed the inspection of four sites (sites 04, 09, 33, and 10). Dr. Malek, in his May 5, 2005 review, stated that the data from all four sites can be used to support the NDA. He found "multiple instances of protocol deviations" that "do not seem to affect the overall validity and reliability of the data." The mild protocol deviations included the following minor protocol violations: not performing laboratory testing; not correctly recording surgery start times; not correctly recording the time to tolerate first solid food; inaccurate recording of treatment compliance (inaccurate recording of missing doses); and performing a PK analysis two hours after the scheduled time. Please see Dr. Malek's May 5, 2005 review for more details.

Medical Reviewer's Comments: This medical officer believes that incorrect recording of surgery start times and incorrect recording of the time to tolerate first solid food may have influenced the results of the primary efficacy endpoint and the important secondary endpoints. However, the DSI audits only uncovered two patients who had an incorrect recording of the time to tolerate first solid food and one patient who had an incorrect recording of the time surgery ended. Therefore, the low prevalence of these incorrect recordings probably did not influence the overall results of the primary and secondary endpoints.

4.5 Compliance with Good Clinical Practices

According to the sponsor, all eight phase 3 studies in the treatment of POI were conducted in compliance with good clinical practice (GCP) guidelines, as described in the International Conference on Harmonization (ICH) Harmonised Tripartite Guidelines for Good Clinical Practice 2000 and the United States Code of Federal Regulations (CFR) dealing with clinical studies. A signed informed consent form was obtained for each patient and IRB approval was obtained by the principal investigators in accordance with 21 CFR 50 and 56. According to the sponsor, all of the trials were conducted in accordance with acceptable ethical standards.

4.6 Financial Disclosures

The sponsor has submitted FDA Form 3454 certifying that the clinical investigators in the eight submitted POI trials:

- Did not participate in any financial arrangement with the sponsor, whereby the value of compensation to the investigators for conducting the study could be affected by the outcome of the study [as defined in 21 CFR 54.2(a)]:
- Had no proprietary interest in this product or significant equity interest in the sponsor [as defined in 21 CFR 54.2(b)]: and
- Was not the recipient of significant payments of other sorts [as defined in 21 CFR 54.2(f)].

5 CLINICAL PHARMACOLOGY

5.1 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 1/2 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." Please see Dr. Sue Chih Lee's review for more details regarding the pharmacokinetics of alvimopan and its metabolite.

5.2 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 "Ki 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."

According to Dr. Sue Chih Lee, in the thorough QT/QTc study, "there was some trend of increase in QTcF with alvimopan dose. However, the increase" did not "appear to be as apparent as moxifloxacin 400 mg even at a high alvimopan dose (24 mg BID)." Please see her review for more details.

5.3 Exposure-Response Relationships

The sponsor conducted a population PK/PD analysis using data obtained from 766 patients with postoperative ileus in two Phase 3 trials (Studies 308 and 001). No clear exposure-response relationship was identified for efficacy or safety.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Proposed Indication – Treatment of Post-Operative Ileus (POI)

In the original NDA submission, the sponsor proposed indication was the following: alvimopan is indicated to accelerate time to recovery of GI function following abdominal or pelvic surgery. During the NDA review cycle, the sponsor changed their proposed indication to the following: alvimopan is indicated to accelerate time to recovery of GI function following major abdominal or complex pelvic surgery.

6.1.1 Methods

This medical officer divided his efficacy evaluation of the proposed POI indication into two surgery populations – **gynecologic surgery patients** (sTAH and rTAH) and **GI surgery patients** (small and large BR) – because these surgical subgroups had profound influence on the effectiveness of the treatment groups.

For the gynecologic surgery subgroup, this medical officer equally evaluated five phase 3 POI studies [the three U.S. efficacy/safety studies (302, 308, and 313); the one U.S. safety study (306); and the one European efficacy/safety study (001)].

For the GI surgery subgroup, this medical officer equally evaluated four similar phase 3 clinical trials [the three U.S. POI studies (302, 308, and 313) and the one European study (001)]. All of these trials had the same complex dosing regimen, the inclusion of the same three doses (placebo, 6 mg of alvimopan, and 12 mg of alvimopan), the same surgical types (BR and rTAH), the same primary endpoint (GI^3) and 6 identical secondary endpoints, and the same prohibited medications. These four trials were all randomized, double-blind, placebo-controlled, parallel-group, multi-center trials.

The sponsor argued that only the three U.S. POI studies (302, 308, and 313) should be considered pivotal and the one European study (001) should not be considered an important efficacy study for the following reasons:

1) The United States and Europe have different peri-operative managements of surgery patients. U.S. surgeons practice more aggressive strategies (such as earlier ambulation and earlier feeding) compared to European surgeons.
2) The three U.S. studies only allowed intravenous patient-controlled anesthesia (PCA) for post-operative pain control; whereas, the one European study allowed PCA and intravenous or intramuscular opioid injection by the nursing staff as needed.
3) The three U.S. studies had a 10 day study period; whereas, the one European study had a 14 day study period.
4) The three U.S. studies had instructions to avoid opioid-sparing medications (NSAIDs could not be the primary mode of analgesia); whereas, the one European study did not have these instructions.
5) The three U.S. studies had a lower proportion of patients with underlying malignancy (about 57% of the U.S. patients had cancer) compared to the one European study (about 75% of the European patients had cancer).

6) The two subpopulations have differences in financial and social pressure related to hospital bed occupancy levels and resource requirements.

Medical Reviewer's Comments: **This medical officer believes that the sponsor's line of reasoning for #6 is valid. All of the treatment groups in Europe appeared to have quicker recovery of their upper and lower GI tracts (their median times to achieve GI^2 and GI^3 were shorter) than all of the treatment groups in the three U.S. POI studies. However, all of the treatment groups in Europe appeared to have longer times to discharge order written (DISCHARGE) and longer times until ready for discharge (READY) than all of the treatment groups in the United States. Therefore, differences in "financial and social pressure related to hospital bed occupancy levels and resource requirements" between the Europe and the United States may have affected the results of two important secondary endpoints (READY and DISCHARGE). Therefore, this medical officer will consider the three U.S. studies as the primary studies and the one European study will be considered secondary in evaluation of the two secondary endpoints (READY and DISCHARGE).**

However, the sponsor's reasoning does not explain the primary efficacy endpoint (GI^3) results. In the sponsor's post-hoc analysis, in both subgroups (patients who received PCA post-operative pain medication and patients who received intravenous or intramuscular opioid injection by the nursing staff as needed) the alvimopan groups demonstrated no statistical significance (compared to the placebo group) for the primary efficacy endpoint.

This medical officer believes that the amount of peri-operative opioids administered probably had a greater effect on the recovery of the upper and lower GI tracts; rather than, the method of peri-operative opioid delivery. Table 12 presents the opioid consumption by post-surgery day in all four important efficacy studies. All three treatment groups in Studies 308 and 001 received equivalent amounts of peri-operative opioids; however, no alvimopan group demonstrated efficacy compared to placebo in the time to recovery upper and lower GI tract motility.

In Study 302, patients who received 12 mg of alvimopan received more peri-operative opioids compared to patients who received 6 mg of alvimopan; and in Study 313, patients who received 6 mg of alvimopan received more peri-operative opioids compared to patients who received 12 mg of alvimopan. In these examples, the treatment groups that received less opioid therapy had shorter times to recovery of both upper and lower GI tract motility. In other words, patients who received fewer opioids had less impairment of bowel motility and recovered faster. In summary, the amount of opioids administered peri-operatively may be a large determinant on the primary efficacy outcome.

Table 12: Opioid consumption per post-surgery day (PSD) in morphine equivalents in the four important efficacy studies (301, 308, 313, and 001)

STUDY*	TREATMENT GROUPS	PSD 0	PSD 1	PSD 2	PSD 3	PSD 4	Median Daily Opioid Use**
302	placebo	n=145 53 mg	n=145 24 mg	n=142 10 mg	n=129 5 mg	n=106 4 mg	19 mg
	Alvimopan 6 mg	n=141 61 mg	n=141 25 mg	n=140 11 mg	n=127 3 mg	n=101 1 mg	22 mg
	Alvimopan 12 mg	n=138 62 mg	n=138 33 mg	n=138 14 mg	n=121 6 mg	n=97 3 mg	25 mg
308	Placebo	n=207 58 mg	n=207 22 mg	n=207 9 mg	n=189 6 mg	n=168 5 mg	17 mg
	Alvimopan 6 mg	n=204 54 mg	n=204 22 mg	n=203 8 mg	n=190 5 mg	n=171 4 mg	16 mg
	Alvimopan 12 mg	n=204 60 mg	n=204 19 mg	n=203 9 mg	n=190 5 mg	n=173 4 mg	17 mg
313	Placebo	n=149 55 mg	n=149 28 mg	n=148 15 mg	n=144 5 mg	n=124 3 mg	20 mg
	Alvimopan 6 mg	n=155 63 mg	n=155 37 mg	n=155 20 mg	n=144 11 mg	n=113 7 mg	27 mg
	Alvimopan 12 mg	n=165 58 mg	n=165 31 mg	n=164 19 mg	n=155 7 mg	n=125 4 mg	22 mg
001	placebo	n=217 31 mg	n=218 19 mg	n=216 8 mg	n=214 0 mg	n=211 0 mg	9 mg
	Alvimopan 6 mg	n=227 30 mg	n=224 17 mg	n=225 7 mg	n=223 0 mg	n=216 0 mg	9 mg
	Alvimopan 12 mg	n=227 33 mg	n=228 19 mg	n=227 5 mg	n=224 0 mg	n=217 0 mg	9 mg

* Studies 302, 308, and 313 included all patients including all surgical subgroups; in contrast; Study 001 only included GI surgery patients.

** Median daily opioid use: the median amount of opioids in morphine equivalents used per post-surgery day. Since the study periods are different in 302, 308, and 313 compared to 001, these numbers cannot be directly compared.

PSD 0: 24 hours before the end of surgery (this includes the surgery time and pre-operative time)

PSD 1: 24 hours after surgery ends

n = number of patients receiving treatment on that day; median is the mg of morphine equivalents on that day

The study period for Studies 302, 308, and 313 ends POD 10; in contrast, the study period for Study 001 ends POD 14

Reference: Volume 164, Table 11.2.4.1, Pages 296-8 ; Volume 167, Table 11.2.4.1, Pages 341-3; Volume 173, Table 11.2.4.1, Pages 246-8; and Study Report 001, Table 13.44, Pages 565-9

6.1.2 General Discussion of Endpoints

Primary Endpoint (GI^3): In Studies 302, 308, 313, and 001, the original, pre-specified, primary efficacy endpoint was the time to recovery of the functions both the **upper and lower GI tracts**, following abdominal or pelvic surgery:

1) The first component of the primary efficacy endpoint was the recovery of the **upper GI tract**: 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 a solid meal without significant nausea/vomiting for four hours after the solid meal and without reversion to a clear or full liquid diet).
2) The second component of the primary efficacy endpoint was the recovery of the **lower GI tract**: the time from the end of surgery to the first flatus or the first BM (whichever occurred first).

The primary efficacy endpoint was the time when both the upper and the lower GI tracts recovered after surgery (which ever occurred last). This 3-component, composite endpoint was identified as **GI^3** and was mathematically expressed as follows:

GI^3 = max [upper GI tract, lower GI tract] = max [solid food, min (flatus, BM)]

In the three U.S. POI studies, the population (GI and gynecologic surgery) for the primary efficacy endpoint was consistent throughout the entire study. In contrast, midway during the European POI study (Study 001) and before un-blinding, amendment #2 modified the population of the primary efficacy endpoint from (GI and gynecologic surgery patients) to only GI surgery patients.

Medical Reviewer's Comments: **Important endpoints have not been standardized for investigational POI trials. This medical officer believes that the pre-specified primary endpoint (GI^3) in the four phase 3 efficacy trials is acceptable because it captures the recovery of the motility of the upper and lower GI tracts. In several DGICDP/sponsor meetings during the development of alvimopan, the DGICDP stressed the importance that this composite endpoint must be both statistically significant and clinically meaningful. In an October 2000 meeting between the DGICDP an the sponsor, the DGICDP stated that "A clinically meaningful difference in recovery time will be one that is on the order of a day or so, not just a few hours." This medical officer believes that a 24 hour difference (or greater) in recovery of both upper and lower GI tract motility between alvimopan and the placebo would be clinically meaningful. However, this medical officer believes that a 10 hour difference (or less) in recovery of both upper and lower GI tract motility between alvimopan and the placebo would not be clinically meaningful. An Advisory Committee Meeting would be helpful at the elucidation of clinically meaningful differences in the recovery of upper and lower GI tract motility.**

Pre-specified secondary efficacy endpoints: In the three U.S. POI trials, the seven secondary endpoints were the following:

#1) The proportion of responders. A responder was defined as a patient with recovery of both the upper and lower GI tracts within 108 hours after BR or rTAH surgery. According to the sponsor, the definition of responder for this study was derived from their pooled phase II POI trials. In these phase II trials, the median time to recovery of GI function was 108 hours in approximately 100 placebo patients who had BR or rTAH surgery.
#2) The time from the end of surgery to the first toleration of solid food **and** the time to the first BM (which ever occurred last). This 2-component, composite endpoint was identified as **GI^2** and was mathematically expressed as follows: **GI^2** = max (solid food, BM). In Studies 308, 313, and 001, GI^2 was a pre-specified secondary endpoint; whereas, in Study 302, GI^2 was adding after un-blinding (post-hoc secondary endpoint).
#3) 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 (identified as **Ready**).
#4) The time from the end of surgery to the time of the first flatus (identified as **Flatus**).
#5) The time from the end of surgery to the time of the first BM (identified as **BM**).
#6) The time from the end of surgery to the time of first toleration of solid food (identified as **Solids**).
#7) The time from the end of surgery to the time that the hospital discharge order was written (identified as **Discharge**).

According to the sponsor, **Discharge** was a better measure of the resolution of POI compared to the time from the end of surgery to the time a patient physically left the hospital because the latter endpoint is influenced by discharge delays including transportation issues.

In Studies 313 and 308, **GI^2** was measured prior to un-blinding; however, in Study 302, **GI^2** was calculated after the blind was broken.

In Study 313, the secondary endpoints were prioritized (the most important endpoint was #1 above and the least important was #7 listed above). In contrast, in Studies 302 and 308, the secondary endpoints were not ordered by priority.

Study 001 had 25 pre-specified secondary endpoints which included all six (#2, #3, #4, #5, #6, and #7) of the time-to-event secondary endpoints in the U.S. POI studies. The other 19 secondary endpoints were the following:

- The time from the end of surgery to the time to first tolerance of enteral fluids
- The time from the end of surgery to the time to return of appetite
- The time from the end of surgery to the time until ready for hospital discharge, based on the medical fitness of the subject as a whole based on the judgment of the investigator
- The time from the end of surgery to the time to discontinuation of IV hydration fluids
- The total number of postoperative emetic episodes
- The maximum severity of pain intensity, nausea intensity and abdominal bloating intensity.

- The average daily postoperative opioid consumption and total pre- and intra-operative opioid level
- The need for and time to re-insertion of NG tube
- The proportion of responders: defined as a patient achieving recovery of GI function within ≤ 96, 108, 120, 144, 168 hours post-surgery
- The proportion of responders: defined as a patient being authorized for discharge within ≤ 120, 168 hours post-surgery

Medical Reviewer's Comments: **This medical officer believes that READY and DISCHARGE are the most important secondary endpoints because these objective endpoints demonstrate a clinically important outcome – a reduction in the duration of hospital stay following abdominal or pelvic surgery. Similar to the primary endpoint, the DGICDP stressed to the sponsor that in the DISCHARGE and READY endpoints, the alvimopan group must have clinical meaningfulness compared to placebo.**

This medical officer agrees with the sponsor that the duration of hospitalization is better represented by the endpoint DISCHARGE than the time from surgery to the time that the patient actually leaves the hospital. The latter endpoint may be influenced by transportation difficulties or social issues; rather, than medical problems. The relative importance of the two endpoints, READY and DISCHARGE, in the efficacy of alvimopan is equivocal. If alvimopan contributes to a serious adverse event (SAE) that delays hospitalization than the endpoint DISCHARGE may be more relevant than the endpoint READY. However, if the events that delay discharge are not related to any surgical issue and not related to AEs from alvimopan than READY may be more clinically relevant.

For secondary endpoint #1 (the responder definition in the U.S. POI trials), the sponsor selected the same cut-off point (108 hours) for rTAH patients as small BR and large BR patients. However, the results of the five phase 3 POI trials demonstrated that the rTAH patients achieve GI[3] sooner than small or large BR patients. Additionally, rTAH surgery does not involve incision into the bowel; whereas, small and large BR is based on bowel surgery. Surgeries that cut into the bowel wall are more likely to produce dysfunction in GI motility than surgeries that do not involve bowel cutting. Therefore, the rTAH/BR grouping for the responder definition was not appropriate. Patients who had rTAH surgery were more likely to achieve the primary efficacy endpoint (GI[3]) than BR patients. Thus, the ability to respond was more dependent on the surgery type than the treatment administered.

Other endpoints: In the U.S. POI studies, 10 additional pre-specified endpoints of interest (tertiary endpoints) were the following:

- Daily and maximum postoperative pain [visual analogue scale (VAS)]
- Pre-operative, post-operative, and total opioid consumption
- Severity of GI symptoms: extent of vomiting episodes, nausea (VAS), and abdominal bloating/distention (VAS)
- Need for postoperative insertion of a nasogastric tube (NGT)
- Need for post-operative chest X-ray.

Studies 302 and 313 had the following additional tertiary variable: total opioid consumption. In addition, Study 302 had another tertiary variable: maximum daily temperature

Medical Reviewer's Comments: **This medical officer agrees with the sponsor that pre-operative, intra-operative, and post-operative opioid consumption are important efficacy endpoints. Higher opioid consumption may increase the likelihood of a post-operative ileus. Thus, if the opioid consumption is not balanced among the treatment groups, the primary efficacy and important secondary efficacy endpoints should be analyzed according to the amount and the type of opioid used during surgery and after surgery.**

Additionally, anti-emetic medication consumption during surgery and the postoperative periods are important efficacy endpoint to measure. The label of zofran® (ondansetron), a 5-HT_3 receptor antagonist, states that "the use of ondansetron in patients following abdominal surgery ... may mask a progressive ileus and/or gastric distension." Therefore, if anti-emetic use is not balanced among the treatment groups, the primary efficacy and important secondary efficacy endpoints should be analyzed according to the amount and the type of post-operative anti-emetic used.

Some component of post-operative nausea and vomiting may be due to post-operative opioid therapy. The tertiary endpoints of vomiting and nausea may assess the ability of alvimopan to decrease these possible opioid AEs. The tertiary endpoints of opioid consumption and pain will assess if alvimopan reverses opioid analgesia.

Additionally, the sponsor conduced post-hoc analyses (including prolonged POI and readmission to the hospital due to POI), which were not pre-specified in the protocol.

6.1.3 Study Design

This section details the study design of Study 313. The study design of Studies 302, 308, and 001 were very similar to Study 313. Study 306, the primary phase 3 safety study also had many similarities to the four phase 3 efficacy trials. This medical officer will compare all the phase 3 trials in this section.

Title for Study 313: "A multi-center, phase III, double-blind, placebo-controlled, parallel study of ADL 8-2698 (Alvimopan; Entereg™) in opioid-induced postoperative bowel dysfunction/postoperative ileus"

Study Objective: The objective of this study was to 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 radical total abdominal hysterectomy (rTAH).

Study Design: Study 313 was a randomized, double-blind, placebo-controlled, multi-center (34 sites), parallel, phase III trial of alvimopan in the treatment of POI in patients undergoing partial small or large BR with primary anastomosis or rTAH in the United States (31 sites) and Canada (3 sites). Patients were stratified by center and randomized in a 1:1:1 ratio to

receive either 6 mg of alvimopan capsules, 12 mg of alvimopan capsules, or placebo capsules by mouth with a sip of water at least 2 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 (POD 7).

POD is 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) is the 24-hour period after the end of surgery (see Table 13).

Table 13: Post-Surgery Day (PSD)

Post-Surgery Day (PSD)	Time of Assessment – Hours after the End of Surgery
0	≤ 24
1	24 to 48
2	48 to 72
3	72 to 96
...	...
10	240 to 264

Reference: Adapted from Volume 173, Page 50, Table 5.

Medical Reviewer's Comments: Study 313 was well-controlled and well-designed.

Eligibility Criteria: Table 14 displays the eligibility criteria of Study 313.

Table 14: Eligibility criteria of Study 313

Inclusion Criteria: To be eligible to participate in the study, patients had to have met the following criteria:	**Exclusion Criteria:** If patients had the following conditions, they were not eligible to participate in the study:
➢ 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 or rTAH. ➢ Were scheduled to receive postoperative pain management with intravenous patient-controlled analgesia (PCA) opioids. ➢ Were scheduled to have the NGT removed at the end of surgery. ➢ Understood the procedures, agreed to participate in the study program, and signed the informed consent form.	➢ Were pregnant or lactating; patients who were not post-menopausal (no menses for at least one year) and were of childbearing potential and not using an accepted method of birth control (i.e., surgically sterile, intra-uterine contraceptive device, oral contraceptive, diaphragm or condom in combination with contraceptive cream, jelly, or foam). ➢ 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. ➢ Were incapable of understanding the informed consent. ➢ Had participated in another clinical drug trial within the last 4 weeks. ➢ Had clinically significant laboratory abnormalities on screening. ➢ Had complete bowel obstruction. ➢ Were scheduled for a total colectomy, colostomy, or ileostomy. ➢ Had a history of any illness or behavior, including substance abuse or dependency that, in the opinion of the Investigator, might have confounded the results of the study or posed additional risk in administering the study procedures to the patient.

Reference: Adapted from Volume 173, Page 35.

Medical Reviewer's Comments: All three efficacy phase III studies (313, 302, and 308) had similar eligibility criteria. Study 313 included three surgical types (rTAH, small BR, and large BR); Study 308 included all four surgical types (sTAH, rTAH, small BR, and large BR patients); and Study 302 included three surgical types (sTAH, rTAH, and large BR). Originally, Study 001 included three surgical types (rTAH, small BR, and large BR) and after amendment #2, Study 001 included only two surgical types (small BR and large BR). Study 302 differed from the other three 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. The sponsor did not detail the rationale for the different surgery types allowed in the three phase III efficacy studies.

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 three U.S. studies included patients who were scheduled to receive postoperative opioids only by PCA.

Overall, this medical officer believes that the four efficacy studies' eligibility criteria were very similar to one another. The main difference between the four studies was the differences in surgical types allowed in the studies. All four studies initially allowed rTAH and large BR patients to be included.

Premature discontinuation of patients in Study 313: A patient could withdraw from the study at any time at the request of the patient, investigator, or the sponsor.

Drugs used in Study 313: Patients were randomly assigned (1:1:1) to receive 6 of alvimopan capsules, 12 mg of alvimopan capsules; or identical placebo capsules, given by mouth with a sip of water at least two 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 6 mg alvimopan dose, patients received one 6 mg alvimopan capsule and one placebo capsule. For each 12 mg alvimopan dose, patients received two 6 mg alvimopan capsules.

Selection of the dose in Study 313: For Study 313 and the other phase 3 efficacy trials, the sponsor selected the two highest doses used in the phase 2 trials (6 mg BID and 12 mg BID) because the top three doses in the phase 2 trials (3 mg BID, 6 mg BID, and 12 mg BID) appeared equally efficacious in the recovery of upper and lower GI tract motility and alvimopan demonstrated no safety signal in the phase 2 trials.

Medical Reviewer's Comments: All four phase 3 trials had identical treatment arms (placebo, alvimopan 6 mg, and alvimopan 12 mg).

Selection of the dosage regimen in Study 313 : The sponsor's argued that the dosing regimen (including one pre-operative dose) would maximize the efficacy of alvimopan because alvimopan would be present in the colonic lumen prior the administration of exogenous opioids during surgery. The sponsor reasoned that alvimopan would block the binding of exogenous opioids to the peripheral μ-opioid receptors in the colon and this would improve colonic motility — the rate-limiting step for the resolution of POI.

Medical Reviewer's Comments: The complex dosage regimen (first dose two hours prior to surgery and then a dose BID from POD 1 to POD 7 or until hospital discharge or study termination) was identical in all four efficacy phase 3 studies (302, 308, 313, and 001) and all three phase 2 trials (13C206, 13C213, 13C214).

The dosing regimen used in the phase 3 studies exposed patients to one dose of study medication before the development of a POI. Additionally, some patients were exposed to one dose of study medication unnecessarily because they received the first dose and then their surgery was canceled. This medical officer believes that the sponsor should have experimented with different dosing regimens during the phase 2 POI studies to avoid unnecessary exposure to study medication. The sponsor should have investigated the administration of the first dose of study drug after surgery.

Schedule of Procedures and Evaluations in Study 313: See Table 15 for a list of the procedures and evaluations during Study 313.

Table15: Schedule of procedures and evaluations in Study 313

Procedure	Screening (Day –14 to Day 0)	Surgery Day 0		Postoperative Days 1-10 (twice daily while subject hospitalized)[1, 2]	Hospital Discharge / Study Termination
		Pre-Surgery	Post-Surgery		
Consent	X				
Medical history	X				
Medication history	X				
Physical examination, including body weight	X				X
Vital signs (Temperature, blood pressure, heart rate, respiratory rate)	X		X	X	X
Electrocardiogram	X				X
Inclusion and Exclusion Screening	X				
Urinalysis, Hematology, and Serum Chemistry	X				X
Biochemical liver tests	X	X[3]			X
Urine Pregnancy Test	X[4]	X[4]			
Study Medication[1]		X[5]		X	
First Bowel Tones			X	X	
First Flatus			X	X	
First Bowel Movement			X	X	
Tolerability of liquids			X	X	
Tolerability of solid food			X	X	
Opioid Consumption			X	X	X
VAS for Pain and Abdominal Bloating[6]			X	X	
VAS for Nausea[7]			X	X	
Adverse Events	X	X	X	X	X[8]
Concomitant Medications	X	X	X	X	X[8]

[1] Dosing continued BID until hospital discharge, or for a maximum of 7 days of postoperative treatment.

[2] Data collection continued until hospital discharge or for a maximum of 10 postoperative days (while patient was hospitalized).

[3] Biochemical liver tests obtained prior to first dose of study drug unless obtained within the previous 24 hours.

[4] Day of surgery or day prior to surgery.

[5] Study medications were administered at least 2 hours prior to the scheduled start of surgery.

[6] Visual Analogue Scales (VAS) for pain and abdominal bloating were completed upon discharge from the recovery room and BID beginning with POD 1 AM assessment.

[7] VAS for nausea was completed upon discharge from the recovery room, every 4 hours on day of surgery while the patient was awake, and BID beginning with POD 1 AM assessment.

[8] All patients were to be contacted by phone within 5–7 days after the last dose of study medication to ascertain the occurrence of adverse events and concomitant medications taken since the last dose of study drug.

Reference: Adapted from Volume 173, Page 40, Table 3

Screening Phase in Study 313: The Screening Phase was Day -14 to Day 0. Within 14 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.

Day of Surgery in Study 313: The day of surgery is also identified as POD 0. The patients were randomly assigned to receive 6 or 12 mg of oral alvimopan or matching placebo capsules by mouth with a sip of water at least two hours prior to the scheduled start of surgery. All other care was determined by the usual surgical routine. Biochemical liver tests were obtained two hours prior to surgery unless obtained within the previous 24 hours.

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 noon of POD 1.

POD 1 to POD 7 in Study 313: Patients received 6 or 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 tolerated. If the patient had no vomiting and no significant nausea, patients were to be offered a liquid diet the morning of POD 1 and were to be offered solid food on POD 2 (the second day after surgery). 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 experienced no vomiting within 4 hours, and there was no reversion to a previous dietary stage. 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 liquid and 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.

Nausea was assessed upon discharge from the recovery room, every 4 hours after surgery on POD 0 (while the patient was awake), and twice daily on POD 1 to POD 10 (if applicable). Patients rated the intensity of nausea on a 0-100 mm VAS scale where "No Nausea" and the "Worst Nausea Imaginable" were graded 0 mm and 100 mm, respectively.

Abdominal bloating and distention were assessed when the patient left the recovery room on POD 0 and twice daily on POD 1 to POD 10 (if applicable). Patients rated the intensity of their abdominal bloating and distention on a 0-100 mm VAS scale where "no uncomfortable abdominal bloating/distention" and the "most uncomfortable abdominal bloating/distention imaginable" were graded 0 mm and 100 mm, respectively.

Emetic episodes were recorded once daily at the afternoon assessment. Any number of retches over a 5 minute period or any number of vomiting episodes in very close succession (without relief) were both graded as one emetic episode. Retching was defined as one or more unproductive emesis episodes in a unique 5-minute period. Vomiting was defined as one or more productive emesis episodes in very close succession, not relieved by a period of relaxation.

Total daily opioid consumption was recorded upon discharge from the recovery room and twice daily on PODs 1-10, while the patient was hospitalized. Patients rated the intensity of their pain on a 0-100 mm scale, anchored by the words "no pain" (0 mm) and "worst pain imaginable" (100 mm).

Auscultation of the abdomen was performed for one full minute twice daily to assess onset of return of bowel tones.

Medical Reviewer's Comments: **The four efficacy phase 3 trials had very similar evaluations and procedures. In the all four POI efficacy studies, the last possible day in the Treatment Period was POD 7. In the three U.S. POI efficacy studies, the last possible study day was POD 10; in contrast, in the one European trial, the last possible study day was POD 14.**

Concomitant Therapy during the Treatment Period in Study 313: Anti-emetics were permitted during the immediate peri-operative period (defined as immediately before, during or for one hour after the end of surgery) as part of the anesthesia protocol. In addition, patients were permitted to receive anti-emetics postoperatively to treat moderate to severe nausea or episodes of vomiting. However, prophylactic use of anti-emetics was prohibited after surgery, including the following medications: metoclopramide, granisetron, ondansetron, dolasetron, promethazine, prochlorperazine, perphenazine, hydroxyzine, droperidol and chlorpromazine.

The concomitant use of opioids and/or local anesthetics administered epidurally, cathartics, enemas, and ketorolac was prohibited. Also prohibited was prophylactic use of low dose naloxone infusions.

Medical Reviewer's Comments: **The prohibited medications during the Treatment Periods in the four phase 3 trials were very similar.**

Since the study evaluations of the first record of flatus, BM, and/or toleration of solid food of the patients were based mostly on patient memory and hospital progress notes, they may not be fully accurate. Many post-operative patients suffer from impaired memory due to altered mental status due to concomitant medications including post-operative opioids and intra-operative, memory-impairing benzodiazepines. Additionally, hospital progress notes may not fully detail all the occurrences of flatus, BM, and emetic episodes. Furthermore, infrequent evaluations (once to twice daily) may have impaired the recording of events in this study. Incomplete evaluations during the phase III studies may lead to misleading results.

Discharge/Termination in Study 313: The surgeon was to evaluate the patient's readiness for hospital discharge based solely upon his/her definition of recovery of GI function at the time of the morning and afternoon assessments (two times a day).

Post-Treatment Period in Study 313: Investigators telephoned patients within 5 to 7 days after the last dose of study medication regarding the use of concomitant medications after discharge from the hospital.

Medical Reviewer's Comments: The post-treatment follow-up was similar in the four phase 3 efficacy studies. All patients were called 5-7 days after the last dose of study medication for assessment of AEs. However, in all four studies no follow-up physical exam, ECG, or laboratory testing were performed.

Statistical Methods in Study 313: The following 5 patient populations were pre-specified in Study 313:

1) Randomized: All patients who were randomized. Patients may or may not have received any study medication.
2) Intention to Treat (ITT): All patients who received any study medication.
3) Safety: All ITT patients who had any safety evaluation data. The safety population was used for all safety analyses.
4) Modified ITT (MITT): All ITT patients who received the expected, protocol-specified surgery and had at least one on-treatment evaluation of flatus, BM, or toleration of solid food. This population was the population pre-specified for the primary efficacy analyses.
5) Per protocol [efficacy evaluable (EE)]: All MITT patients who did not have major protocol violations. In general, major protocol violations included entering the study without meeting all inclusion/exclusion criteria, not receiving protocol-specified surgery, failing to remove the NGT prior to the first postoperative study medication dose, receiving prohibited concomitant medication, having epidural pain management, or not receiving treatment per randomization. Analyses of the EE population were pre-specified as the secondary analyses in Study 313.

Medical Reviewer's Comments: All four phase 3 efficacy trials defined identical statistical populations.

The MITT population appropriately excluded ITT patients who were not likely to develop POI. Patients who had certain surgeries (such as laparoscopic gallbladder surgeries) that are not likely to develop POI should be excluded from the MITT population. Additionally, the MITT population appropriately excluded ITT patients who had an ileostomy or a colostomy because flatus and BMs (components of the primary efficacy endpoint) may be difficult to measure in patients with ostomies.

However, this medical officer believes that the MITT population inappropriately excluded patients who had an unexpected protocol specified surgery. Under these rules, if a patient, scheduled for a large BR, had a small BR instead that patient would be excluded from the MITT population. This medical officer believes that the MITT population, the population used for the primary efficacy analysis, should include all

patients who were scheduled to have one of the four pre-specified surgeries in the three phase III efficacy trials: large BR, small BR, sTAH, or rTAH.

Statistical Methods for the Primary Efficacy Endpoint in Study 313: There were two null hypotheses:

1) Hypothesis 1: There was no difference between the alvimopan 6 mg group and placebo group in the time to recovery of GI function, and
2) Hypothesis 2: There was no difference between the alvimopan 12 mg group and placebo group in the time to recovery of GI function.

Two nominal p-values for the comparisons between alvimopan and placebo were calculated using the Wald Chi-square test from the Cox proportional hazard model. In order to control the family-wise error rate to be 0.05 for the two hypotheses, the Hochberg step-up method was used to interpret the significance of a nominal p-value.

A summary table was generated that included the number of patients analyzed, the number and proportion of patients censored, the median time to recovery of GI function and its 95% confidence intervals, hazard ratios and their 95% confidence intervals, the Wald Chi-square p-values, and significance conclusion based on Hochberg's step–up method for controlling the overall Type I error (alpha) to be 5% or less. The cumulative proportions of all patients reaching the primary endpoint were plotted as a function of the time by using both the Kaplan-Meier product limit method and the Cox proportional hazard model.

The magnitude of the treatment effect was expressed as the difference in mean time (in hours) to event (recovery of GI motility) between the alvimopan 6 mg arm and the placebo arm and between the alvimopan 12 mg arm and the placebo arm. The mean time to event was estimated by the use of the area under the Kaplan-Meier survival curve over time.

Medical Reviewer's Comments: All four phase 3 efficacy trials had similar statistical analysis plans for the primary efficacy endpoint. Dr. Sonia Castillo, the statistical reviewer, provided more information regarding the statistical analyses in the four phase III efficacy studies in her review. Please see her review.

Supportive Study (Study 14CL306)

Study 14CL306 (identified as Study 306) was a supportive study for the gynecologic surgery subgroup. Study 306 was a randomized, placebo-controlled, double-blind, parallel-group, multi-center phase 3 safety study in patients scheduled to have sTAH. See Table 16 for the main differences between Study 306 and the four important phase 3 studies (302, 308, 313, and 001).

Table 16: Differences between the four important efficacy studies (302, 308, 313, and 001) and the one safety study (306)

	Studies 302, 308, 313, and 001	Study 306
The primary efficacy endpoint	GI^3	General safety endpoints
Surgical type(s)	All had rTAH and large BR Some had sTAH and/or small BR	Only sTAH
Treatment groups	Placebo Alvimopan 6 mg Alvimopan 12 mg	Placebo Alvimopan 12 mg
Randomization	1:1:1	1:4
Treatment Period	Only inpatient	Inpatient and Outpatient
Minimum study dosing	Until hospital discharge or achievement of primary efficacy endpoint	Not applicable. All patients were to receive the maximum dosing schedule of 7.5 days

Reference: Study 306 (Volume 171)

Study 306 was similar to the four important efficacy studies (302, 308, 313, and 001) in many ways. All five studies had the following similar characteristics:

- Were randomized, placebo-controlled, double-blind, parallel-group, multi-center phase 3 studies
- Had endpoint GI^3 as a primary endpoint (Studies 302, 308, 313, and 001) or a secondary endpoint (Study 306)
- Had five identical time-to-event secondary efficacy endpoints (time to first flatus, to first BM, to GI^2, to tolerability of solids, to hospital discharge order written)
- Had similar complex dosing regimens: take the first dose 2 hours prior to surgery (POD 0), then take subsequent doses twice daily POD 1 to POD 7 for a maximum of 7.5 days
- Had the identical primary population evaluated (the MITT population)
- Had similar eligibility criteria including exclusion of patients scheduled for laparoscopic procedures; the exclusion of patients with significant concomitant opioid analgesia; and the exclusion of patients with an American Society of Anesthesiologists (ASA) Physical Status Score of > III.

Medical Reviewer's Comments: Although Study 306 had study design differences from the four important efficacy trials, Study 306 had many similarities and it contained a large population of gynecologic patients. Alvimopan was administered to 408 gynecologic surgery patients in Study 306; whereas, alvimopan was given to only 303 gynecologic patients in all four important efficacy studies. Thus, 57% of the gynecologic surgery patients who received alvimopan were in Study 306. Despite its distinction from the other four efficacy studies, Study 306 should be considered at least

a supportive study in the efficacy evaluation of the gynecologic subpopulation in the treatment of POI.

6.1.4 Efficacy Findings

Disposition of patients: In the POI subpopulation, a total of 3326 surgery patients were randomized to alvimopan (1 mg, 3 mg, 6 mg, or 12 mg) or placebo in eight POI studies [three phase 2 studies (13C206, 13C214, and 13C213), one phase 3 safety study (14CL306), three phase 3 U.S. efficacy studies (14CL302, 14CL308, and 14CL313), and one phase 3 European efficacy study (SB-767905/001)]. In these eight POI studies, 898 and 1321 surgery patients were randomized to 6 mg and 12 mg of alvimopan, respectively (see Table 17).

Table 17: Patient disposition in the four important efficacy studies (Studies 302, 308, 313, and 001)

Population		Randomized	ITT	Safety	MITT	EE
		N	N (% of Randomized)	N (% of Randomized)	N (% of Randomized)	N (% of Randomized)
Study 302	Placebo	153	153	153	145	144
	6 mg	152	152	150	141	137
	12 mg	146	146	146	138	135
	Total	**451**	**451 (100%)**	**449 (99.6%)**	**424 (94.0%)**	**416 (92.2%)**
Study 308	Placebo	224	224	224	207	199
	6 mg	220	220	220	204	198
	12 mg	222	222	221	204	200
	Total	**666**	**666 (100%)**	**665 (99.8%)**	**615 (92.3%)**	**590 (88.6%)**
Study 313	Placebo	165	165	165	149	142
	6 mg	169	169	169	155	150
	12 mg	176	176	176	165	160
	Total	**510**	**510 (100%)**	**510 (100%)**	**469 (92.0%)**	**452 (88.6%)**
Study 001	Placebo	305	282	292	267	164
	6 mg	302	292	294	271	172
	12 mg	304	293	297	271	164
	Total	**911**	**876 (96.2%)**	**883 (96.9%)**	**809 (88.8%)**	**500 (54.9%)**
Total for all four studies		**2538**	**2503 (98.6%)**	**2507 (98.8%)**	**2317 (91.3%)**	**1958 (77.1%)**

ITT (intention to treat) patients received one or more doses of study medication;
Safety patients were ITT patients who had at least one safety evaluation data;
MITT (Modified ITT) patients were ITT patients who received the expected, protocol-specified surgery and had at least one evaluation of flatus, BM, or toleration of solid food. The MITT population was the population used for the primary analyses for the efficacy endpoints; and
EE (efficacy evaluable) patients were MITT patients who did not have any protocol violations.
Reference: Adapted from 1) ISE, Volume 267, Table 9.2, Page 195; 2) ISS, Volume 211, Table 20, Page 65-66; 3) ISE, Volume 267, Table 1.1; Page 309; 4)) ISE, Volume 267, Table 7, Page 68; and 5) Study Report 001, Table 12.2. Page 217.

Three important U.S. phase 3 efficacy studies: A total of 1627 surgery patients were randomized in Studies 302, 308, and 313. All randomized surgery patients in the three important efficacy studies received at least one dose of study medication. In Studies 302,

308, and 313, the MITT population (the primary population used for efficacy analyses) had 424, 615, and 469 patients, respectively (please see Table 18). Reasons for exclusion from the MITT populations included cancellation of surgery after administration of the pre-operative dose, undergoing a non-protocol specified surgery, or withdrawal from treatment immediately after the surgery (see Table 18). In Studies 302, 308, and 313, the EE population (the confirmatory population used for efficacy analyses) had 416, 590, and 452 patients, respectively.

Table 18: Patient disposition in the MITT population and reasons for exclusion from the MITT population in U.S. POI Studies (302, 308, and 313)

		MITT population N	Total patients excluded from MITT* N (%)	Reasons for exclusion from MITT		
				Surgery was canceled N (%)	Had non-protocol specified surgery N (%)	Did not have any post-op efficacy assessment N (%)
Study 302	Placebo	145	8 (5.2)	2 (1.3)	4 (2.6)	2 (1.3)
	6 mg	141	11 (7.2)	6 (3.9)	2 (1.3)	3 (2.0)
	12 mg	138	8 (5.5)	3 (2.1)	2 (1.4)	3 (2.1)
	Total	**424**	27 (6.0)	11 (2.4)	8 (1.8)	8 (1.8)
Study 308	Placebo	207	17 (7.6)	5 (2.2)	4 (1.8)	8 (3.6)
	6 mg	204	16 (7.3)	3 (1.4)	9 (4.1)	4 (1.8)
	12 mg	204	18 (8.1)	4 (1.8)	4 (1.8)	10 (4.5)
	Total	**615**	51 (7.7)	12 (1.8)	17 (2.6)	22 (3.3)
Study 313	Placebo	149	16 (9.7)	1 (0.6)	6 (3.6)	9 (5.5)
	6 mg	155	14 (8.3)	2 (1.2)	6 (3.6)	6 (3.6)
	12 mg	165	11 (6.3)	3 (1.7)	2 (1.1)	6 (3.4)
	Total	**469**	41 (8.0)	6 (1.2)	14 (2.7)	21 (4.1)

* ITT patients were excluded from the MITT population
The MITT population was the population used for the primary analyses for the efficacy endpoints.
Reference: Adapted from 1) ISE, Volume 267, Page 46, Table 4 and ISE, Volume 267, Table 1, Page 9.

One important European phase 3 efficacy study: Out of a total of 911 surgery patients randomized in Study 001, 876 (96.2%) received at least one dose of study medication. In Study 001, of the 883 ITT patients, 809 were in the MITT population and 500 were in the EE population. Please see Table 19 for details.

Table 19: Patient disposition in the MITT population and reasons for exclusion from the MITT population in Study 001

MITT population N	Patients excluded from the randomized population* n (%)	Reasons for exclusion from MITT population*		
		Surgery was canceled n	Had non-protocol specified surgery n	Did not have any post-op efficacy assessment n
Placebo (N=267)	38 (12)	23	1	15
6 mg of alvimopan (N=271)	31 (10)	10	10	17
12 mg of alvimopan (N=271)	33 (11)	11	9	18

* Patients may have more than one reason for exclusion from the MITT population.
Reference: Adapted from Study Report 001, Table 12.4, Page 220

Baseline Demographics for the four important efficacy studies: Table 20 delineates the demographics and baseline characteristics of the MITT populations in the four important efficacy trials (Studies 302, 308, 313, and 001). The mean ages of patients in Studies 302, 308, 313, and 001 were 58, 57, 61, and 63, respectively. The percentage of Caucasians in Study 001 (99%) was much higher than the percentage of Caucasians in the three U.S. POI studies (ranging from 76% in Study 308 to 87% in Study 313). In Studies 302 and 308, females comprised of approximately two-thirds of the population; whereas, in Studies 313 and 001, females involved about one-half of the population. The mean BMI in the European Study (26) was slightly lower than the mean BMI in the U.S. POI studies (ranging from 28 in Study 313 to 29 in Study 308).

In each of the four important efficacy trials, there were no statistical differences in age, race, and gender demographics among the three treatment groups (placebo, 6 mg of alvimopan, and 12 mg of alvimopan).

Medical Reviewer's Comments: Overall, the baseline demographics of the study populations in Studies 302, 313, 308, and 001 were acceptable. The mean age in the POI studies was related to the surgery type. Studies with a higher percentage of gynecologic surgery (sTAH or rTAH) had a younger population; in contrast, studies with a higher percentage of BR surgery had an older population. The mean age in the European study was higher than the mean age in the U.S. studies.

Studies with a higher proportion of gynecologic surgery (sTAH and rTAH) had a higher proportion of women. Studies 302 and 308 had higher proportions of gynecologic surgery patients (compared to studies 313 and 001), and therefore studies 302 and 308 had higher percentage of female patients.

The racial diversity in the U.S. POI populations was similar to the racial diversity in the United States; except the study populations had a lower percentage of Hispanics and a

slightly higher percentage of Caucasians. The higher percentage of Caucasian patients in the European study (compared to the U.S. studies) probably reflects the baseline racial mixture of the countries.

Table 20: Baseline demographics for the MITT populations* in Studies 302, 308, and 313 and Safety population in Study 001

		Study 302	Study 308	Study 313	Study 001
Population	Randomized patients, N	451	666	510	911
	MITT patients, N	424	615	469	809
	Safety patients, N	449	665	510	883
Age	Mean age (SD)	57.8 (13.8)	56.9 (15.1)	60.5 (14.8)	63.3 (12.9)
	≥ 65 years, N (%)	143 (33.7)	208 (33.8)	208 (44.3)	()
Race	Caucasian, N (%)	350 (82.5)	468 (76.1)	410 (87.4)	870 (99)
	Black, N (%)	53 (12.5)	89 (14.5)	40 (8.5)	7 (<1)
	Hispanic, N (%)	17 (4.0)	42 (6.8)	13 (2.8)	0 (<1)
	Asian, N (%)	2 (0.5)	11 (1.8)	3 (0.6)	1 (<1)
	Other, N (%)	2 (0.5)	5 (0.8)	3 (0.6)	5 (<1)
Gender	Male N (%)	139 (32.8)	222 (36.1)	234 (49.9)	459 (52)
	Female N (%)	285 (67.2)	393 (63.9)	235 (50.1)	424 (48)
BMI	Mean BMI (SD)	28.3 (5.8)	28.5 (6.9)	27.8 (5.7)	26.4 (4.6)
	BMI < 30 kg/m^2 N (%)	266 (62.7)	422 (68.6)	334 (71.2)	700 (81)
	BMI ≥ 30 kg/m^2 N (%)	155 (36.6)	193 (31.4)	128 (27.3)	159 (19)

*MITT patients were ITT patients who received the expected, protocol-specified surgery and had at least one on-treatment evaluation of flatus, BM, or toleration of solid food.

Reference: Adapted from ISE, Volume 267, Table 5, Page 49 and Study Report for 001, Page 69, Section 6.4.1 Table 9, Page 69

Surgery type for the four important efficacy studies: Table 21 presents the number and proportion of patients who had left large BR, right large BR, small BR, sTAH, and rTAH surgeries. In the pooled data of the four important efficacy trials, 79.5% of the patients had GI surgery (large or small BR) and 18.9% of the patients had gynecologic surgery (sTAH or rTAH). The most common surgery type was large BR surgery (73.7% of the total). In Study 313, the overwhelming majority of patients (96.1%) had small or large BR surgery. Within each study, no statistical significant differences in surgery type were observed among the three treatment groups (placebo, 6 mg of alvimopan, and 12 mg of alvimopan).

Medical Reviewer's Comments: The pathogenesis of POI may be partly due to bowel manipulation during surgery. Surgeries with greater bowel incision (such as large bowel surgeries) may be more likely to have greater bowel motility dysfunction than surgeries that lack bowel cutting. Therefore, the important efficacy endpoints should be analyzed by surgical subgroup. Additionally, surgeries with longer durations may require more intra-operative opioid administration and therefore may have greater dysfunction of bowel motility. Thus, prolonged surgeries may contribute to prolongation of POI.

All four efficacy studies did not obtain possible 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. This medical officer requests the sponsor to obtain data on past history of ileus including POI.

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 three U.S. studies did not collect data on past surgical history. Patients with prior abdominal surgery have a greater likelihood of developing adhesions, and these patients may be at higher risk for POI. Therefore, in future POI trials, the sponsor should collect past surgical history of abdominal and/or pelvic surgeries.

Table 21: Surgery types of the MITT populations in Studies 302, 308, and 313 and the Safety population in Study 001

SURGERY TYPES n (%)	Study 302 (N=424)	Study 308 (N=615)	Study 313 (N=469)	Study 001 (N=883)	Total (N=2394)
BOWEL RESECTION (BR)					
Large BR	296 (69.8%)	373 (60.7%)	395 (84.2%)	700 (79.2%)	1764 (73.7%)
Left Large BR	151 35.6%)	232 37.7%)	246 52.5%)	330 37.4%)	959 (40.1%)
Right Large BR	145 34.2%)	141 22.9%)	149 31.8%)	259 (29.3%)	694 (29.0%)
Other				111 (12.6%)	111 (4.6%)
Small BR	0 (0%)	45 (7.3%)	56 (11.9%)	38 (4.3%)	139 (5.8%)
All BR PATIENTS	**296 (69.8%)**	**418 (68%)**	**451 (96.1%)**	**738 (83.6%)**	**1903 (79.5%)**
ABDOMINAL HYSTERECTOMY					
sTAH	96 (22.6%)	90 (14.6%)	0 (0%)*		191 (8.0%)
rTAH	32 (7.5%)	107 (17.4%)	18 (3.8%)	106 (12.0%)	261 (10.9%)
All TAH PATIENTS	**128 (30.1%)**	**197 (32%)**	**21 (3.9%)**	**106 (12.0%)**	**452 (18.9%)**
OTHER					
				20 (2.3%)	39 (1.6%)

* There were 3 sTAH patients in Study 313. These patients were included in pooled MITT population of Studies 302, 308, and 313; however, these 3 patients were excluded from the MITT population in Study 313.

Reference: Adapted from ISE, Volume 267, Table 9.11, Page 210; ISE, Volume 267, Table 6, Page 51; and ISE, Volume 267, Page 240, Table 12.24.

Primary indication for surgery in the four important efficacy studies: In the three U.S. POI efficacy studies, a summary of the primary indications for surgery (for the safety populations) are provided in Table 22. In the European POI efficacy study, a summary of the general indications for surgery (for the safety populations) are provided in Table 23.

Table 22: Primary indications for surgery in the U.S. efficacy studies (302, 308, and 313)

Primary Indication	Study 302 (N=449) Number (%)	Study 308 (N=665) Number (%)	Study 313 (N=510) Number (%)
Colon or Rectal Cancer	202 (45.0)	241 (36.2)	275 (53.9)
Diverticular Disease	56 (12.5)	74 (11.1)	56 (11.0)
Uterine Fibroids	45 (10.0)	66 (9.9)	0
Uterine Cancer	28 (6.2)	58 (8.7)	17 (3.3)
Ostomy Reversal	14 (3.1)	40 (6.0)	34 (6.7)
Crohn's Disease	—	37 (5.6)	34 (6.7)
Intestinal Polyps	13 (2.9)	22 (3.3)	31 (6.1)
Cervical Cancer	7 (1.6)	23 (3.5)	3 (0.6)
Ovarian Cancer	8 (1.8)	20 (3.0)	4 (0.8)
Rectal Prolapse	9 (2.0)	5 (0.8)	17 (3.3)
Intestinal Fistula	6 (1.3)	7 (1.1)	10 (2.0)
Abnormal Bleeding	—	16 (2.4)	—
Menorrhagia	15 (3.3)	—	—
Small Bowel Cancer	—	11 (1.7)	4 (0.8)
Chronic Pelvic Pain	8 (1.8)	—	—
Dysmenorrhea	7 (1.6)	—	—
Endometriosis	3 (0.7)	3 (0.5)	—
Ovarian Cysts	—	3 (0.5)	—
Pelvic Pain	—	1 (0.2)	—
Other Indication	19 (4.2)	27 (4.1)	19 (3.7)
No Surgery Performed	9 (2.0)	11 (1.7)	6 (1.2)
Colon, Rectal, Uterine, Cervical, Ovarian, or Small Bowel Cancer	245 (54.6)	353 (53.1)	303 (59.4)

This numbers represent the safety populations.
Reference: Adapted from ISE, Volume 267, Section 14.0, Table 10.3.2.3, Page 200.

Table 23 Reasons for surgery in Study 001 (the European POI study)

	Number (%) of subjects					
	Placebo (N=292)		Alvimopan 6mg (N=294)		Alvimopan 12mg (N=297)	
Primary reason for planned surgery						
Malignancy	221	(76)	232	(79)	241	(81)
Inflammatory bowel disease	25	(9)	25	(9)	19	(6)
Other	46	(16)	37	(13)	37	(12)

This numbers represent the safety populations.
Reference: Study Report for 001, Table 11, Page 71

Medical Reviewer's Comments: **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. Studies 313 and Studies 001 had higher proportion of patients scheduled for cancer surgery compared to (Studies 302 and 308). This disparity is consistent with the higher mean age seen in Studies 313 and 001 (cancer patients tend to be older). Study 001 had the highest portion of patients receiving cancer surgery compared to all three U.S. POI studies.**

Surgery Duration for the four important efficacy studies: Table 24 delineates the mean and median surgery durations in Studies 302, 308, 313, and 001. The median elapsed time between the initial dose of study drug and the start of surgery in the U.S. POI studies (Studies 302, 308, and 313) was greater than the median elapsed time between the initial dose of study drug and the start of surgery in the European study. The median surgery durations for the four efficacy studies were 1.6, 1.9, 2.1, and 2.4 for Studies 302, 313, 308, and 001, respectively.

Table 24: Surgery duration and duration between the first dose and surgery in Studies 302, 308, 313, and 001

	Study 302 (N=424)	Study 308 (N=615)	Study 313 (N=469)	Study 001 (N=883)
Elapsed Time between first dose and surgery (hours)				
Mean (SD)	3.0 (1.2)	3.5 (1.5)	3.3 (1.5)	2.4 (0.94)
Median	2.7	3.0	3.0	2.3
Surgery Duration (hours)				
Mean (SD)	1.9 (1.0)	2.4 (1.1)	2.1 (1.0)	2.6 (1.1)
Median	1.6	2.1	1.9	2.4

Studies 302, 308, and 313 are denoted by the MITT population; whereas, Study 001 is represented by the safety population.

Reference: Adapted from Volume 164, Page 177, Table 10.3.1.2 .1; Volume 167, Page 173, Table 10.3.1.2.1; Volume 173, Table 10.3.1.2 .1, Page 159; and Volume 173, Table 12.22, Page 238

Medical Reviewer's Comments: **The minor differences in the median time between the first dose of study drug and the start of surgery should not modify the outcomes of the studies.**

Efficacy Results:

Pre-specified primary endpoint: In the four important efficacy studies, the pre-specified primary endpoint (GI^3) was the time to recovery of both the **upper GI tract** motility (the time from the end of surgery to the time of the first toleration of solid food) **and** the **lower GI tract** motility [the time from the end of surgery to the first flatus or the first BM (whichever occurred first)], following abdominal or pelvic surgery.

Midway through Study 001, amendment #2 modified the primary population analyzed in the primary efficacy endpoint. After amendment #2, the primary efficacy endpoint in Study 001 was the recovery of both the upper and lower GI tract motility (GI^3) following only GI surgery. Therefore, in Study 001, all patients with small BR or large BR were analyzed in

the primary efficacy endpoint; however, all patients who had rTAH surgery were not analyzed in the primary efficacy endpoint. Thus, all of the below analyses for Study 001 were calculated only with GI surgery patients in Study 001. In contrast, the primary efficacy endpoint for the three U.S. POI trials was analyzed with both GI and gynecologic surgery patients.

Of the four important phase 3 efficacy studies, the alvimopan 6 mg treatment group compared to the placebo group achieved a statistically significant difference in two studies (302 and 313) for the primary efficacy endpoint. Please see Table 25 for the results of the primary efficacy endpoint in the four important phase 3 efficacy trials.

Of the four important phase 3 efficacy studies, the alvimopan 12 mg treatment group (compared to placebo) achieved a statistically significant difference in only one study (313) for the primary efficacy endpoint. Please see Table 25 for the results of the primary efficacy endpoint in the four important phase 3 efficacy trials.

Medical Reviewer's Comments: For the overall POI population (including both major surgery subgroups), the efficacy of both alvimopan doses in the treatment of POI based on the primary efficacy endpoint is equivocal. Since the efficacy of the primary efficacy endpoint was highly dependent on the surgical subgroup, the results of the subgroup analysis of the primary efficacy endpoint are very important. This medical officer will comment on the clinical significance of the subgroup results for the GI and gynecologic surgery groups (please see the Medical Reviewer's Comments for the subgroup analyses). Additionally, the results of the two clinically important secondary endpoints (READY and DISCHARGE) are important.

Table 25: Time to recovery of GI track motility (the primary efficacy endpoint, GI[3]) in Studies 302, 308, 313, and 001

	Treatment Group	MITT N	Censored N (%)	Median[a] Time (hours)	Hazard Ratio[b]	p-value[c]
Study 302	**Placebo**	145	19 (13.1)	93.6		
	Alvimopan 6 mg	141	10 (7.1)	78.2	1.45	**0.003***
	Alvimopan 12 mg	138	18 (13.0)	87.3	1.28	0.059
Study 308	**Placebo**	207	20 (9.7)	94.8		
	Alvimopan 6 mg	204	18 (8.8)	90.7	1.20	0.080
	Alvimopan 12 mg	204	19 (9.3)	86.4	1.24	0.038
Study 313	**Placebo**	149	26 (17.4)	103.0		
	Alvimopan 6 mg	155	16 (10.3)	95.8	1.28	**0.047***
	Alvimopan 12 mg	165	16 (9.7)	91.9	1.54	**<0.001***
Study 001	**Placebo**	229	19 (8)	81.3		
	Alvimopan 6 mg	237	18 (8)	74.6	1.22	0.042
	Alvimopan 12 mg	238	19 (8)	76.9	1.13	0.200

Note the primary efficacy endpoint for the three U.S. studies included all the original surgical types including small BR, large BR, sTAH, and rTAH patients. In contrast, the primary efficacy endpoint for the European study included only small BR and large BR patients (sTAH and rTAH patients were not included in the primary efficacy endpoint).
a Sponsor's analysis: Estimate time in hours was calculated from a Cox proportional hazards model that included treatment and stratified by surgery type (BR/rTAH or sTAH)
b Hazard ratio of alvimopan to placebo was calculated from a Cox proportional hazards model that included treatment and stratified by surgery type (BR/rTAH or sTAH). The FDA's hazard ratios are identical.
c p-value was calculated from the Wald-Chi-square tests for pair-wise comparisons between alvimopan and placebo from the Cox proportional hazards model. The FDA's p-values are identical.
* Indicates statistical significance after adjustment for multiplicity according to Hochberg's methods
Reference: Adapted from Volume 164, Table 11.1.1.1, Page 219; Volume 167, Table 11.1.1.1, Page 227; Volume 173, Table 11.1.1.1, Page 204; and ISE, Volume 267, Table 3.1.1, Page 664

Subgroup analysis of the primary efficacy endpoint by surgical type:
In the alvimopan POI program, the most important subpopulation was the surgical type. There were two main surgery types: 1) gynecologic surgery (sTAH and rTAH) and 2) GI surgery (small and large BR surgery). See Tables 26 and 27 for the primary efficacy results for the GI and gynecologic subgroups, respectively.

1) GI Surgery (large bowel resection and small bowel resection)
In the GI surgery subpopulation, of the **four** important phase 3 efficacy studies, the 6 mg alvimopan treatment group demonstrated statistical significance compared to the placebo group in one study (302) for the primary efficacy endpoint.

In the GI surgery subpopulation, of the **four** important phase 3 efficacy studies, the 12 mg alvimopan treatment group demonstrated statistical significance compared to the placebo group in one study (313) for the primary efficacy endpoint.

Medical Reviewer's Comments: **For the GI subgroup, two adequate and well-controlled trials demonstrated no efficacy for the 6 mg alvimopan dose (Studies 308 and 313) and two different adequate and well-controlled trials demonstrated no efficacy for the 12 mg alvimopan dose (Studies 302 and 001) in the primary efficacy endpoint (GI^3).**

It is unclear why the lower alvimopan dose (6 mg) demonstrated efficacy (statistical significance compared to placebo) in Study 302 and the higher alvimopan dose (12 mg) did not demonstrate any efficacy (statistical significance compared to placebo) in the same study. Therefore, the efficacy results of the 6 mg alvimopan group are questionable.

Additionally, the clinical meaning of the positive efficacy results for recovery of upper and lower GI tract motility is equivocal. For the GI subpopulation, the sponsor calculated the mean and median times to achieve recovery of upper and lower GI tract motility (GI^3) for the three treatment groups. Additionally, Dr. Sonia Castillo, the FDA's statistical reviewer, computed the median times to GI^3. For the GI subpopulation, the median time difference (the sponsor's analysis) for GI^3 between the 6 mg alvimopan group and the placebo group was 9.8 hours in Study 302 (a study with statistical significance). For the GI subpopulation, the median time difference (the sponsor's analysis) for GI^3 between the 12 mg alvimopan group and the placebo group was 10.5 hours in Study 313 (a study with statistical significance). The clinical meaningfulness of these times is debatable. Additionally, Dr. Castillo notes that the hazard ratios are more appropriate statistical variables and mean/median time differences have much less statistical value. Therefore, she recommends looking solely at the hazard ratios and the survival curves, instead of the mean/median time differences. Please see Dr. Castillo's review for more details.

Table 26: Time to recovery of GI tract motility (the primary efficacy endpoint, GI[3]) for the GI surgery subgroup (large and small BR) in Studies 302, 308, 313, and 001

Study	Treatment Group	N	Mean Time in Hours Sponsor's analysis	Median Time in Hours Sponsor's analysis[b]	Median Time in Hours FDA's analysis[c]	Hazard Ratio[d] (95% CI)	p-value[d]
302	Placebo	99	113.9	104.3	108.3		
	Alvimopan 6 mg	99	97.9	94.5	93.3	1.48 (1.10,1.98)	**0.009***
	Alvimopan 12 mg	98	103.6	96.7	97.5	1.30 (0.96,1.74)	0.086
308	Placebo	142	122.1	113.0	109.8		
	Alvimopan 6 mg	137	112.4	101.0	104.5	1.23 (0.96,1.56)	0.106
	Alvimopan 12 mg	139	109.7	99.6	98.0	1.32 (1.03,1.68)	0.029
313	Placebo	142	119.2	103	98.9		
	Alvimopan 6 mg	149	106.3	96.5	96.5	1.25 (0.97,1.60)	0.084
	Alvimopan 12 mg	160	99	92.5	94.1	1.49 (1.17, 1.91)	**0.002***
001[a]	Placebo	229	81.3	81.3	81.3		
	Alvimopan 6 mg	237	84.2	74.6	74.6	1.22 (1.01,1.47)	0.042
	Alvimopan 12 mg	238	87.8	76.9	76.9	1.13 (0.94,1.37)	0.20

a The primary efficacy analysis for Study 001 included only the BR subpopulation; therefore, this BR subgroup analysis is identical to the primary efficacy analysis. In contrast, the primary efficacy analysis for the three U.S. studies (302, 308, and 313) included all of the surgical types (the BR, rTAH, and sTAH patients); therefore, this BR subgroup analysis appears different than the primary analysis.

b Sponsor's median analysis: Estimate time in hours was calculated from a Cox proportional hazards model

c FDA median analysis: Estimated time-to-event from the Kaplan-Meier survival curve

d The sponsor's and FDA's hazard ratios and the p-values are identical

***Statistically significant after adjustment for multiple comparisons using the Hochberg method**

Reference: Volume 173, Table 11.3.2.5, Page 308; Volume 167, Table 11.1.3.3, Page 250; Volume 167, Table 11.1.3.5, Page 256; Volume 167, Section 11.1.4; Table 22, Page 88; Volume 164, Table 11.1.1.1, Page 219; Volume 164, Table 11.3.2.5, Page 362; Volume 164; Section 11.1.4, Table 21, Page 91; Volume 173, Section 11.1.4, Table 22, Page 86; and Study 001 Report, Table 13.4, Page 420

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_____ Deliberative Process

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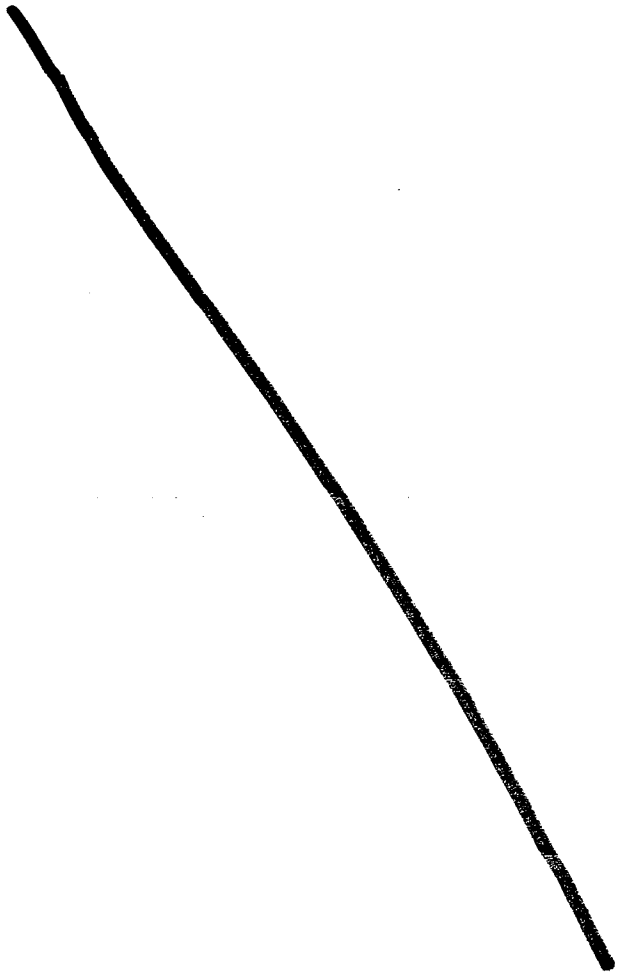

Important Pre-Specified Secondary Endpoints: In the three efficacy phase III trials, two of the most important secondary endpoints were **READY** (the time from the end of surgery to the time ready for hospital discharge based solely on recovery of GI function as defined by the surgeon) and **DISCHARGE** (the time from the end of surgery to the time that the hospital discharge order was written).

READY (an important pre-specified secondary endpoint)
For READY, there are three important studies (302, 308, and 313) and one supportive efficacy study (001). Please see the **Medical Reviewer's Comments** in Section 6.1.1 for the relative importance of the four studies for this endpoint. Table 28 presents **READY**, the important secondary endpoint, in the GI subgroup in the four efficacy trials (302, 308, 313, and 001).

In the GI surgery subpopulation, of the three important phase 3 efficacy studies, the 6 mg alvimopan treatment group demonstrated statistical significance compared to the placebo group in all three studies (302, 308, and 313) for **READY**. In the GI surgery subpopulation, the 6 mg alvimopan treatment group failed to demonstrate statistical significance compared to the placebo group in the one supportive study (001) for **READY.**

In the GI surgery subpopulation, of the three important phase 3 efficacy studies, the 12 mg alvimopan treatment group demonstrated statistical significance compared to the placebo group in three studies (302, 308, and 313) for **READY**. In the GI surgery subpopulation, the 12 mg alvimopan treatment group failed to demonstrate statistical significance compared to the placebo group in the one supportive study (001) for **READY.**

Medical Reviewer's Comments: **This medical officer believes that READY and DISCHARGE were the two most important pre-specified secondary endpoints in the four efficacy trials and a large difference between the alvimopan groups and the placebo group in these two endpoints would demonstrate a clinical meaningful benefit — shorter hospitalization.**

Since the primary efficacy endpoint (GI^3) demonstrated some efficacy in the GI subgroup and no efficacy in the gynecologic subgroup, this medical officer concentrated the secondary endpoint analyses only on the GI subgroup.

The sponsor's median analysis is by the Cox proportional hazard model; whereas, the FDA's median analysis is by the Kaplan Meier curves. The sponsor's analysis makes incorrect assumptions (including inappropriate grouping of rTAH and BR surgeries in GI tract recovery). The FDA's median analysis takes the pure data and does not use inappropriate assumptions.

For the GI subpopulation, the median time difference (the sponsor's analysis) for READY between the 6 mg alvimopan group and the placebo group was 15.3, 6.4, and 13.9 hours in Studies 302, 308 and 313 (studies with statistical significance), respectively. For the GI subpopulation, the median time difference (the sponsor's analysis) for READY between the 12 mg alvimopan group and the placebo group was 14.5, 8.0, and 17.3 hours in Studies 302, 308 and 313 (studies with statistical significance), respectively. This medical officer believes that for READY, a 6 to 8 hour time difference is not clinically significant and the clinical meaningfulness of a 15 hour or 18 hour time difference is debatable. Thus, both alvimopan doses appear to have statistical significance and unclear clinical benefit in Studies 302 and 313. However, Dr. Castillo notes that the hazard ratios and the survival curves are more appropriate statistical variables and mean/median time differences have much less statistical value. Therefore,

she recommends looking at the hazard ratios and the survival curves; and not evaluating the mean/median time differences. Please see Dr. Castillo's review.

Table 28: Time to ready for hospital discharge (an important secondary efficacy endpoint, READY) for the GI surgery subgroup (large and small BR) in Studies 302, 308, 313, and 001

Study	Treatment Group	N	Median Time in Hours Sponsor's analysis[a]	Median Time in Hours FDA's analysis[b]	Hazard Ratio[c]	p-value[c]
302	Placebo	84	112.8	113.0		
	Alvimopan 6 mg	86	97.5	96.6	1.60	**0.003***
	Alvimopan 12 mg	84	98.3	99.5	1.52	**0.010***
308	Placebo	142	117.5	119.0		
	Alvimopan 6 mg	137	111.1	113.3	1.33	**0.021***
	Alvimopan 12 mg	139	109.5	107.5	1.40	**0.008***
313	Placebo	142	112.5	111.1		
	Alvimopan 6 mg	149	98.6	101.8	1.30	**0.035***
	Alvimopan 12 mg	160	95.2	95.0	1.54	**<0.001***
001**	Placebo	229	137.5	137.5		
	Alvimopan 6 mg	237	125.3	125.3	1.16	0.134
	Alvimopan 12 mg	238	127.2	127.2	1.11	0.287

The FDA statistical analysis is identical to the sponsor's analyses for the hazard ratio and the corresponding p-value.

*** Indicates statistical significance after adjustment for multiplicity according to Hochberg's methods**

**** For the READY secondary endpoint Study 001 is a supportive study; whereas, Studies 302, 308, and 313 are the primary studies.**

a Sponsor's median analysis: Estimate time in hours was calculated from a Cox proportional hazards model that included treatment

b FDA median analysis: Estimated time-to-event from the Kaplan-Meier survival curve

c The sponsor's and FDA's hazard ratios and the p-values are identical

Reference: Volume 164, Table 11.3.2.5, Page 362; Volume 167, Table 11.1.3.3, Page 250; Volume 173, Table 11.3.2.5, Page 308; and Study Report 001, Table 13.7, Page 430

DISCHARGE (an important pre-specified secondary endpoint)
For **DISCHARGE**, there are three important studies (302, 308, and 313) and one supportive efficacy study (001). Please see the **Medical Reviewer's Comments** in Section 6.1.1 for the relative importance of the four studies for this endpoint. Table 29 presents **DISCHARGE**, the important secondary endpoint, in the GI subgroup in the four efficacy trials (302, 308, 313, and 001).

In the GI surgery subpopulation, of the three important phase 3 efficacy studies, the 6 mg alvimopan treatment group demonstrated statistical significance (compared to placebo) in two studies (302 and 308) for **DISCHARGE**. In the GI surgery subpopulation, the 6 mg alvimopan treatment group failed to demonstrate statistical significance (compared to placebo) in the one supportive study (001) for **DISCHARGE.**

In the GI surgery subpopulation, of the three important phase 3 efficacy studies, the 12 mg alvimopan treatment group demonstrated statistical significance (compared to placebo) in two studies (308, and 313) for **DISCHARGE**. In the GI surgery subpopulation, the 12 mg alvimopan treatment group failed to demonstrate statistical significance (compared to placebo) in the one supportive study (001) for **DISCHARGE.**

Medical Reviewer's Comments: Since the primary efficacy endpoint (GI^3) demonstrated some efficacy in the GI subgroup and no efficacy in the gynecologic subgroup, this medical officer concentrated the secondary endpoint analyses only on the GI subgroup.

The sponsor's median analysis is by the Cox proportional hazard model; whereas, the FDA's median analysis is by the Kaplan Meier curves. The sponsor's analysis makes incorrect assumptions (including inappropriate grouping of rTAH and BR surgeries in GI tract recovery). The FDA's median analysis takes the pure data and does not use inappropriate assumptions.

For the GI subpopulation, the median time difference (the sponsor's analysis) for DISCHARGE between the 6 mg alvimopan group and the placebo group was 17.5 and 16.6 hours in Studies 302 and 308 (studies with statistical significance), respectively. For the GI subpopulation, the median time difference (the sponsor's analysis) for DISCHARGE between the 12 mg alvimopan group and the placebo group was 17.9 and 17.6 hours in Studies 308 and 313 (studies with statistical significance), respectively. This medical officer believes that the clinical significance of a 16 hour or 17 hour median time difference is debatable. In addition, Dr. Castillo notes that the hazard ratios are more appropriate statistical variables and mean/median time differences have much less statistical value. Therefore, she recommends looking at the hazard ratios and the survival curves; and not evaluating the mean/median time differences. See Dr. Castillo's review.

Table 29: Time to discharge order written (an important secondary efficacy endpoint, DISCHARGE) for the GI surgery subgroup (large and small BR) in Studies 302, 308, 313, and 001

Study	Treatment Group	N	Median Time in Hours Sponsor's analysis[a]	Median Time in Hours FDA's analysis[b]	Hazard Ratio[c]	p-value[c]
302	Placebo	99	134.1	136.4		
	Alvimopan 6 mg	99	116.6	116.4	1.56	**0.002***
	Alvimopan 12 mg	98	118.0	120.1	1.29	0.084
308	Placebo	142	137.1	139.8		
	Alvimopan 6 mg	137	120.5	120.5	1.42	**0.004***
	Alvimopan 12 mg	139	119.2	117.5	1.56	**<0.001***
313	Placebo	142	133.3	121.8		
	Alvimopan 6 mg	149	117.9	119.8	1.24	0.089
	Alvimopan 12 mg	160	115.6	115.8	1.42	**0.004***
001**	Placebo	229	192.8	192.8		
	Alvimopan 6 mg	237	191.5	191.5	1.08	0.471
	Alvimopan 12 mg	238	191.5	191.5	1.07	0.493

Reference: Volume 164, Table 11.3.2.5, Page 363; Volume 167, Table 11.1.3.3, Page 251; Volume 173, Table 11.3.2.5, Page 309; and Study Report 001, Table 13.7, Page 432

a Sponsor's median analysis: Estimate time in hours was calculated from a Cox proportional hazards model that included treatment

b FDA median analysis: Estimated time-to-event from the Kaplan-Meier survival curve

c The sponsor's and FDA's hazard ratios and the p-values are identical

The FDA statistical analysis is identical to the sponsor's analyses for the hazard ratio and the corresponding p-value.

*** Indicates statistical significance after adjustment for multiplicity according to Hochberg's methods**

**** For the READY secondary endpoint Study 001 is a supportive study; whereas, Studies 302, 308, and 313 are the primary studies.**

Responder analyses

In the U.S. POI trials (302, 308, and 313), the sponsor's responder analysis was one of the six pre-specified secondary endpoints. A small BR, large BR, or rTAH patient was considered a responder if he/she achieved recovery of upper and lower GI tract motility (GI^3) within 108 hours after surgery. Additionally, a sTAH patient was considered a responder if he/she achieved GI^3 within 60 hours after surgery. The cut-off points (108 and 60 hours) were derived from the phase 2 study results. The cut-off points were the median times to achieve GI^3 in the pooled phase 2 POI studies for each of the respective surgical populations (BR/rTAH and sTAH). Please see Table 30 for the sponsor's responder analysis.

In the one European study (001), the sponsor pre-specified five responder analyses. Patients were considered responders if they achieved the primary efficacy endpoint (GI^3) within the cut-off point. The following five cut-off points were pre-specified: 96, 108, 120, 144, and 168 hours. For example: for the 108 hour cut off point, BR patients were responders if they achieved GI^3 within 108 hours after surgery. Please see Table 30 for delineation of the 108 cut-off responder analysis (by the sponsor).

Table 30: Sponsor's responder analysis for Studies 302, 308, 313, and 001

Studies	Treatment Group	Responders n/N@	Odds Ratio	p-value
302	Placebo	69/133 (52%)		
	Alvimopan 6 mg	95/136 (70%)	2.15	**0.003***
	Alvimopan 12 mg	89/128 (70%)	2.13	**0.004***
308	Placebo	121/202 (60%)		
	Alvimopan 6 mg	125/197 (64%)	1.16	0.485
	Alvimopan 12 mg	137/197 (70%)	1.52	0.049
313	Placebo	79/138 (57%)		
	Alvimopan 6 mg	93/146 (64%)	1.31	0.267
	Alvimopan 12 mg	108/155 (70%)	1.72	0.028
001	Placebo	162/214 (76%)		
	Alvimopan 6 mg	176/222 (79%)	1.23	0.371
	Alvimopan 12 mg	167/220 (76%)	1.01	0.960

Statistical significance adjusted according to Hochberg methods

@ The MITT population

Reference: Volume 164, Section 11.1.3.1, Table 18, Page 87; Volume 167, Section 11.1.3.1, Table 17, Page 83; Volume 173, Section 11.1.3.1, Table 17, Page 79; Study Report for 001, Table 32, Page 91

Medical Reviewer's Comments: In the sponsor's responder analysis, rTAH patients and BR patients should not have been grouped together since these patients achieve recovery of GI motility at different times. Thus, the sponsor's incorrect classification of the surgical types in the responder definition reduces the adequacy of this secondary endpoint. Additionally, the sponsor did not include censored patients in the denominator. Patients who did not finish the study and who did not achieve GI^3 should be placed in the denominator and left out of the numerator. Given the weaknesses of

the sponsor's responder definition Dr. Sonia Castillo, the FDA statistical reviewer, performed a post-hoc responder analyses (see Table 31).

FDA post-hoc responder analyses: In the FDA's responder analyses, a responder was defined as a GI surgery patient (small or large BR patient) who achieved GI[3], recovery of both upper and lower GI tract motility. The FDA's responder analyses were based only on the GI surgery subgroup because the gynecologic surgery subgroup had no efficacy in the primary efficacy endpoint. The MITT population was chosen for all the analyses because this population was the sponsor's primary population. Additionally, patients who were censored were included in the denominator and left out of the numerator (they were considered failures). This medical officer chose the following five cut off points for the responder analyses: 72 hours (3 days), 96 hours (4 days), 108 hours (5 days), 120 hours (6 days), and 144 hours (7 days). Of the five chosen time points, four (96, 108, 120, and 144) were used by the sponsor in Study 001 and one was new (72 hours). Please see the FDA's post-hoc responder analyses in Table 31.

A total of 40 responder analyses (2 doses times 5 time points times 4 surgeries) were performed. Out of these 40 post-hoc analyses, only 4 analyses demonstrated statistical significance of alvimopan over placebo and the other 36 analyses were negative. The four positive analyses were the following: the 6 mg dose at 108 hours (4.5 days) in Study 302; the 12 mg dose at 108 hours in Study 302; the 12 mg dose at 120 hours (5 days) in Study 313; and the 12 mg dose at 144 hours (6 days) in Study 313.

In summary, the FDA's responder analyses do not support the efficacy of both alvimopan doses in the treatment of POI.

Table 31: FDA's statistical post-hoc responder analyses for the four important POI efficacy studies (302, 308, 313, and 001)

Recovery of GI Function (GI^3)		Day 3 (72 hrs)		Day 4 (96 hrs)		Day 4.5 (108 hrs)		Day 5 (120 hrs)		Day 6 (144 hrs)	
	N	% R	D	% R	D	% R	D	% R	D	% R	D
Study 302											
Placebo	99	15.2		39.4		47.5		61.6		76.8	
Alvimopan 6 mg	99	21.2	6.0	53.5	14.1	64.6	**17.1***	75.8	14.2	85.9	9.1
Alvimopan 12 mg	98	16.3	1.1	44.9	5.5	63.3	**15.8***	72.4	10.8	83.7	6.9
Study 308											
Placebo	142	12.0		36.6		50.0		59.9		73.9	
Alvimopan 6 mg	137	11.0	-1.0	38.0	1.4	53.3	3.3	68.6	8.7	82.5	8.6
Alvimopan 12 mg	139	19.4	7.4	45.3	8.7	60.4	10.4	69.8	9.9	82.0	8.1
Study 313											
Placebo	142	21.1		45.1		53.5		59.2		70.4	
Alvimopan 6 mg	149	22.2	1.1	46.3	1.2	59.1	5.6	64.4	5.2	78.5	8.1
Alvimopan 12 mg	160	24.4	3.3	50.0	4.9	64.4	10.9	73.8	**14.6***	83.8	**13.4***
Study 001											
Placebo	229	34.1		65.5		70.7		77.3		82.1	
Alvimopan 6 mg	237	42.6	8.5	68.8	3.3	74.3	3.6	79.8	2.5	86.9	4.8
Alvimopan 12 mg	238	38.5	4.4	63.6	-1.9	69.9	-0.8	77.0	-0.3	85.8	3.7

% R = the percentage of responders
D = Difference between the alvimopan treatment group and placebo
Reference: Dr. Castillo's statistical review

Tertiary Endpoints of Interest:

One of the 10 tertiary endpoints was the proportion of patients that had reinsertion of their naso-gastric tubes post-surgery. Reinsertion of naso-gastric tubes may indicate the failure of the study medications in the treatment of POI. The sponsor performed an analysis of the proportion of patients that had reinsertion of their naso-gastric tubes post-surgery. The sponsor pooled the results of the three U.S. studies and performed only one multiplicity adjustment for the two comparisons (placebo versus alvimopan 6 mg and placebo versus alvimopan 12 mg). Additionally, the sponsor used the safety population for their analysis. Please see Table 32 for the sponsor's pooled analysis.

Table 32: Reinsertion of naso-gastric tube post-surgery (Sponsor's pooled analysis from Studies 302, 308, and 313)

	Treatment Groups	n/M (%)	Difference	p-value*
Pooled Studies (302, 308, and 313	Placebo	51/534 (9.6)		
	Alvimopan 6 mg	29/530 (5.5)	-4.1	0.014
	Alvimopan 12 mg	30/534 (5.6)	-3.9	0.020

* P-values were calculated from two-sided Fisher's Exact tests. Adjustment for two groups (placebo versus alvimopan 6 mg and placebo versus alvimopan 12 mg). However, no multiplicity adjustment for at least seven secondary endpoints and at least 9 other tertiary endpoints.
Reference: ISE, Table 25, Page 118

Medical Reviewer's Comments: For the tertiary endpoint following surgery (reinsertion of nasogastric tube), this medical officer organized the individual results from the four important efficacy trials (302, 308, 313, and 001) in Table 33. Only the 12 mg alvimopan group (compared to placebo) had a p-value less than 0.05. Therefore, 7 of the 8 analyses were negative. Additionally, since multiplicity adjustments of this endpoint were not made the significance of the one positive finding can not be determined.

Table 33: Reinsertion of naso-gastric tube post-surgery in the four important efficacy studies (302, 308, 313, and 001)

	Treatment Groups	n/M (%)	Difference	p-value*
302	Placebo	10/145 (6.9)		
	Alvimopan 6 mg	3/141 (2.1)	-4.8	0.085
	Alvimopan 12 mg	10/138 (7.2)	0.3	1.000
308	Placebo	17/207 (8.2)		
	Alvimopan 6 mg	12/204 (5.9)	-2.3	0.442
	Alvimopan 12 mg	12/204 (5.9)	-2.3	0.442
313	Placebo	22/149 (14.8)		
	Alvimopan 6 mg	13/155 (8.4)	-6.4	0.105
	Alvimopan 12 mg	8/165 (4.8)	-9.9	0.004
001	Placebo	14/229 (6)		
	Alvimopan 6 mg	15/237 (6)	0.2	1.00
	Alvimopan 12 mg	11/239 (5)	-1.4	0.54

N = total number of MITT patients in the treatment group
n = number of MITT patients requiring naso-gastric tube reinsertion post-surgery
* P-value was calculated from Fisher's Exact tests. This tertiary endpoint was not adjusted for multiplicity (at least 7 secondary endpoints and at least 10 tertiary endpoints
Reference: Volume 164, Table 11.2.12.1, Page 329; Volume 167, Table 11.2.12.1, Page 374; Volume 173, Table 11.2.12.1, Page 279; and Study Report for 001 Table 31, Page 90

Sponsor's post-hoc analyses:
The sponsor performed an analysis on the proportion of patients that developed a prolonged POI (see Table 34).

Medical Reviewer's Comments: The sponsor's prolonged POI analysis was flawed for the following reasons:

1) **The analysis was a post-hoc analysis**
2) **The analysis did not clearly define prolonged POI.**

Given the above flaws, this medical officer will not interpret the results of this post-hoc analysis.

Table 34: Proportion of patients with a prolonged POI (Sponsor's pooled analysis of 302, 308, and 313)

	Treatment Groups	n/M (%)	Difference	p-value*
Pooled Studies (302, 308, and 313	Placebo	29/534 (5.4)		
	Alvimopan 6 mg	10/530 (1.9)	-3.5	0.003
	Alvimopan 12 mg	9/534 (1.5)	-3.9	<0.001

* P-values were calculated from two-sided Fisher's Exact tests. Adjustment for two groups (placebo versus alvimopan 6 mg and placebo versus alvimopan 12 mg). However, no multiplicity adjustment for at least seven secondary endpoints and at least 9 other tertiary endpoints.
Reference: ISE, Table 25, Page 118

Medical Reviewer's Comments: FDA post-hoc analysis – Opioid Consumption
Table 12 in Section 6.1.1 presents the opioid consumption by post-surgery day in all four important efficacy studies (please see the Medical Reviewer's Comments in Section 6.1.1 for interpretation of this exploratory analysis.

6.1.5 Clinical Microbiology
A clinical microbiology review is not applicable.

6.1.6 Efficacy Conclusions

[redacted]. Therefore, no efficacy was demonstrated in the treatment of POI in gynecologic patients.

In the GI surgery subpopulation, **the 6 mg alvimopan dose** demonstrated statistical significance compared to placebo in the **primary efficacy endpoint (GI^3)** in only one (302) of the four important phase 3 trials (302, 308, 313, and 001). In Study 302, the 6 mg alvimopan group and the placebo group achieved GI^3 in 94.5 and 104.3 hours, respectively, according to the sponsor's median analysis of the GI subpopulation. The sponsor calculated a 9.8 hour median difference in GI recovery between the 6 mg alvimopan group and the placebo group. This medical officer believes that the clinical meaningfulness of 9.8 hour difference in time to GI recovery is questionable and that the validity of the sponsor's methods for calculating this difference is debatable. Furthermore, the statistical failure of the higher alvimopan dose (12 mg) in Study 302 diminishes the positive statistical results of the 6 mg dose in this study. In the GI surgery subpopulation, the 6 mg alvimopan dose demonstrated statistical significance compared to placebo in **READY**, the important secondary endpoint, in three (302, 308, and 313) out of the four efficacy trials and the 6 mg alvimopan dose demonstrated statistical significance compared to placebo in **DISCHARGE**, the important secondary endpoint, in two (302 and 308) out of the four efficacy trials. However, the clinical meaningfulness of these results is debatable.

In the GI surgery subpopulation, **the 12 alvimopan dose** demonstrated statistical significance compared to placebo in **GI^3** in one (313) of the four phase 3 trials. In Study 313, the 12 mg alvimopan group and the placebo group achieved GI3 in 92.5 and 103 hours, respectively, according to the sponsor's median analysis of the GI subpopulation. The sponsor calculated a10.5 hour median difference in GI recovery between the 12 mg alvimopan group and the placebo group. This medical officer believes that the clinical meaningfulness of 10.5 hour difference in time to GI recovery is questionable and that the validity of the sponsor's methods for calculating this difference is debatable. In the GI surgery subpopulation, the 12 mg alvimopan dose demonstrated statistical significance compared to placebo in **READY** in three (302, 308, and 313) out of the four efficacy trials and the 12 mg alvimopan dose demonstrated statistical significance compared to placebo in **DISCHARGE** in two (308 and 313) out of the four efficacy trials. However, the clinical meaningfulness of these results is debatable.

In summary, the clinical data do not support the efficacy of the 6 mg or 12 mg alvimopan dose in the treatment of postoperative ileus in the gynecologic subpopulation. The clinical data do not support the efficacy of the 6 mg alvimopan dose in the treatment of postoperative ileus in the GI subpopulation. In the GI subpopulation, the 12 mg alvimopan dose demonstrated some efficacy in the treatment of postoperative ileus; however, the following major deficiencies remain:

1) Only one out of four adequate and well-controlled trials demonstrated statistical significance of the 12 mg dose compared to placebo in the primary efficacy endpoint.
2) The clinical meaningfulness of the one positive statistical result — the 12 mg alvimopan dose in the primary efficacy endpoint in Study 313 — is questionable.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

In the entire alvimopan development program (36 completed alvimopan trials), there were 18 deaths. All 18 deaths occurred in the POI subpopulation (13C206, 13C213, 13C214, 302, 308, 306, 313, and 001). Of the 18 deaths, 7 occurred in patients taking placebo, 5 occurred in patients taking 6 mg of alvimopan, and 6 occurred in patients taking 12 mg of alvimopan.

Possible Treatment-Related Deaths: According to the investigators, only one patient [a 47 year old female who died of acute purulent peritonitis (14CL313-05-05005)] possibly died due to the study treatment (6 mg of alvimopan). Please see Table 35 for a description about this patient.

Table 35: One possible treatment-related death in the alvimopan 6 mg group

Patient ID#	Cause of Death	Medical History	Surgery Date Surgery Type	Date of Onset* Date of Death
14CL313-05-05005	Autopsy showed acute purulent peritonitis, severe CAD	47 year old white female [with a past history of morbid obesity, 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 ([redacted]). On POD 23 [redacted] she was found at home unresponsive.	6/24/02 small BR	7/17/02 [redacted]

Medical Reviewer's Comments: This medical officer believes that the 47 year old female's death was not due to the study treatment (6 mg of alvimopan) for the following two reasons: the patient had other co-morbidities that likely contributed to her death and there was no temporal relationship between the study medication administration and the onset of her death. Most likely the 47 year old women died from an overwhelming infection, originating in the small bowel, and an underlying poor immune condition (diabetes). Furthermore, the onset of her peritonitis (the disease that killed her) occurred as an outpatient — 18 days after she received her last alvimopan dose in the hospital. Therefore, her death was not likely due to alvimopan.

Deaths (Not Treatment-Related): All of the deaths in the placebo, 6 mg alvimopan, and 12 mg alvimopan treatment groups are listed in Tables 36, 37, and 38, respectively, in the 36 alvimopan trials.

Medical Reviewer's Comments: There was a slightly lower death rate in the alvimopan treatment group compared to the placebo treatment group. In the entire population, the death rate of patients/subjects who took alvimopan was 0.38% (11 deaths out of a total alvimopan population of 2902); whereas, the death rate of patients/subjects who took placebo was 0.57% (7 deaths out of a total placebo population of 1233). In the POI subpopulation, the death rate of patients who took alvimopan was 0.48% (11 deaths out of an alvimopan subpopulation of 2285); whereas, the death rate of patients who took placebo was 0.67% (7 placebo deaths out of a total placebo subpopulation of 1041).

This medical officer believes that death rate was higher in the POI subpopulation (compared to the death rate in the entire population) because the POI patients had higher co-morbidity compared to patients not in the POI subpopulation. Over 55% of the POI subpopulation had cancer (such as colon cancer, ovarian cancer, cervical cancer, or uterine cancer). Additionally, the POI population was older than the non-POI population.

Table 36: Deaths in the placebo treatment group in the 36 alvimopan trials

Patient ID#	Cause of Death	Medical History	Surgery Date Surgery Type	Date of Onset* Date of Death
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 [redacted]
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 [redacted] She was readmitted on [redacted] for abdominal abscess and gram negative septic shock. She developed aspiration pneumonia.	11/6/02 **Right Large BR**	11/21/02 [redacted]
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 [redacted]

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

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, Pages 148, 165, and 202

Table 36 Continued: Deaths in the placebo treatment group in the 36 alvimopan trials

Patient ID#	Cause of Death	Medical History	Surgery Date Surgery Type	Date of Onset* Date of Death
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 [redacted]
001-263	Cause of death not reported	61 year old male (with history of colon cancer) discharged on POD 7. POD 9 ([redacted]) died	11/13/03	[redacted]
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 ([redacted] . On POD 6 ([redacted]) developed wound infection then hypotension. Laparotomy showed abdominal abscess, peritonitis, and anastomotic leakage. Had ileostomy. On POD 8 ([redacted] , she died due to septic shock.	3/12/04 **Right Large BR**	3/16/04 [redacted]
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 ([redacted]). Treatment was discontinued because of reinsertion of nasogastric tube. On POD 7 ([redacted] 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 ([redacted]) had massive UGIB and died on POD 40 [redacted] .	7/21/04 **Left Large BR**	8/29/04 [redacted]

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

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, Pages 148, 165, and 202

Table 37: Deaths in the 6 mg alvimopan treatment group in the 36 alvimopan trials

Patient ID#	Cause of Death	Medical History	Surgery Date/ Type	Date of Onset*/ Death
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
14CL308-31-01182	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
14CL313-05-05005	Autopsy showed acute purulent peritonitis, severe CAD	47 year old white female [with a past history of morbid obesity, 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.	6/24/02 **small BR**	7/17/02
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
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

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

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 38: Deaths in the 12 mg alvimopan treatment group in the 36 alvimopan trials

Patient ID#	Cause of Death	Medical History	Surgery Date Surgery Type	Date of Onset* Date of Death
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 shortness of breath 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 needed mechanical ventilation and died on POD 57.	5/2/02 **Right Large BR**	6/9/02 [redacted]
14CL302-01118	CHF	71 year old white male (with a history of colon cancer, HTN, MI, and hyperlipidemia) Surgery found metastatic colon cancer to the entire small bowel mesentery and pelvis and required a colostomy. Discontinued from study medication. On POD 5 had CHF and died on POD 12 of CHF.	3/20/02 **Left Large BR**	3/29/02 [redacted]
14CL313-13-13015	Acute MI	64 year old male (with a history of recurrent colon cancer, prostate cancer, renal cell carcinoma, and DM) discharged on POD 6. Readmitted for CP on POD 8 (diagnosed with an acute MI had 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 [redacted]
001-273	CVA	70 year old female (with history of recent TIA in 4/03 and colon cancer) had a CVA with left hemiparesis on POD 2 [redacted]. Study medication was withdrawn on POD 5. On POD 9 [redacted], had anastomosis leak with peritonitis. Had exploratory laparotomy. Died on POD 16 [redacted]	5/13/03 **Large BR**	5/15/03 [redacted]
001-448	Sudden death	63 year old male (with history of AAA) had left large BR for rectal cancer. Postoperative course complicated by mild wound infection. Stopped treatment on POD 7. Discharged on POD 13 [redacted]. Died during sleep at home on POD 16 [redacted]. No autopsy was performed.	5/5/04 **Left Large BR**	5/21/04 [redacted]
001-570	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 ([redacted] because had epidural anesthesia. On POD 5 ([redacted]) had tachycardia and tachypnea. Diagnosed with sepsis from peritonitis from anastomosis dehiscence. Had exploratory laparotomy on POD 5 [redacted] and had correction of dehiscence. Died on POD 5 [redacted]	10/31/03 **Left Large BR**	11/5/03 [redacted]

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

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, Pages 166, 183, and 191.

7.1.2 Other Serious Adverse Events

In the entire POI subpopulation (containing 2285 patients on alvimopan and 1041 patients on placebo for a total population of 3326 patients), the number and percentage of patients who had at least one SAE for the placebo, the 6 mg alvimopan, and the 12 mg alvimopan treatment groups were approximately 184 (17.7%), 113 (12.6%), and 146 (11.1%), respectively.

In the U.S. POI subgroup, the number and percentage of patients who had at least one SAE for the placebo, the 6 mg alvimopan, and the 12 mg alvimopan treatment groups were 151 (20.2%), 76 (12.6%), and 106 (10.4%), respectively. In the European POI subgroup (Study 001), the number and percentage of patients who had at least one SAE for the placebo, the 6 mg alvimopan, and the 12 mg alvimopan treatment groups were 33 (11%), 37 (13%), and 40 (13%), respectively. Please see Table 39 for a list of the SAEs in the 7 U.S. POI studies (13C206, 12C213, 13C214, 302, 306, 308, and 313) and Table 40 for a list of the SAEs in the one European POI study (001).

In the entire healthy subject subpopulation (containing 214 subjects on alvimopan and 58 subjects on placebo for a total population of 272 subjects), there were no SAEs.

In the entire non-cancer OBD subpopulation (containing 220 patients on alvimopan and 89 patients on placebo for a total population of 309), there were four SAEs. Please see Table 41 for the list and the description of those SAEs. Only one of the four SAEs in this population was considered probably related to the treatment, according to the investigators.

Medical Reviewer's Comments: **Both the 6 mg and 12 mg alvimopan treatment regimens were associated with less SAEs compared to the placebo treatment group.**

This medical officer agrees that only one of the four SAEs in the non-cancer OBD subpopulation was treatment-related. The 48 year old white male (with a past medical history of low back pain and lumbar fusions and taking concomitant chronic narcotics for pain control) developed acute abdominal pain about 1.5 hours after receiving a 3 mg alvimopan dose. After treatment with narcotic medications in the hospital, his abdominal pain resolved. Alvimopan, an opioid antagonist, may have precipitated opioid withdrawal in this patient on chronic opioids. Since all of the POI trials excluded patients on opioid medications (with the exception of one opioid administration in a recent colonoscopy procedure), the POI trials did not assess possible opioid withdrawal in patients on chronic opioids.

The sponsor's proposed label states that alvimopan [redacted] In the sponsor's proposed label, the sponsor plans to state that alvimopan [redacted] This medical officer agrees with this contraindication.

All SAEs appeared to be equally distributed in the alvimopan treatment and the placebo groups in both the U.S. and European POI populations. Occasionally, the placebo treatment groups appeared to have a higher percentage of particular SAEs compared to the alvimopan groups.

Table 39: Summary of patients reporting SAEs in the U.S. POI subpopulation (Studies 13C206, 12C213, 13C214, 302, 306, 308, and 313)

Overall		Alvimopan		
SOC Preferred Term/Severity	Placebo (N=748) N (%)	6 mg (N=604) N (%)	12 mg (N=1024) N (%)	Total (N=1690) N (%)
Subjects with at least one AE				
Total	151 (20.2)	76 (12.6)	106 (10.4)	189 (11.2)
Mild	13 (1.7)	5 (0.8)	11 (1.1)	16 (0.9)
Moderate	68 (9.1)	39 (6.5)	41 (4.0)	84 (5.0)
Severe	70 (9.4)	32 (5.3)	54 (5.3)	89 (5.3)
Injury, Poisoning and Procedural Complications	76 (10.2)	39 (6.5)	47 (4.6)	87 (5.1)
Gastrointestinal disorder NOS postoperative	24 (3.2)	15 (2.5)	17 (1.7)	32 (1.9)
Postoperative fistula NOS	2 (0.3)	7 (1.2)	2 (0.2)	9 (0.5)
Postoperative ileus	35 (4.7)	10 (1.7)	9 (0.9)	19 (1.1)
Therapeutic procedural complication	3 (0.4)	2 (0.3)	8 (0.8)	10 (0.6)
Wound dehiscence	2 (0.3)	3 (0.5)	6 (0.6)	10 (0.6)
Infections and Infestations	43 (5.7)	25 (4.1)	28 (2.7)	55 (3.3)
Postoperative abscess	10 (1.3)	12 (2.0)	9 (0.9)	23 (1.4)
Postoperative wound infection	12 (1.6)	6 (1.0)	9 (0.9)	15 (0.9)
Urinary tract infection NOS	4 (0.5)	0	0	1 (0.1)
Vascular Disorders	12 (1.6)	7 (1.2)	15 (1.5)	23 (1.4)
Deep venous thrombosis NOS	6 (0.8)	3 (0.5)	2 (0.2)	5 (0.3)
Pulmonary embolism	4 (0.5)	4 (0.7)	11 (1.1)	16 (0.9)
Gastrointestinal Disorders	22 (2.9)	9 (1.5)	6 (0.6)	17 (1.0)
Diarrhea NOS	4 (0.5)	0	0	0
Vomiting NOS	4 (0.5)	1 (0.2)	1 (0.1)	3 (0.2)
Cardiac Disorders	13 (1.7)	5 (0.8)	11 (1.1)	16 (0.9)
Atrial fibrillation	5 (0.7)	1 (0.2)	2 (0.2)	3 (0.2)
Renal and Urinary Disorders	6 (0.8)	4 (0.7)	2 (0.2)	7 (0.4)
Renal failure acute	4 (0.5)	1 (0.2)	0	1 (0.1)

Reference: Adapted from ISS, Volume 211, Table 99, Page 236

Table 40: Summary of patients reporting SAEs in the European POI study (001)

System Organ Class Preferred Term	PLACEBO (N=292)	ALVIMOPAN 6MG (N=294)	ALVIMOPAN 12MG (N=297)
ANY EVENT	33 (11%)	37 (13%)	40 (13%)
Gastrointestinal disorders			
Any event	9 (3%)	10 (3%)	10 (3%)
Abdominal pain	0	0	4 (1%)
Peritonitis	2 (<1%)	1 (<1%)	1 (<1%)
Nausea	0	2 (<1%)	1 (<1%)
Ascites	1 (<1%)	1 (<1%)	0
Intestinal obstruction	1 (<1%)	1 (<1%)	0
Small intestinal obstruction	2 (<1%)	0	0
Upper gastrointestinal haemorrhage	1 (<1%)	1 (<1%)	0
Abdominal distension	0	0	1 (<1%)
Abdominal haematoma	0	1 (<1%)	0
Abdominal pain upper	0	1 (<1%)	0
Anal haemorrhage	0	0	1 (<1%)
Duodenal ulcer	0	1 (<1%)	0
Gastric outlet obstruction	0	0	1 (<1%)
Ileus paralytic	1 (<1%)	0	0
Mesenteric vein thrombosis	0	1 (<1%)	0
Oesophagitis	0	0	1 (<1%)
Peritoneal haemorrhage	1 (<1%)	0	0
Retroperitoneal haemorrhage	0	1 (<1%)	0
Vomiting	0	1 (<1%)	0
Injury, poisoning and procedural complications			
Any event	9 (3%)	10 (3%)	9 (3%)
Anastomotic leak	2 (<1%)	3 (1%)	2 (<1%)
Wound dehiscence	2 (<1%)	2 (<1%)	3 (1%)
Postoperative ileus	2 (<1%)	1 (<1%)	0
Post procedural haematoma	0	1 (<1%)	1 (<1%)
Anastomotic stenosis	0	1 (<1%)	0
Failure to anastomose	0	1 (<1%)	0
Overdose	1 (<1%)	0	0
Post procedural haemorrhage	0	0	1 (<1%)
Post procedural pain	0	1 (<1%)	0
Postoperative wound complication	0	0	1 (<1%)
Procedural hypotension	1 (<1%)	0	0
Seroma	0	0	1 (<1%)
Wound evisceration	1 (<1%)	0	0
Infections and infestations			
Any event	5 (2%)	11 (4%)	9 (3%)
Postoperative infection	1 (<1%)	4 (1%)	3 (1%)
Abdominal abscess	1 (<1%)	2 (<1%)	1 (<1%)
Sepsis	1 (<1%)	0	1 (<1%)
Wound infection	0	1 (<1%)	1 (<1%)
Abdominal infection	1 (<1%)	0	0
Bronchitis	0	1 (<1%)	0
Cellulitis	0	0	1 (<1%)
Central line infection	0	1 (<1%)	0
Liver abscess	0	0	1 (<1%)
Post procedural cellulitis	1 (<1%)	0	0
Septic shock	0	1 (<1%)	0
Subdiaphragmatic abscess	0	0	1 (<1%)
Wound abscess	0	1 (<1%)	0
Cardiac disorders			
Any event	5 (2%)	3 (1%)	7 (2%)
Atrial fibrillation	2 (<1%)	1 (<1%)	2 (<1%)
Myocardial infarction	0	2 (<1%)	2 (<1%)
Cardiac arrest	2 (<1%)	0	1 (<1%)
Cardiac failure	1 (<1%)	0	0
Cardio-respiratory arrest	0	0	1 (<1%)

Reference: Study Report 001, Table 14.24, Pages 785-789

Table 40 Continued: Number and percentage of patients with SAEs in Study 001

System Organ Class Preferred Term	PLACEBO (N=292)	ALVIMOPAN 6MG (N=294)	ALVIMOPAN 12MG (N=297)
Cardiopulmonary failure	0	1 (<1%)	0
Myocardial ischaemia	1 (<1%)	0	0
Tachyarrhythmia	0	0	1 (<1%)
Respiratory, thoracic and mediastinal disorders			
Any event	2 (<1%)	3 (1%)	6 (2%)
Pulmonary embolism	0	0	3 (1%)
Hypoxia	0	0	2 (<1%)
Pneumonia aspiration	1 (<1%)	1 (<1%)	0
Respiratory depression	0	2 (<1%)	0
Chronic obstructive airways disease exacerbated	1 (<1%)	0	0
Pleural effusion	0	0	1 (<1%)
Pneumothorax	0	0	1 (<1%)
Vascular disorders			
Any event	2 (<1%)	3 (1%)	5 (2%)
Haemorrhage	1 (<1%)	0	2 (<1%)
Hypertension	0	0	1 (<1%)
Hypertensive crisis	0	1 (<1%)	0
Labile blood pressure	0	1 (<1%)	0
Lymphocele	0	1 (<1%)	0
Lymphoedema	1 (<1%)	0	0
Peripheral occlusive disease	0	0	1 (<1%)
Phlebitis	0	0	1 (<1%)
General disorders and administration site conditions			
Any event	3 (1%)	3 (1%)	2 (<1%)
Pyrexia	0	1 (<1%)	1 (<1%)
Asthenia	0	0	1 (<1%)
Chest discomfort	1 (<1%)	0	0
Death	1 (<1%)	0	0
Fat necrosis	1 (<1%)	0	0
Multi-organ failure	0	1 (<1%)	0
Pain	0	1 (<1%)	0
Sudden death	0	0	1 (<1%)
Nervous system disorders			
Any event	1 (<1%)	1 (<1%)	2 (<1%)
Cerebrovascular accident	0	0	1 (<1%)
Reversible ischaemic neurological deficit	0	0	1 (<1%)
Sedation	0	1 (<1%)	0
Stupor	0	0	1 (<1%)
Transient ischaemic attack	1 (<1%)	0	0
Renal and urinary disorders			
Any event	4 (1%)	0	0
Renal failure	2 (<1%)	0	0
Hydronephrosis	1 (<1%)	0	0
Renal impairment	1 (<1%)	0	0
Blood and lymphatic system disorders			
Any event	2 (<1%)	0	0
Anaemia	1 (<1%)	0	0
Splenic haemorrhage	1 (<1%)	0	0
Hepatobiliary disorders			
Any event	0	1 (<1%)	0
Hepatitis	0	1 (<1%)	0
Immune system disorders			
Any event	0	0	1 (<1%)

Reference: Study Report 001, Table 14.24, Pages 785-789

Table 40 Continued: Number and percentage of patients with SAEs in Study 001

System Organ Class Preferred Term	PLACEBO (N=292)	ALVIMOPAN 6MG (N=294)	ALVIMOPAN 12MG (N=297)
Anaphylactic reaction	0	0	1 (<1%)
Investigations			
Any event	0	1 (<1%)	0
Electrocardiogram abnormal	0	1 (<1%)	0
Metabolism and nutrition disorders			
Any event	0	1 (<1%)	0
Metabolic acidosis	0	1 (<1%)	0
Musculoskeletal and connective tissue disorders			
Any event	0	1 (<1%)	0
Musculoskeletal pain	0	1 (<1%)	0
Reproductive system and breast disorders			
Any event	1 (<1%)	0	0
Pelvic haemorrhage	1 (<1%)	0	0

Reference: Study Report 001, Table 14.24, Pages 785-789

Table 41: Listing of all the SAEs in the OBD non-cancer program

Study Patient	SAE requiring hospitalization	Study Drug	Medical History	Relation to study drug
13C208/ 04-558	Chest pain	Alvimopan 0.5 mg/day	74 year old white male (with a history of HTN, back pain, asthma, GERD, bipolar disorder, and anxiety) experienced chest pain, shortness of breath, diaphoresis, and nausea about 5 hours after receiving his second daily dose of 0.5 mg of alvimopan. The patient was admitted for these symptoms. The SAE resolved and the patient was discharged the following day.	Not related
13C304/ 003-001	Exacerbation of COPD	Alvimopan 0.5 mg/day	64 year old white female (with a history of COPD, asthma, CAD, HTN, GERD, and chronic pain) developed an out-patient pneumonia on study day 9 and COPD exacerbation on study day 32 (11 days after the end of the alvimopan treatment). The patient was not compliant with her study medication from study day 1 to 21 (she took about 60% of her pills). She required hospitalization for a COPD exacerbation on study day 32 and subsequently died.	Not related
13C304/ 015-007	Worsening diverticulosis	Alvimopan 1 mg/day	55 year old white male (with a history of chronic pain, diverticulosis, constipation, COPD, HTN, hyperlipidemia, pancreatitis, alcohol and opioid abuse, and depression) was hospitalized for diverticulosis. He completed 21 days of 1 mg alvimopan/day study treatment. On study day 30 (nine days after stopping study treatment) he was diagnosed with diverticulitis and study day 48 (27 days after stopping study treatment) he was hospitalized for diverticulitis.	Not related
CT001-001-005	Abdominal pain and vomiting	Alvimopan 1 mg/day	48 year old male (with a history of multiple lumbar fusions, low back pain, and opioid-induced constipation) was taking oxycodone, hydrocodone and other medications. He received ascending daily doses of 0.125, 0.25, 1, and 3 mg of alvimopan. About 1.5 hours after the 3 mg alvimopan dose on day 4 of the study, the patient developed generalized abdominal pain, nausea, vomiting, and two bowel movements. He was hospitalized. 3.5 hours later, after receiving IV ranitidine, IV lorazepam, and IV morphine sulfate, his abdominal pain resolved. He was discharged the following day.	Probably Related

Reference: Adapted from ISS, Volume 211, Section 6.1.5.2, Table 62, Page 149

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

In the U.S. POI population, the overall proportion of patients – who discontinued treatment due to at least one AE – was lower in the alvimopan groups compared to placebo. In the U.S. POI population, 78 (7.6%) out of 1024 alvimopan 12 mg patients discontinued study medication; 50 (8.3%) out of 604 alvimopan 6 mg patients discontinued study medication; and 98 (13.1%) out of 748 placebo patients discontinued study medication. In the U.S. POI population, patients in all treatment groups discontinued most frequently due to GI-related adverse events (primarily nausea and vomiting). In the U.S. POI population, the incidence for discontinuation due to nausea and vomiting were comparable among treatment groups. In the U.S. POI population, there were few discontinuations overall for prolonged POI for both alvimopan treatment groups compared to placebo. In the placebo group, 25 (3.3%) out of 748 discontinued due to prolonged POI; in the alvimopan 6 mg group, 10 (1.7%) out of 604 patients discontinued due to prolonged POI; and in the alvimopan 12 mg group, 11 (1.1%) out of 1024 discontinued due to prolonged POI.

In the European POI population (Study 001), the overall proportion of patients who discontinued treatment due to at least one AE was similar in all groups. In the placebo group, 19 (7%) out of 292 discontinued; in the alvimopan 6 mg group, 24 (8%) out of 294 discontinued; and in the alvimopan 12 mg group, 15 (5%) out of 297 discontinued.

Table 42 and Table 43 lists the AEs that caused study discontinuation in the U.S. POI population (Studies 13C206, 12C213, 13C214, 302, 306, 308, and 313) and in the European POI population (Study 001), respectively.

Medical Reviewer's Comments: Since alvimopan is an opioid-antagonist, one theoretical AE would be diarrhea. However, post-operative patients are not likely to have diarrhea because they do not eat full meals and they may have had bowel preparations prior to surgery.

Fewer discontinuations due to prolonged POI in the alvimopan groups (compare to the placebo group) may indicate positive efficacy benefits of alvimopan. However, the efficacy analysis has multiple flaws (please see the Medical Reviewer's Comments in the subsection "Sponsor's post-hoc analyses" in Section 6.1.4 of this review). This medical officer encourages the sponsor to formally test this hypothesis in another clinical trial.

Table 42: All AEs causing discontinuation for the U.S. POI population

SOC Preferred Term	Placebo (N=748) N (%)	Alvimopan 6 mg (N=604) N (%)	Alvimopan 12 mg (N=1024) N (%)	Alvimopan Total (N=1690) N (%)
Subjects with at least one AE	98 (13.1)	50 (8.3)	78 (7.6)	135 (8.0)
Gastrointestinal Disorders	60 (8.0)	30 (5.0)	57 (5.6)	93 (5.5)
Abdominal distension	10 (1.3)	6 (1.0)	7 (0.7)	14 (0.8)
Abdominal pain NOS	0	2 (0.3)	1 (0.1)	3 (0.2)
Ascites	0	1 (0.2)	0	1 (0.1)
Constipation	0	0	2 (0.2)	2 (0.1)
Diarrhea NOS	2 (0.3)	0	7 (0.7)	7 (0.4)
Dyspepsia	0	1 (0.2)	6 (0.6)	7 (0.4)
Dyspepsia aggravated	0	0	1 (0.1)	1 (0.1)
Epigastric discomfort	1 (0.1)	0	0	0
Flatulence	1 (0.1)	1 (0.2)	3 (0.3)	4 (0.2)
Gastritis NOS	1 (0.1)	0	0	0
Gastro-esophageal reflux disease	0	1 (0.2)	1 (0.1)	2 (0.1)
Gastrointestinal hemorrhage NOS	1 (0.1)	0	0	0
Hiccups	1 (0.1)	2 (0.3)	1 (0.1)	3 (0.2)
Intestinal ischemia	0	0	0	1 (0.1)
Intestinal perforation NOS	0	0	0	1 (0.1)
Mallory-Weiss syndrome	1 (0.1)	0	0	0
Nausea	34 (4.5)	14 (2.3)	30 (2.9)	47 (2.8)
Nausea aggravated	1 (0.1)	0	1 (0.1)	2 (0.1)
Edema uvula	0	1 (0.2)	0	1 (0.1)
Esophagitis NOS	1 (0.1)	0	0	0
Peritoneal hemorrhage	1 (0.1)	0	0	0
Peritonitis	0	0	0	1 (0.1)
Rectal hemorrhage	0	0	1 (0.1)	1 (0.1)
Retching	0	1 (0.2)	1 (0.1)	2 (0.1)
Vomiting NOS	29 (3.9)	12 (2.0)	20 (2.0)	33 (2.0)
Injury, Poisoning and Procedural Complications	31 (4.1)	15 (2.5)	18 (1.8)	33 (2.0)
Anaphylactoid reaction	1 (0.1)	0	0	0
Gastrointestinal disorder NOS postoperative	4 (0.5)	3 (0.5)	1 (0.1)	4 (0.2)
Gastroparesis postoperative	0	0	1 (0.1)	1 (0.1)
Nausea postoperative	1 (0.1)	0	0	0
Post procedural pain	0	1 (0.2)	0	1 (0.1)
Postoperative fistula NOS	0	1 (0.2)	0	1 (0.1)
Postoperative ileus	25 (3.3)	10 (1.7)	11 (1.1)	21 (1.2)
Therapeutic procedural complication	0	0	2 (0.2)	2 (0.1)
Vomiting postoperative	1 (0.1)	0	0	0

Reference: Adapted from the ISS, Volume 211, Table 98, Pages 233-235

Table 42 Continued: All AEs causing discontinuation for the U.S. POI population

SOC Preferred Term	Placebo (N=748) N (%)	Alvimopan 6 mg (N=604) N (%)	Alvimopan 12 mg (N=1024) N (%)	Alvimopan Total (N=1690) N (%)
Injury, Poisoning and Procedural Complications (Continued)				
Wound dehiscence	0	0	3 (0.3)	3 (0.2)
Wound evisceration	0	0	1 (0.1)	1 (0.1)
Vascular disorders	5 (0.7)	1 (0.2)	4 (0.4)	5 (0.3)
Cerebrovascular accident	0	1 (0.2)	0	1 (0.1)
Hypertension aggravated	0	0	1 (0.1)	1 (0.1)
Hypertension NOS	0	0	1 (0.1)	1 (0.1)
Hypotension aggravated	1 (0.1)	0	0	0
Hypotension NOS	2 (0.3)	0	0	0
Iliac vein thrombosis	1 (0.1)	0	0	0
Pulmonary embolism	1 (0.1)	0	2 (0.2)	2 (0.1)
Respiratory, Thoracic and Mediastinal Disorders	5 (0.7)	2 (0.3)	1 (0.1)	4 (0.2)
Abnormal Chest Sounds NOS	0	0	0	1 (0.1)
Acute respiratory distress syndrome	1 (0.1)	0	0	0
Acute respiratory failure	0	1 (0.2)	0	1 (0.1)
Pharyngolaryngeal pain	1 (0.1)	0	0	0
Pharynx discomfort	0	1 (0.2)	0	1 (0.1)
Pneumonia aspiration	1 (0.1)	0	0	0
Respiratory arrest (excl neonatal)	1 (0.1)	0	0	0
Respiratory failure (excl neonatal)	1 (0.1)	0	1 (0.1)	1 (0.1)
Skin and Subcutaneous Tissue Disorders	3 (0.4)	2 (0.3)	1 (0.1)	4 (0.2)
Face edema	0	0	1 (0.1)	1 (0.1)
Pruritus generalized	1 (0.1)	0	0	0
Pruritus NOS	2 (0.3)	1 (0.2)	1 (0.1)	3 (0.2)
Sweating increased	0	1 (0.2)	0	1 (0.1)
Urticaria NOS	0	0	1 (0.1)	1 (0.1)
Psychiatric disorders	4 (0.5)	1 (0.2)	3 (0.3)	4 (0.2)
Anxiety NEC	3 (0.4)	1 (0.2)	0	1 (0.1)
Confusion	1 (0.1)	0	2 (0.2)	2 (0.1)
Delirium tremens	0	0	1 (0.1)	1 (0.1)
Delusion NOS	1 (0.1)	0	0	0
Paranoia	0	0	1 (0.1)	1 (0.1)
Infections and infestations	3 (0.4)	1 (0.2)	1 (0.1)	3 (0.2)
Peritonitis bacterial NOS	1 (0.1)	0	0	0
Pneumonia NOS	1 (0.1)	1 (0.2)	0	1 (0.1)
Postoperative abscess	1 (0.1)	0	1 (0.1)	2 (0.1)

Reference: Adapted from the ISS, Volume 211, Table 98, Pages 233-235

Table 42 Continued: All AEs causing discontinuation for the U.S. POI population

SOC Preferred Term	Placebo (N=748) N (%)	Alvimopan 6 mg (N=604) N (%)	Alvimopan 12 mg (N=1024) N (%)	Alvimopan Total (N=1690) N (%)
Nervous System Disorders	4 (0.5)	1 (0.2)	1 (0.1)	2 (0.1)
Dizziness	1 (0.1)	0	0	0
Headache NOS	1 (0.1)	1 (0.2)	1 (0.1)	2 (0.1)
Somnolence	1 (0.1)	0	0	0
Transient ischemia attack	1 (0.1)	0	0	0
Cardiac Disorders	4 (0.5)	1 (0.2)	1 (0.1)	2 (0.1)
Atrial fibrillation	0	0	1 (0.1)	1 (0.1)
Bradycardia NOS	1 (0.1)	0	0	0
Cardiac arrest	0	1 (0.2)	0	1 (0.1)
Myocardial infarction	2 (0.3)	0	0	0
Tachycardia NOS	1 (0.1)	0	0	0
Investigations	2 (0.3)	0	0	1 (0.1)
Alanine aminotransferase increased	1 (0.1)	0	0	0
Aspartate aminotransferase increased	1 (0.1)	0	0	0
Blood lactate dehydrogenase increased	1 (0.1)	0	0	0
Blood pressure increased	1 (0.1)	0	0	0
Oxygen saturation decreased	0	0	0	1 (0.1)
Metabolism and Nutrition Disorders	2 (0.3)	1 (0.2)	0	1 (0.1)
Hypokalemia	0	1 (0.2)	0	1 (0.1)
Hypovolemia	2 (0.3)	0	0	0
Blood and Lymphatic System Disorders	1 (0.1)	0	1 (0.1)	1 (0.1)
Anemia NOS	0	0	1 (0.1)	1 (0.1)
Anemia NOS aggravated	1 (0.1)	0	0	0
General disorders and Administration Site Conditions	1 (0.1)	1 (0.2)	0	1 (0.1)
Chest pain	0	1 (0.2)	0	1 (0.1)
Pyrexia	1 (0.1)	0	0	0
Immune System Disorders	0	1 (0.2)	0	1 (0.1)
Hypersensitivity NOS	0	1 (0.2)	0	1 (0.1)
Musculoskeletal and Connective Tissue Disorders	1 (0.1)	0	1 (0.1)	1 (0.1)
Back pain	1 (0.1)	0	0	0
Pain in limb	0	0	1 (0.1)	1 (0.1)
Ear and Labyrinth Disorders	0	0	1 (0.1)	1 (0.1)
Vertigo	0	0	1 (0.1)	1 (0.1)
Neoplasms Benign, Malignant and Unspecified (incl. cysts and polyps)	0	1 (0.2)	0	1 (0.1)
Colon cancer metastatic	0	1 (0.2)	0	1 (0.1)

Reference: Adapted from the ISS, Volume 211, Table 98, Pages 233-235

Table 43: Number (%) of patients with AEs leading to discontinuation of study drug in Study 001

Preferred term	Number (%) of subjects					
	Placebo (N=292)		Alvimopan 6mg (N=294)		Alvimopan 12mg (N=297)	
At least one AE leading to permanent discontinuation of study drug	19	(7)	24	(8)	15	(5)
Vomiting	6	(2)	5	(2)	3	(1)
Nausea	2	(<1)	5	(2)	2	(<1)
Postoperative ileus	2	(<1)	1	(<1)	0	
Haemorrhage	0		0		2	(<1)
Hypertension	0		0		2	(<1)
Hypertensive crisis	0		2	(<1)	0	
Respiratory depression	0		2	(<1)	0	

Reference: Adapted from Study 001 Report, Section 8.4, Table 43, Page 103

Discontinuation from treatment in the four important phase 3 efficacy studies

Table 44 lists the reasons proportions of patients that completed treatment and the general reasons why patients discontinued treatment (including AEs, protocol violations). The proportions of patients who discontinued treatment in the three treatment groups (placebo, alvimopan 6 mg, and alvimopan 12 mg) due to AEs and protocol violations were similar.

Table 44: Patients who discontinued study treatment in the four important efficacy trials (302, 308, 313, and 001)

Study	Treatment Groups	Randomized N (%)	Completed Treatment N (%)	Discontinued Treatment N (%)			
				AE	Withdrew Consent or Administrative	Protocol Violation	Other
302	Placebo	153 (100)	121 (79.1)	22 (14.4)	2 (1.3)	6 (3.9)	2 (1.3)
	Alvimopan 6 mg	152 (100)	128 (84.2)	10 (6.6)	1 (0.7)	9 (5.9)	4 (2.6)
	Alvimopan 12 mg	146 (100)	107 (73.3)	26 (17.8)	4 (2.8)	6 (4.1)	3 (2.1)
308	Placebo	224 (100)	176 (78.6)	29 (12.9)	4 (1.8)	11 (4.9)	4 (1.8)
	Alvimopan 6 mg	220 (100)	187 (85.0)	17 (7.7)	2 (0.9)	12 (5.5)	2 (0.9)
	Alvimopan 12 mg	222 (100)	184 (82.9)	17 (7.7)	3 (1.4)	14 (6.3)	4 (1.8)
313	Placebo	165 (100)	116 (70.3)	28 (17.0)	4 (2.4)	16 (9.7)	1 (0.6)
	Alvimopan 6 mg	169 (100)	130 (76.9)	19 (11.2)	5 (3.0)	14 (8.3)	1 (0.6)
	Alvimopan 12 mg	176 (100)	142 (80.7)	15 (8.5)	7 (3.9)	10 (5.7)	2 (1.1)
001	Placebo	292 (100)	209 (72)	26 (3)	18 (6)	30 (10)	9 (3)
	Alvimopan 6 mg	294 (100)	223 (76)	29 (6)	11 (4)	14 (5)	17 (6)
	Alvimopan 12 mg	297 (100)	226 (76)	23 (5)	11 (4)	25 (8)	12 (4)
Total	Placebo	834 (100)	622 (75)	105 (13)	28 (3)	63 (8)	16 (2)
	Alvimopan 6 mg	835 (100)	668 (79)	75 (9)	19 (2)	49 (6)	24 (3)
	Alvimopan 12 mg	841 (100)	659 (78)	81 (10)	25 (3)	55 (7)	21 (2)

Reference: Adapted from Volume 167, Table 8, Page 75; Volume 167, Table 7, Page 70; Volume 173, Table 7, Page 66;and Study Report for 001, Table 4, Page 65

7.1.3.2 Adverse events associated with dropouts

Please see Section 7.1.3.1 of this review.

7.1.3.3 Other significant adverse events

In the U.S. POI subpopulation, other significant (non-serious) AEs that did not contribute to study drug discontinuation were elevated liver tests. The number of patients who had elevated liver tests (≥ 3 times normal) in the alvimopan 12 mg group, the alvimopan 6 mg group, and the placebo group were 18, 12, and 18, respectively. Thus, there was no difference between the three treatment groups in number of elevated liver tests. Most liver test elevations were isolated and most decreased or returned to normal during the treatment period.

In the European POI subpopulation, other significant (non-serious) AEs that did not contribute to study drug discontinuation were wound dehiscence and urinary retention. In the European POI subpopulation, one patient in alvimopan 6 mg group had his/her dose interrupted because of wound dehiscence. This patient's AE was not considered serious. In the European POI subpopulation, 3, 4, and 4 patients developed urinary retention in the placebo group, the alvimopan 6 mg group, and the alvimopan 12 mg group, respectively. No cases of urinary retention were graded as serious and no patients were discontinued from the study drug as a result of the event.

Therefore in the entire POI population, there appeared to be no difference in concerning AEs (that were not serious and did not require discontinuation from the study).

7.1.4 Other Search Strategies

Since alvimopan is an opioid antagonist, it is possible that alvimopan may reverse opioid analgesia post-surgery.

Additionally, it is possible that a sudden reversal of opioid activity could produce opioid withdrawal symptoms [such as sweating, shaking, headache, drug craving, nausea, vomiting, abdominal cramping, diarrhea, insomnia, confusion, agitation, behavioral changes, tears, rhinorrhea, restlessness, tachycardia, yawning, tremor, piloerection (hair standing on end), mydriasis (pupil dilation, pain)].

Medical Reviewer's Comments: Table 45 lists the numbers and frequencies of opioid-withdrawal symptoms in the placebo and alvimopan treatment groups in the seven U.S. POI studies. Table 44 is derived from the sponsor's table that lists all the AEs reported in ≥1% of U.S. POI patients. The alvimopan treatment groups did not appear to have a higher risk (compared to placebo) of the combination of these symptoms. This finding supports the sponsor's position that alvimopan does not contribute to opioid withdrawal in the POI population who are not taking concomitant opioids.

However, patients who take concomitant opioids are at much higher risk of opioid withdrawal than the POI population. Therefore, the lack of opioid-withdrawal symptoms in the POI population can not be extrapolated to the OBD population. Patients with OBD are on chronic concomitant opioids and are at much higher risk of having opioid-withdrawal. Therefore, alvimopan should be contraindicated in surgery

patients who use chronic opioids. The sponsor has proposed adding this contraindication to the label and this medical officer agrees to this contraindication.

Table 45: The numbers and frequencies of opioid-withdrawal symptoms in the placebo and alvimopan treatment groups in the seven US POI studies (13C206, 13C213, 13C214, 302, 308, 313 and 306)

Symptoms	Placebo	Alvimopan 6 mg	Alvimopan 12 mg	All Alvimopan Treatment Groups[a]
	(N=748)	(N=604)	(N=1024)	(N=1690)
	N (%)	N (%)	N (%)	N (%)
Nausea	461 (62)	340 (56)	639 (62)	1017 (60)
Vomiting	198 (27)	135 (22)	246 (24)	394 (23)
Headache	71 (10)	64 (11)	112 (11)	182 (11)
Insomnia	67 (9)	64 (11)	90 (9)	162 (10)
Tachycardia	63 (8)	51 (8)	65 (6)	122 (7)
Diarrhea	57 (8)	47 (8)	66 (6)	115 (7)
Anxiety	30 (4)	24 (4)	46 (5)	72 (4)
Post-procedural pain	27 (4)	27 (5)	26 (3)	63 (4)
Abdominal pain	28 (4)	15 (3)	33 (3)	52 (3)
Confusion	35 (5)	20 (3)	19 (2)	41 (2)
Sweating increased	8 (1)	10 (2)	8 (1)	19 (1)
Agitation	8 (1)	9 (2)	9 (1)	18 (1)

Reference: Adapted from ISS, Table 31, Page 85-86
a All alvimopan treatment groups include the 1 mg and 3 mg groups in the three phase 2 POI studies and it includes the 6 mg and 12 mg alvimopan treatment groups in the phase 2 (13C206, 13C213, and 13C214) and four U.S. phase 3 studies (302, 308, 313 and 306).

Medical Reviewer's Comments: Table 46 delineates the peri-operative pain (as VAS scores) of patients in the four important efficacy studies (301, 308, 313, and 001). This medical officer presented the mean VAS scores because the mean and median scores were very similar. In all four efficacy studies, all treatment groups have similar pain scores prior to surgery (PSD 0) and postoperatively (PSD 1 to PSD 4). The results of the remainder of the study periods are similar. This supports the sponsor's case that alvimopan does not impair opioid analgesia in POI patients who are not on concomitant opioid medications.

Table 46: Mean peri-operative pain (severity in VAS score) by post surgical day in the four important efficacy studies (301, 308, 313, and 001)

STUDY*	TREATMENT GROUPS	PSD 0	PSD 1	PSD 2	PSD 3	PSD 4
302	placebo	53	47	37	29	29
	Alvimopan 6 mg	51	46	35	35	21
	Alvimopan 12 mg	50	46	37	33	31
308	Placebo	42	29	23	20	18
	Alvimopan 6 mg	46	31	25	21	19
	Alvimopan 12 mg	43	29	24	22	19
313	Placebo	45	29	26	22	18
	Alvimopan 6 mg	47	30	25	22	22
	Alvimopan 12 mg	44	29	22	20	19
001	placebo	38	29	23	19	16
	Alvimopan 6 mg	34	27	22	19	15
	Alvimopan 12 mg	38	30	22	19	17

* Studies 302, 308, and 313 included all patients including all surgical subgroups; in contrast; Study 001 only included GI surgery patients

PSD 0 is 24 hours before the end of surgery (this includes the surgery time and pre-operative time)

PSD 1 is 24 hours after surgery ends

Patients rated the intensity of their pain on a 0-100 mm VAS scale. VAS scores were completed twice daily.

The study period for Studies 302, 308, and 313 ends POD 10; the study period for Study 001 ends POD 14.

Reference: Volume 164, Table 11.2.2.1, Pages 287-9 ; Volume 167, Table 11.2.2.1, Pages 332-4; Volume 173, Table 11.2.2.1, Pages 237-9; and Study Report 001, Table 13.104, Pages 463-8.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

All of the phase 2 and 3 POI trials had similar procedures to evaluate AE data. AEs were obtained from abnormalities in physical exams (PEs) including vital signs (measured twice daily during the Treatment Period), laboratory tests (measured prior to and at hospital discharge), and ECGs (collected prior to and at hospital discharge). Laboratory testing included CBC with differential, hepatic panel, basic metabolic panel, LDH, and urinalysis. During the Treatment Period (POD 0 to POD 10 or until hospital discharge), patients received routine postoperative care including frequent vital signs, daily brief physical exams, possible laboratory testing, and possible other special studies. Investigators interviewed patients twice daily and they monitored the patient's hospital records.

The follow-up procedures for eliciting AEs differed in the phase 2 and 3 trials. Safety Study 306 had the most complete follow-up. In Study 306, patients had a follow-up visit 7-10 days after the last dose of study drug. In Study 306, if the patients were home, they would follow-up with investigators during a clinic visit; or if the patients were hospitalized, they would be visited by investigators in the hospital. The follow-up visit included a complete PE with vital signs, laboratory tests including EKGs, and assessments of AEs.

Patients in the other POI trials (13C206, 13C213, 13C214, 302, 308, 313 and 001) had less complete follow-up. In these studies, a follow-up visit was scheduled if the patient was still hospitalized; however, no follow up visit was obtained for outpatients. In Studies 13C206 and 13C214 and in the initial 302 protocol, outpatients were called within 14 days after hospital discharge. In Studies 13C213, 308, 313, and 001 and in the amended 302 study, outpatients were called 5-7 days after the last dose of study medication. During the telephone call, AE assessments were obtained; however, no PEs, vital signs, laboratory tests, or ECGs were obtained. In these patients, the last thorough evaluation was obtained on the hospital discharge day. If the outpatients did not respond to three telephone calls, then a certified letter was sent to the patients.

Medical Reviewer's Comments: Study 306's follow-up clinic visit to evaluate possible AEs – 7-10 days after the last dose of study treatment – was acceptable because of the following reasons: 1) 95% of alvimopan and its metabolite are out of the body in five days after the last dose (according to Dr. Sue Chih Lee, the pharmaceutics reviewer) 2) the POI trials and the proposed use is of short duration (up to 7.5 days of therapy).

However, the seven other studies (13C206, 13C213, 13C214, 302, 308, 313 and 001) did not have acceptable follow-up periods. It was possible for hospitalized patients in on of the POI clinical trials to achieve the primary efficacy endpoint (GI^3) in the morning and be send home later that day. In this example, the discharge procedures (including physical exam, laboratory testing, and ECG testing) 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, these patients had incomplete post-treatment follow-up. A follow-up 5-7 telephone call may not elicit all AEs.

This medical officer believes that the post-treatment follow-up was insufficient to adequately elicit possible AEs in all of the POI trials (except for Study 306).

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

All of the five phase 3 POI trials used the Medical Dictionary for Regulatory Activities Terminology (MedDRA) version 4.1 nomenclature to classify AEs. Of the three phase 2 POI trials, two used MedDRA and one (Study 13C206) used Coding Symbols for a Thesaurus of Adverse Reactions Terms (COSTART) nomenclature to classify AEs. AEs in Study 13C206 (coded with COSTART) were re-coded using MedDRA version 4.1.

7.1.5.3 Incidence of common adverse events

U.S. POI population

Table 47 lists the number and frequency of all AEs reported in ≥ 1% of all patients for the U.S. POI population. Data shown in this table are listed in MedDRA preferred term in decreasing order of frequency.

In the U.S. POI population, nausea was the most frequently reported AE among all the treatment groups. The incidence of nausea was comparable among treatment groups: 62%

for the placebo group, 56% for the alvimopan 6 mg group, and 62% for the alvimopan 12 mg group. In the U.S. POI population, the incidence of most AEs were comparable among the alvimopan and placebo treatment groups.

In the U.S. POI population, the incidence of GI-related AEs (including abdominal distension, flatulence, diarrhea, dyspepsia, and abdominal pain) were comparable among the alvimopan and placebo treatment groups.

European POI population

Table 48 lists the number and frequency of all AEs reported in ≥ 1% of all patients for the European POI population (Study 001). Data shown in this table are listed in MedDRA preferred term in decreasing order of frequency.

In the European POI population, the incidence of most AEs were comparable among the alvimopan and placebo groups.

Similar to the U.S. POI population, nausea was the most frequently reported AE among all the treatment groups in the European POI population. The incidence of nausea was slightly higher among the alvimopan groups than the placebo group: 9% for the alvimopan 6 mg group, 9% for the alvimopan 12 mg group; and 7 % for the placebo group. However, in the larger U.S. POI population, the incidence of nausea was comparable among the three groups.

Medical Reviewer's Comments: **The frequencies of AEs in the alvimopan and placebo treatment groups appear similar. The placebo treatment group was associated with more AEs than the alvimopan treatment groups. Reports of urinary retention were higher in the alvimopan groups than the placebo groups. However, this does not make biologic sense because opioid inhibition (by alvimopan) would lead to less urinary retention; not more urinary retention. Furthermore, in the European POI population, the incidence of urinary retention was comparable among the placebo and alvimopan groups. Most likely, the higher rate of urinary retention in the alvimopan groups in the U.S. POI trials was due to chance.**

The most common drug-related AEs (including nausea, vomiting, abdominal distension, pyrexia, flatulence, pruritus, constipation, headache, and hypotension) are symptoms commonly experienced by post-operative patients. Therefore, these AEs are more likely due to the underlying situation than due to alvimopan.

Table 47: All AEs reported in ≥ 1% of all patients in the U.S. POI population (Studies 13C206, 13C213, 13C214, 302, 308, 313 and 306)

		Alvimopan		
Preferred Term	Placebo (N=748) N (%)	6 mg (N=604) N (%)	12 mg (N=1024) N (%)	Total (N=1690) N (%)
Nausea	461 (61.6)	340 (56.3)	639 (62.4)	1017 (60.2)
Vomiting NOS	198 (26.5)	135 (22.4)	246 (24.0)	394 (23.3)
Abdominal distension	109 (14.6)	76 (12.6)	115 (11.2)	203 (12.0)
Pyrexia	103 (13.8)	73 (12.1)	108 (10.5)	187 (11.1)
Flatulence	89 (11.9)	56 (9.3)	130 (12.7)	195 (11.5)
Pruritus NOS	94 (12.6)	70 (11.6)	116 (11.3)	190 (11.2)
Constipation	84 (11.2)	35 (5.8)	138 (13.5)	178 (10.5)
Headache NOS	71 (9.5)	64 (10.6)	112 (10.9)	182 (10.8)
Hypotension NOS	85 (11.4)	70 (11.6)	83 (8.1)	159 (9.4)
Insomnia	67 (9.0)	64 (10.6)	90 (8.8)	162 (9.6)
Hypertension NOS	67 (9.0)	65 (10.8)	90 (8.8)	157 (9.3)
Tachycardia NOS	63 (8.4)	51 (8.4)	65 (6.3)	122 (7.2)
Oliguria	75 (10.0)	47 (7.8)	59 (5.8)	108 (6.4)
Diarrhea NOS	57 (7.6)	47 (7.8)	66 (6.4)	115 (6.8)
Hypokalemia	63 (8.4)	50 (8.3)	57 (5.6)	108 (6.4)
Postoperative ileus	71 (9.5)	41 (6.8)	42 (4.1)	84 (5.0)
Dyspepsia	44 (5.9)	27 (4.5)	64 (6.3)	102 (6.0)
Body temperature increased	52 (7.0)	41 (6.8)	50 (4.9)	91 (5.4)
Dizziness	41 (5.5)	27 (4.5)	66 (6.4)	96 (5.7)
Urinary tract infection NOS	39 (5.2)	17 (2.8)	55 (5.4)	75 (4.4)
Anemia NOS	33 (4.4)	23 (3.8)	43 (4.2)	70 (4.1)
Anxiety NEC	30 (4.0)	24 (4.0)	46 (4.5)	72 (4.3)
Post procedural pain	27 (3.6)	27 (4.5)	26 (2.5)	63 (3.7)
Breath sounds decreased	35 (4.7)	20 (3.3)	24 (2.3)	53 (3.1)
Postoperative wound infection	36 (4.8)	24 (4.0)	27 (2.6)	51 (3.0)
Hypomagnesemia	34 (4.5)	23 (3.8)	29 (2.8)	52 (3.1)
Back pain	26 (3.5)	16 (2.6)	38 (3.7)	56 (3.3)
Abdominal pain NOS	28 (3.7)	15 (2.5)	33 (3.2)	52 (3.1)
Hypertension aggravated	28 (3.7)	23 (3.8)	27 (2.6)	51 (3.0)
Urinary retention	17 (2.3)	19 (3.1)	41 (4.0)	60 (3.6)
Confusion	35 (4.7)	20 (3.3)	19 (1.9)	41 (2.4)
Edema peripheral	27 (3.6)	21 (3.5)	24 (2.3)	48 (2.8)
Atelectasis	29 (3.9)	18 (3.0)	27 (2.6)	45 (2.7)
Postoperative wound site erythema	22 (2.9)	21 (3.5)	19 (1.9)	41 (2.4)
Dyspnea NOS	24 (3.2)	11 (1.8)	19 (1.9)	35 (2.1)
Bradycardia NOS	26 (3.5)	15 (2.5)	16 (1.6)	32 (1.9)

Reference: ISS, Section 5.8.2, Table 31, Page 85-86

Table 47 Continued: All AEs reported in ≥ 1% of all patients in the U.S. POI population (Studies 13C206, 13C213, 13C214, 302, 308, 313 and 306)

		Alvimopan		
	Placebo (N=748)	6 mg (N=604)	12 mg (N=1024)	Total (N=1690)
Preferred Term	N (%)	N (%)	N (%)	N (%)
Pharyngolaryngeal pain	22 (2.9)	12 (2.0)	21 (2.1)	35 (2.1)
Wheezing	21 (2.8)	16 (2.6)	12 (1.2)	30 (1.8)
Hiccups	13 (1.7)	16 (2.6)	20 (2.0)	36 (2.1)
Gastrointestinal disorder NOS postoperative	21 (2.8)	13 (2.2)	11 (1.1)	24 (1.4)
Rash NOS	13 (1.7)	7 (1.2)	22 (2.1)	30 (1.8)
Anemia NOS aggravated	15 (2.0)	13 (2.2)	13 (1.3)	27 (1.6)
Oxygen saturation decreased	18 (2.4)	9 (1.5)	10 (1.0)	22 (1.3)
Arthralgia	13 (1.7)	10 (1.7)	14 (1.4)	26 (1.5)
Cough	15 (2.0)	8 (1.3)	15 (1.5)	24 (1.4)
Aspartate aminotransferase increased	10 (1.3)	8 (1.3)	18 (1.8)	26 (1.5)
Crackles lung	16 (2.1)	6 (1.0)	11 (1.1)	20 (1.2)
Dysuria	12 (1.6)	7 (1.2)	15 (1.5)	23 (1.4)
Sinus tachycardia	8 (1.1)	9 (1.5)	18 (1.8)	27 (1.6)
Atrial fibrillation	16 (2.1)	7 (1.2)	11 (1.1)	18 (1.1)
Hypophosphatemia	14 (1.9)	13 (2.2)	7 (0.7)	20 (1.2)
Alanine aminotransferase increased	8 (1.1)	6 (1.0)	19 (1.9)	25 (1.5)
Infusion site edema	7 (0.9)	12 (2.0)	13 (1.3)	26 (1.5)
Retching	6 (0.8)	8 (1.3)	19 (1.9)	27 (1.6)
Chest pain	11 (1.5)	6 (1.0)	14 (1.4)	20 (1.2)
Weakness	9 (1.2)	7 (1.2)	15 (1.5)	22 (1.3)
Blood magnesium decreased	7 (0.9)	10 (1.7)	9 (0.9)	23 (1.4)
Blood potassium decreased	11 (1.5)	8 (1.3)	8 (0.8)	19 (1.1)
Pleural effusion	15 (2.0)	7 (1.2)	8 (0.8)	15 (0.9)
Pruritus generalized	11 (1.5)	5 (0.8)	14 (1.4)	19 (1.1)
Blood phosphorus decreased	12 (1.6)	7 (1.2)	7 (0.7)	16 (0.9)
Gastro-esophageal reflux disease	7 (0.9)	9 (1.5)	11 (1.1)	21 (1.2)
Pain in limb	8 (1.1)	8 (1.3)	12 (1.2)	20 (1.2)
Abnormal chest sounds NOS	10 (1.3)	3 (0.5)	9 (0.9)	17 (1.0)
Hypocalcemia	8 (1.1)	10 (1.7)	9 (0.9)	19 (1.1)
Sweating increased	8 (1.1)	10 (1.7)	8 (0.8)	19 (1.1)
White blood cell count increased	7 (0.9)	11 (1.8)	9 (0.9)	20 (1.2)
Agitation	8 (1.1)	9 (1.5)	9 (0.9)	18 (1.1)
Dehydration	10 (1.3)	8 (1.3)	5 (0.5)	15 (0.9)
Hot flushes NOS	5 (0.7)	3 (0.5)	15 (1.5)	20 (1.2)
Therapeutic procedural complication	5 (0.7)	3 (0.5)	17 (1.7)	20 (1.2)
Wound dehiscence	8 (1.1)	4 (0.7)	13 (1.3)	17 (1.0)

Reference: ISS, Section 5.8.2, Table 31, Page 85-86

Table 48: All AEs reported in ≥ 1% of all patients in the European POI population (Study 001)

Preferred Term	Placebo (N=292)	Alvimopan 6 mg (N=294)	Alvimopan 12 mg (N=297)
Any event	159 (54%)	146 (50%)	161 (54%)
Nausea	21 (7%)	25 (9%)	28 (9%)
Vomiting	21 (7%)	16 (5%)	13 (4%)
Hypertension	14 (5%)	11 (4%)	19 (6%)
Pyrexia	17 (6%)	11 (4%)	16 (5%)
Wound infection	11 (4%)	12 (4%)	14 (5%)
Diarrhoea	10 (3%)	17 (6%)	6 (2%)
Hypotension	7 (2%)	8 (3%)	8 (3%)
Urinary tract infection	6 (2%)	6 (2%)	7 (2%)
Hypokalaemia	4 (1%)	5 (2%)	8 (3%)
Anaemia	9 (3%)	4 (1%)	3 (1%)
Urine output decreased	6 (2%)	4 (1%)	6 (2%)
Body temperature increased	3 (1%)	3 (1%)	7 (2%)
Oliguria	2 (<1%)	7 (2%)	3 (1%)
Abdominal pain	3 (1%)	2 (<1%)	6 (2%)
Atrial fibrillation	5 (2%)	2 (<1%)	4 (1%)
Urinary retention	3 (1%)	4 (1%)	4 (1%)
Constipation	5 (2%)	2 (<1%)	3 (1%)
Cystitis	4 (1%)	2 (<1%)	4 (1%)
Dizziness	3 (1%)	2 (<1%)	5 (2%)
Dyspepsia	1 (<1%)	6 (2%)	3 (1%)
Insomnia	2 (<1%)	3 (1%)	5 (2%)
Tachycardia	4 (1%)	2 (<1%)	4 (1%)
Wound dehiscence	2 (<1%)	4 (1%)	4 (1%)
Back pain	2 (<1%)	3 (1%)	4 (1%)
Blood potassium decreased	2 (<1%)	3 (1%)	4 (1%)
Dyspnoea	5 (2%)	4 (1%)	0

Reference: Adapted from Study Report 001, Table 14.8, Page 643

7.1.5.4 Common adverse event tables
Please see Section 7.1.5.3

7.1.5.5 Identifying common and drug-related adverse events

U.S. POI population

Table 49 lists the number and frequency of all treatment-related AEs reported in ≥ 1% of all patients for the U.S. POI population. Data shown in this table are listed in MedDRA preferred term in decreasing order of frequency.

In the U.S. POI population, the frequencies of treatment-related AEs in the alvimopan and placebo populations were comparable. Treatment-related diarrhea had higher incidence in the alvimopan treatment groups compared to the placebo treatment group. However, no dose-related trend was found. Treatment-related elevated AST and elevated ALT had a

higher incidence in the 12 mg alvimopan group compared to placebo and the 6 mg alvimopan group.

European POI population

Table 50 lists the number and frequency of all treatment-related AEs reported in ≥ 0.5% of all patients for the European POI population. Data shown in this table are listed in MedDRA preferred term in decreasing order of frequency.

In the European POI population, the frequencies of treatment-related AEs were comparable in the alvimopan and placebo populations. The incidence of increased ALT and increased AST as treatment-related AEs were similar among the three groups. The incidence of increased ALT and increased AST as treatment-related AEs were not listed in Table 50 because the in each category total number of events represented less than 0.05% of all patients. The incidence of treatment-related increased ALT for the placebo, 6 mg alvimopan, and 12 mg alvimopan groups were 2 (< 1%), 0 (0%), and 2 (< 1%), respectively. The incidence of treatment-related increased AST for the placebo, 6 mg alvimopan, and 12 mg alvimopan groups were 2 (< 1%), 0 (0%), and 2 (< 1%), respectively.

Medical Reviewer's Comments: Overall, the incidence of treatment-related AEs among the alvimopan treatment groups and the placebo group were similar.

Table 49: All Treatment-Related AEs reported in ≥ 1% of all patients for the U.S. POI population (13C206, 13C213, 13C214, 302, 308, 313 and 306)

		Alvimopan		
	Placebo (N=748)	6 mg (N=604)	12 mg (N=1024)	Total (N=1690)
Preferred term	N (%)	N (%)	N (%)	N (%)
Nausea	166 (22.2)	126 (20.9)	228 (22.3)	370 (21.9)
Vomiting NOS	75 (10.0)	54 (8.9)	73 (7.1)	134 (7.9)
Flatulence	38 (5.1)	22 (3.6)	65 (6.3)	89 (5.3)
Abdominal distension	38 (5.1)	21 (3.5)	42 (4.1)	65 (3.8)
Constipation	29 (3.9)	10 (1.7)	45 (4.4)	55 (3.3)
Pruritus NOS	22 (2.9)	14 (2.3)	34 (3.3)	50 (3.0)
Diarrhea NOS	14 (1.9)	20 (3.3)	32 (3.1)	53 (3.1)
Headache NOS	10 (1.3)	12 (2.0)	22 (2.1)	34 (2.0)
Dyspepsia	10 (1.3)	6 (1.0)	25 (2.4)	33 (2.0)
Postoperative ileus	11 (1.5)	13 (2.2)	13 (1.3)	27 (1.6)
Insomnia	10 (1.3)	6 (1.0)	20 (2.0)	27 (1.6)
Abdominal pain NOS	10 (1.3)	2 (0.3)	16 (1.6)	20 (1.2)
Aspartate aminotransferase increased	6 (0.8)	5 (0.8)	17 (1.7)	22 (1.3)
Alanine aminotransferase increased	5 (0.7)	3 (0.5)	18 (1.8)	21 (1.2)

Reference: ISS, Table 94, Page 226

Table 50: All Treatment-Related AEs reported in ≥ 0.5% of all patients for the European POI population (Study 001)

Preferred Term	PLACEBO (N=292)	ALVIMOPAN 6MG (N=294)	ALVIMOPAN 12MG (N=297)
Any event	30 (10%)	27 (9%)	28 (9%)
Nausea	8 (3%)	7 (2%)	7 (2%)
Vomiting	8 (3%)	5 (2%)	4 (1%)
Diarrhoea	5 (2%)	8 (3%)	2 (<1%)
Hypertension	2 (<1%)	0	3 (1%)

Reference: Study Report for 001, Table 14.12, Page 662

7.1.5.6 Additional analyses and explorations

Since there are no clear drug-related AEs, additional analyses were not performed.

7.1.6 Less Common Adverse Events

Table 51 lists the number and frequency of less common AEs (< 1% and more than 0.5%) that occurred in the U.S. POI population (Studies 13C206, 13C213, 13C214, 302, 308, 313 and 306) in decreasing order of frequency. Table 52 lists the number and frequency of less common AEs (< 1% and more than 0.25%) that occurred in the European POI population (Study 001) in decreasing order of frequency.

Table 51: Less common AEs reported in < 1% and > 0.5% of patients in the U.S. POI population (Studies 13C206, 13C213, 13C214, 302, 308, 313 and 306)

Preferred Term	Placebo (N=748) N (%)	Alvimopan			
		1-3 mg (N=62) N (%)	6 mg (N=604) N (%)	12 mg (N=1024) N (%)	Total (N=1690) N (%)
BLOOD LACTATE DEHYDROGENASE	5 (0.7)	0	9 (1.5)	10 (1.0)	19 (1.1)
CELLULITIS	8 (1.1)	0	1 (0.2)	15 (1.5)	16 (0.9)
NAUSEA POSTOPERATIVE	9 (1.2)	0	6 (1.0)	9 (0.9)	15 (0.9)
POST PROCEDURAL HAEMORRHAGE	8 (1.1)	0	5 (0.8)	11 (1.1)	16 (0.9)
HAEMOGLOBIN DECREASED	5 (0.7)	2 (3.2)	10 (1.7)	6 (0.6)	18 (1.1)
HYPERGLYCAEMIA NOS	8 (1.1)	0	7 (1.2)	7 (0.7)	14 (0.8)
POST PROCEDURAL DRAINAGE	6 (0.8)	0	9 (1.5)	7 (0.7)	16 (0.9)
RIGORS	2 (0.3)	1 (1.6)	7 (1.2)	12 (1.2)	20 (1.2)
BLOOD GLUCOSE INCREASED	9 (1.2)	0	7 (1.2)	5 (0.5)	12 (0.7)
BLOOD PRESSURE INCREASED	7 (0.9)	0	4 (0.7)	10 (1.0)	14 (0.8)
HAEMATURIA	9 (1.2)	0	5 (0.8)	7 (0.7)	12 (0.7)
POSTOPERATIVE HAEMATOMA	8 (1.1)	0	4 (0.7)	9 (0.9)	13 (0.8)
PRODUCTIVE COUGH	8 (1.1)	0	7 (1.2)	6 (0.6)	13 (0.8)
VENTRICULAR EXTRASYSTOLES	8 (1.1)	0	6 (1.0)	7 (0.7)	13 (0.8)
ABDOMINAL PAIN UPPER	9 (1.2)	1 (1.6)	4 (0.7)	6 (0.6)	11 (0.7)
BLADDER SPASM	5 (0.7)	2 (3.2)	2 (0.3)	11 (1.1)	15 (0.9)
MUSCLE SPASMS	9 (1.2)	0	4 (0.7)	7 (0.7)	11 (0.7)

Reference: Adapted from ISS, Table 5.9.2.2.1, Pages 15016-8

Table 51 Continued: Less common AEs reported in < 1% and > 0.5% of patients in the U.S. POI population (Studies 13C206, 13C213, 13C214, 302, 308, 313 and 306)

ABDOMINAL DISCOMFORT	5	(0.7)	0		1	(0.2)	13	(1.3)	14	(0.8)
BLOOD URINE PRESENT	11	(1.5)	3	(4.8)	3	(0.5)	2	(0.2)	8	(0.5)
HYPOVOLAEMIA	9	(1.2)	1	(1.6)	4	(0.7)	5	(0.5)	10	(0.6)
HYPOXIA	5	(0.7)	1	(1.6)	7	(1.2)	6	(0.6)	14	(0.8)
PAIN NOS	2	(0.3)	2	(3.2)	3	(0.5)	12	(1.2)	17	(1.0)
POSTOPERATIVE ABSCESS	6	(0.8)	1	(1.6)	8	(1.3)	4	(0.4)	13	(0.8)
POSTOPERATIVE BRUISE	3	(0.4)	2	(3.2)	3	(0.5)	11	(1.1)	16	(0.9)
BLOOD IN STOOL	7	(0.9)	0		6	(1.0)	5	(0.5)	11	(0.7)
HAEMATOCRIT DECREASED	9	(1.2)	1	(1.6)	4	(0.7)	4	(0.4)	9	(0.5)
ERUCTATION	4	(0.5)	0		4	(0.7)	9	(0.9)	13	(0.8)
HYPONATRAEMIA	8	(1.1)	1	(1.6)	3	(0.5)	4	(0.4)	8	(0.5)
OEDEMA NOS	5	(0.7)	1	(1.6)	2	(0.3)	8	(0.8)	11	(0.7)
LEUKOCYTOSIS	4	(0.5)	0		3	(0.5)	8	(0.8)	11	(0.7)
HYPOAESTHESIA	2	(0.3)	2	(3.2)	7	(1.2)	3	(0.3)	12	(0.7)
PULMONARY EMBOLISM	3	(0.4)	1	(1.6)	3	(0.5)	7	(0.7)	11	(0.7)
RESPIRATORY DEPRESSION	4	(0.5)	0		6	(1.0)	4	(0.4)	10	(0.6)
CANDIDAL INFECTION NOS	5	(0.7)	0		2	(0.3)	6	(0.6)	8	(0.5)
CARDIAC FAILURE CONGESTIVE	6	(0.8)	0		3	(0.5)	4	(0.4)	7	(0.4)
DRY MOUTH	4	(0.5)	0		5	(0.8)	4	(0.4)	9	(0.5)
RESTLESSNESS	6	(0.8)	0		2	(0.3)	5	(0.5)	7	(0.4)
ANAEMIA POSTOPERATIVE	3	(0.4)	0		2	(0.3)	7	(0.7)	9	(0.5)

Reference: Adapted from ISS, Table 5.9.2.2.1, Pages 15016-8

Table 52: Less common AEs reported in < 1% and > 0.25% of patients in the European POI population (Study 001)

Preferred Term	Placebo (N=292)	Alvimopan 6 mg (N=294)	Alvimopan 12 mg (N=297)
Abdominal distension	2 (<1%)	3 (1%)	3 (1%)
Anastomotic leak	2 (<1%)	4 (1%)	2 (<1%)
Anxiety	3 (1%)	1 (<1%)	4 (1%)
Confusional state	3 (1%)	3 (1%)	2 (<1%)
Haematuria	4 (1%)	3 (1%)	1 (<1%)
Headache	5 (2%)	3 (1%)	0
Oxygen saturation decreased	4 (1%)	1 (<1%)	3 (1%)
Postoperative ileus	5 (2%)	3 (1%)	0
Postoperative infection	2 (<1%)	3 (1%)	3 (1%)
Bradycardia	5 (2%)	1 (<1%)	1 (<1%)
Hiccups	1 (<1%)	2 (<1%)	4 (1%)
Hyperglycaemia	1 (<1%)	3 (1%)	3 (1%)
Asthenia	3 (1%)	1 (<1%)	2 (<1%)
Dermatitis allergic	3 (1%)	2 (<1%)	1 (<1%)
Lower respiratory tract infection	3 (1%)	0	3 (1%)
Oedema peripheral	2 (<1%)	2 (<1%)	2 (<1%)
Polyuria	3 (1%)	0	3 (1%)
Procedural complication	0	3 (1%)	3 (1%)
Sleep disorder	1 (<1%)	4 (1%)	1 (<1%)
Alanine aminotransferase increased	3 (1%)	0	2 (<1%)
Anaemia postoperative	1 (<1%)	2 (<1%)	2 (<1%)
Aspartate aminotransferase increased	3 (1%)	0	2 (<1%)
Atelectasis	2 (<1%)	3 (1%)	0
Dehydration	3 (1%)	1 (<1%)	1 (<1%)
Haemoglobin decreased	2 (<1%)	2 (<1%)	1 (<1%)
Hypomagnesaemia	1 (<1%)	3 (1%)	1 (<1%)
Ileus	2 (<1%)	1 (<1%)	2 (<1%)
Rash	1 (<1%)	4 (1%)	0
Chest pain	4 (1%)	0	0
Cough	2 (<1%)	1 (<1%)	1 (<1%)
Gastrooesophageal reflux disease	2 (<1%)	0	2 (<1%)
Hyperhidrosis	1 (<1%)	2 (<1%)	1 (<1%)
Hypoalbuminaemia	1 (<1%)	3 (1%)	0
Hypoxia	1 (<1%)	1 (<1%)	2 (<1%)

Reference: Adapted from Study Report 001, Table 14.8, Pages 643-5

Table 52 Continued: Less common AEs reported in <1% and > 0.25% of patients in the European POI population (Study 001)

Preferred Term	Placebo (N=292)	Alvimopan 6 mg (N=294)	Alvimopan 12 mg (N=297)
Ileus paralytic	2 (<1%)	1 (<1%)	1 (<1%)
Myocardial infarction	0	2 (<1%)	2 (<1%)
Myocardial ischaemia	3 (1%)	1 (<1%)	0
Pain	1 (<1%)	2 (<1%)	1 (<1%)
Peritonitis	2 (<1%)	1 (<1%)	1 (<1%)
Pyuria	1 (<1%)	1 (<1%)	2 (<1%)
Rectal haemorrhage	1 (<1%)	2 (<1%)	1 (<1%)
Wound haemorrhage	2 (<1%)	1 (<1%)	1 (<1%)
Abdominal pain upper	2 (<1%)	0	1 (<1%)
Arthralgia	0	1 (<1%)	2 (<1%)
Ascites	1 (<1%)	1 (<1%)	1 (<1%)
Bone pain	1 (<1%)	2 (<1%)	0
Bronchitis	2 (<1%)	1 (<1%)	0
Cardiac arrest	2 (<1%)	0	1 (<1%)
Disorientation	2 (<1%)	0	1 (<1%)
Erythema	3 (1%)	0	0
Haematoma	1 (<1%)	0	2 (<1%)
Haemorrhage	1 (<1%)	0	2 (<1%)
Hallucination	2 (<1%)	0	1 (<1%)
Hypertensive crisis	0	3 (1%)	0
Localised oedema	3 (1%)	0	0
Operative haemorrhage	0	2 (<1%)	1 (<1%)
Oral candidiasis	1 (<1%)	2 (<1%)	0
Phlebitis	1 (<1%)	1 (<1%)	1 (<1%)
Pneumonia	2 (<1%)	0	1 (<1%)
Post procedural haemorrhage	0	0	3 (1%)
Post procedural pain	0	2 (<1%)	1 (<1%)
Pulmonary embolism	0	0	3 (1%)
Somnolence	1 (<1%)	1 (<1%)	1 (<1%)
Syncope	2 (<1%)	0	1 (<1%)
White blood cell count increased	1 (<1%)	2 (<1%)	0

Reference: Adapted from Study Report 001, Table 14.8, Pages 643-5

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

For all the European and U.S. POI studies, the following laboratory studies were performed during the Screening Period: a complete blood count (CBC) with differential; a basic metabolic panel (BMP); a hepatic panel, total bilirubin, direct bilirubin, LDH, and total protein; calcium; and a urinalysis. Additionally, a urine pregnancy test for female patients of child bearing potential and biochemical liver tests for all patients were preformed on POD -1 or POD 0. Prior to discharge from the hospital or at study termination, BMPs, hepatic panels, CBCs with differentials, and urinalysis were collected for patients in the European and U.S. POI studies. In the phase 3 safety study (Study 306), these laboratory

tests were repeated during the follow-up clinical visit (7-10 days after the last dose of study medication). In the seven other phase 2 and 3 POI studies in the U.S. and Europe, follow-up laboratory testing was not performed.

Please see Table 53 for a list of the blood tests performed at baseline and after study drug treatment. The percentage of patients who did not have blood tests after study drug administration was comparable among patients in the alvimopan and placebo groups. The percentage of patients who did not have the routine laboratory testing at the end of study drug treatment ranged from 13% to 29%.

Medical Reviewer's Comments: **Routine coagulation studies including INR and PTT were not routinely performed. These tests should have been measured to assess possible hemorrhagic AEs before and after study drug administration. Additionally, TSH, and phosphorus testing were not routinely performed.**

The absence of follow-up blood tests (one week after the last dose of study medication) may impair the assessment of blood test abnormalities AEs. This medical officer believes that follow-up laboratory testing should have been performed in all of the POI studies. Please see Medical Reviewer's Comments under Section 7.1.5.1 of this review.

Table 53: The number and percentage of blood tests performed at baseline and at the end of study drug administration in the U.S. POI trials (Studies 13C206, 13C213, 13C214, 302, 308, 313 and 306)

Laboratory Parameter	Treatment Group N*	Missing end of study parameters n** (%)	Laboratory Parameter	Treatment Group N*	Missing end of study parameters n** (%)
ALT	Placebo (N=735)	184 (25)	**Sodium**	Placebo (N=740)	183 (25)
	Alvimopan Groups (N=1670)	363 (22)		Alvimopan Groups (N=1675)	381 (23)
AST	Placebo (N=738)	185 (25)	**Potassium**	Placebo (N=740)	181 (24)
	Alvimopan Groups (N=1672)	363 (22)		Alvimopan Groups (N=1675)	376 (22)
Alkaline Phosphatase	Placebo (N=739)	181 (25)	**BUN**	Placebo (N=735)	189 (26)
	Alvimopan Groups (N=1669)	360 (22)		Alvimopan Groups (N=1668)	395 (24)
Direct Bilirubin	Placebo (N=669)	251 (38)	**Creatinine**	Placebo (N=739)	185 (25)
	Alvimopan Groups (N=1521)	501 (33)		Alvimopan Groups (N=1670)	381 (23)
Total Bilirubin	Placebo (N=737)	183 (25)	**Glucose**	Placebo (N=736)	195 (27)
	Alvimopan Groups (N=1671)	369 (22)		Alvimopan Groups (N=1673)	397 (24)
Albumin	Placebo (N=734)	211 (29)	**Calcium**	Placebo (N=728)	205 (28)
	Alvimopan Groups (N=1661)	428 (26)		Alvimopan Groups (N=1643)	404 (25)
GGT[a]	Placebo (N=20)	9 (45)	**TSH[b]**	Placebo (N=0)	2 (100)
	Alvimopan Groups (N=41)	21 (51)		Alvimopan Groups (N=2)	2 (100)
LDH	Placebo (N=636)	193 (30)	**Phosphorus[b]**	Placebo (N=2)	2 (100)
	Alvimopan Groups (N=1486)	381 (26)		Alvimopan Groups (N=0)	N/A
WBC	Placebo (N=744)	174 (23)	**INR[b]**	Placebo (N=21)	19 (90)
	Alvimopan Groups (N=1679)	364 (22)		Alvimopan Groups (N=30)	29 (97)
Hematocrit	Placebo (N=744)	118 (16)	**PTT[b]**	Placebo (N=20)	18 (90)
	Alvimopan Groups (N=1681)	225 (13)		Alvimopan Groups (N=30)	29 (97)
Platelets	Placebo (N=743)	174 (24)			
	Alvimopan Groups (N=1673)	369 (22)			

Reference: ISS, Table 107, Page 256-8; Table 109, Page 260; Table 6.3.1 Pages 17265-99; Table 6.1.1 Pages 16563-75
a Values for GGT were only collected for one phase 2 study (Study 13C206);
b TSH, Phosphorus, INR, and PTT tests were not routinely performed in the POI studies
* N is # of patients who had the test at baseline
** n is # of patients who did not have the test at the end of the study

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

This medical officer selected all of the U.S. POI studies (Studies 13C206, 13C213, 13C214, 302, 308, 313 and 306) to compare laboratory values between the treatment groups because the POI studies were all placebo-controlled, had high doses of alvimopan (up to 24 mg/day), included the proposed patient population (surgery patients undergoing elective bowel resection), and included the proposed duration of use (up to 8 days).

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency
There were no significant differences in the mean changes from baseline among the alvimopan and placebo groups in the U.S. POI studies.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal
There were no significant differences in the percentage of outliers among the alvimopan and placebo groups in the U.S. POI studies.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities
There were no significant differences in the percentage of outliers or dropouts among the alvimopan and placebo groups in the U.S. POI studies.

7.1.7.4 Additional analyses and explorations
In the U.S. POI studies, there were no significant differences in laboratory values among the 6 mg and 12 mg alvimopan treatment groups.

7.1.7.5 Special assessments

Table 54 shows the U.S. POI patients who had elevated liver tests (≥ 3 times normal) at baseline and after treatment. 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).

Medical Reviewer's Comments: There were no significant differences in elevated liver tests (≥ 3 times normal) among the alvimopan and placebo treatment groups.

Table 54: U.S. POI patients with elevated liver tests (≥ 3 times normal)

Liver Test	Visit (1)	placebo (N=748) N (%)	alvimopan 1-3 mg (N=62) N (%)	alvimopan 6 mg (N=604) N (%)	alvimopan 12 mg (N=1024) N (%)	alvimopan total (N=1690) N (%)
ALT	Baseline	0	0	4 (0.7)	0	4 (0.2)
	End of Treatment	4 (0.5)	0	4 (0.7)	4 (0.4)	8 (0.5)
	End of Study	4 (0.5)	0	5 (0.8)	4 (0.4)	9 (0.5)
	Total Post Baseline	6 (0.8)	0	5 (0.8)	5 (0.5)	10 (0.6)
AST	Baseline	1 (0.1)	0	1 (0.2)	2 (0.2)	3 (0.2)
	End of Treatment	1 (0.1)	1 (1.6)	4 (0.7)	8 (0.8)	13 (0.8)
	End of Study	1 (0.1)	1 (1.6)	5 (0.8)	9 (0.9)	15 (0.9)
	Total Post Baseline	4 (0.5)	1 (1.6)	6 (1.0)	11 (1.1)	18 (1.1)
Alkaline Phos	Baseline	2 (0.3)	0	0	0	0
	End of Treatment	3 (0.4)	0	0	1 (0.1)	1 (0.1)
	End of Study	3 (0.4)	0	0	1 (0.1)	1 (0.1)
	Total Post Baseline	4 (0.5)	0	0	1 (0.1)	1 (0.1)
Direct Bilirubin	Baseline	0	0	2 (0.3)	1 (0.1)	3 (0.2)
	End of Treatment	2 (0.3)	0	2 (0.3)	1 (0.1)	3 (0.2)
	End of Study	2 (0.3)	0	2 (0.3)	1 (0.1)	3 (0.2)
	Total Post Baseline	3 (0.4)	0	2 (0.3)	2 (0.2)	4 (0.2)
Total Bilirubin	Baseline	0	0	3 (0.5)	1 (0.1)	4 (0.2)
	End of Treatment	1 (0.1)	0	0	0	0
	End of Study	1 (0.1)	0	0	0	0
	Total Post Baseline	2 (0.3)	0	1 (0.2)	0	1 (0.1)
GGT	Baseline	1 (0.1)	0	0	0	0
	End of Treatment	2 (0.3)	0	0	0	0
	End of Study	2 (0.3)	0	0	0	0
	Total Post Baseline	2 (0.3)	0	0	0	0
LDH	Baseline	1 (0.1)	0	1 (0.2)	1 (0.1)	2 (0.1)
	End of Treatment	1 (0.1)	0	2 (0.3)	3 (0.3)	5 (0.3)
	End of Study	1 (0.1)	0	2 (0.3)	3 (0.3)	5 (0.3)
	Total Post Baseline	2 (0.3)	0	2 (0.3)	3 (0.3)	5 (0.3)

Reference: Adapted from ISS, Table 6.2.5.2.1, Pages 17068-9

7.1.8 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.

7.1.8.1 Selection of studies and analyses for overall drug-control comparisons

Vital signs from the seven U.S. POI trials will be analyzed. Please see Section 7.1.7.1 for the rationale behind this decision.

7.1.8.2 Standard analyses and explorations of vital signs data

7.1.8.2.1 Analyses focused on measures of central tendencies
In the U.S. POI studies, there were no significant differences in the mean or median systolic and diastolic blood pressures, heart rates, respiratory rates, and body temperatures among the placebo and alvimopan groups.

7.1.8.2.2 Analyses focused on outliers or shifts from normal to abnormal
In the U.S. POI studies, there were no significant differences in vital sign outliers among the placebo and alvimopan treatment groups.

7.1.8.2.3 Marked outliers and dropouts for vital sign abnormalities
In the U.S. POI studies, there were no significant differences among the placebo and alvimopan treatment groups in vital sign outliers or dropouts due to abnormal vital signs.

7.1.8.3 Additional analyses and explorations
In the U.S. POI studies, there were no significant differences in vital signs among the 6 mg and 12 mg alvimopan treatment groups.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECGs
In all of the POI studies, ECGs were performed at baseline. In the four main efficacy phase 3 trials (Studies 302, 308, 313, and 001); ECGs were performed at hospital discharge/study termination. In Study 13C206, ECGs were performed 1-14 days after the last dose of study medication. In the Safety Study 306, ECGs were performed 7-10 days after the last dose of study medication. In Study 13C214, 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 13C213, ECGs were performed on POD 3, POD 5, and hospital discharge/study termination.

Non-clinical Studies
The in vitro assays for cardiovascular effects including the effect of alvimopan and its metabolite (ADL 08-0011) on cloned hERG channels expressed in mammalian cells and isolated dog Purkinje fibers were completely negative for any significant cardiovascular pharmacologic effect.

QT/QT_c Clinical Studies
Study SB-767905/016 was a standard four arm (placebo, alvimopan 6 mg BID, alvimopan 24 mg BID, and moxifloxacin 400 mg q day) QT study (randomized, placebo-controlled, and actively-controlled) in healthy subjects. Additionally, Study 13C214 evaluated the QT/QT_c interval.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

All of the U.S. POI studies (Studies 13C206, 13C213, 13C214, 302, 308, 313 and 306) were selected for ECG assessment. Please see the rationale for the selection of these studies in Section 7.1.7.1. Additionally, Study SB-767905/016 was selected for QT analysis because it was a standard QT study that was placebo-controlled and active-controlled in healthy subjects.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency
There were no significant ECG abnormalities (including QT prolongations) that were different among the placebo and alvimopan groups.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal
In the U.S. POI studies, there were no significant differences in shifts from normal to abnormal ECGs among the alvimopan and placebo groups. Please see Table 55 for a summary of the ECG changes from baseline in the U.S. POI population. Only five U.S. POI patients (with normal baseline ECGs) had abnormal ECGs after study drug administration.

Table 55: Summary of ECG changes at the end of the study (compared to the baseline) for the U.S. POI population (Studies 13C206, 13C213, 13C214, 302, 308, 313 and 306)

Baseline	EOS		
	Normal N (%)	Abnormal but NCS N (%)	Abnormal and CS N (%)
Normal			
Placebo (N=235)	167 (71.1)	67 (28.5)	1 (0.4)
Alvimopan 6 mg (N=166)	108 (65.1)	57 (34.3	1 (0.6)
Alvimopan 12 mg (N=429)	325 (75.8)	101 (23.5)	3 (0.7)
Abnormal but NCS			
Placebo (N=224)	66 (29.5)	157 (70.1)	1 (0.4)
Alvimopan 6 mg (N=179)	47 (26.3)	129 (72.1)	3 (1.7)
Alvimopan 12 mg (N=331)	117 (35.3)	211 (63.7)	3 (0.9)
Abnormal and CS			
Placebo (N=5)	1 (20)	1 (20)	3 (60)
Alvimopan 6 mg (N=4)	0	1 (25)	3 (75)
Alvimopan 12 mg (N=5)	1 (20)	2 (40)	2 (40)

Reference: ISS, Table 42, Page 107
EOS – end of study; CS – clinically significant; NCS – not clinically significant

In Study 13C214, there were no significant QT prolongations in the alvimopan groups following surgery. However, 2 patients who received placebo had significant QT prolongations in the postoperative period.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

In the U.S. POI studies, there were no significant differences in ECG outlier abnormalities for the placebo and alvimopan groups. Additionally, there were no differences in the percentages of dropouts for arrhythmias including atrial fibrillation, bradycardia, and tachycardia among the placebo and alvimopan groups.

7.1.9.4 Additional analyses and explorations

In the U.S. POI studies, there were no significant differences in ECG abnormalities or QT prolongations among the 6 mg and 12 mg alvimopan groups. Please see Dr. Sue Chih Lee's detailed review of the QT study (Study SB-767905/016) in her NDA review.

7.1.10 Immunogenicity

Alvimopan is not a protein and does demonstrate evidence for immunogenicity.

7.1.11 Human Carcinogenicity

Since the proposed alvimopan dosage regimen is for short-term use — up to 7.5 days of therapy [one dose prior to surgery (POD 0) then BID on POD 1 to POD 7] — human carcinogenicity studies were not required.

Non-clinical genotoxicity studies were negative. Non-clinical carcinogenicity studies were not required because of the proposed short duration of alvimopan use.

7.1.12 Special Safety Studies

Please see Section 7.1.9 and Dr. Sue Chih Lee's detailed review for more information regarding the QT study (SB-767905/016). There were no other studies designed to evaluate specific safety concerns.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no evidence of withdrawal phenomena; however, the POI studies were of short duration and efficacy was not measured after the study treatment was stopped. There is no evidence of abuse potential with alvimopan.

7.1.14 Human Reproduction and Pregnancy Data

There were no pregnant patients in the short-term alvimopan development program.

7.1.15 Assessment of Effect on Growth

Alvimopan was not studied in the pediatric population. Height measurements were not routinely performed in the alvimopan development program.

7.1.16 Postmarketing Experience

Alvimopan has never been approved in the United States or any foreign country; therefore, no post-marketing data is available.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources Used to Evaluate Safety

The safety population in this review consists of 4181 patients (2902 in the alvimopan group, 1279 in the control group) in 36 alvimopan studies. Table 56 lists the 36 studies and highlights the most important studies for this safety review — the seven POI studies in the United States and the one POI study in Europe. The eight POI studies contain 3326 patients (2285 who received alvimopan and 1041 who received placebo). In the eight POI studies, of the 2285 patients who received alvimopan, 898 and 1321 patients received the 6 mg alvimopan dose and the 12 mg alvimopan dose, respectively (the remaining 66 patients received 1 mg or 3 mg of alvimopan).

Table 56: A summary of the 36 alvimopan studies that comprise the entire safety population

Study	Type of Study	Treatment Arms	N	Day(s)
1) 14C114	Single-dose Healthy subjects	Alvimopan 12 mg	6	1
2) 14CL115	Single-dose Healthy subjects	Placebo Alvimopan 12 mg	18	1
3) RC99-CP006 (CP006)	Single-dose Healthy subjects	Placebo Alvimopan 2 mg	Phase 1: 6 Phase 2: 14	1
4) 13C111	Single-dose Healthy subjects	Alvimopan 1 mg Alvimopan 3 mg Alvimopan 9 mg	42	1
5)14CL124	Single-dose Healthy subjects	Alvimopan 12 mg	24	1
6) 14CL127	Single-dose Healthy subjects	12 mg of Alvimopan	36	1
7) H3G-LC-BGGA	Multiple-dose Healthy subjects	Placebo Alvimopan doses ranged from 1.2 mg/day to 120 mg/day	8	1 day then 3 days
8) 14CL118	Multiple-dose Healthy subjects	Placebo Alvimopan 12 mg BID	10	4.5
9) 14CL119	Multiple-dose Healthy subjects	Placebo BID Alvimopan 6 mg BID, 12 mg BID, 18 mg BID, and 24 mg BID	40	4.5
10) RC99-CP007 (CP007)	Multiple-dose Healthy subjects	Placebo Alvimopan 3 mg TID	13	4
11) 13C109	Multiple-dose Healthy subjects	Placebo Alvimopan 2 mg (two doses)	63	1
12) RC98-CP001 (CP001)	Multiple-dose Healthy subjects	Placebo Alvimopan 0.25 mg to 36 mg TID	44	4
13) H3G-LC-BGGC	Multiple-dose Healthy subjects	Placebo; Alvimopan 24 mg TID; Alvimopan 2.4 mg TID	8	4 to 5
14) 14CL116	Renal failure	Alvimopan 12 mg	24	1
15) 14CL117	Hepatic failure	Alvimopan 12 mg	20	1
16) 14CL123	Geriatric	Alvimopan 12 mg	18	1
17) 14CL125	Crohn's disease	Alvimopan 12 mg	12	1
18) 14CL126	Hepatic failure	Alvimopan 12 mg	10	1
19) RC99-CT001	OBD non-cancer	Alvimopan 0.125 mg, 0.25 mg 1 mg, and then 3 mg	7	4
20) RC99-CT002	OBD non-cancer	Placebo Alvimopan 0.125 mg, 0.25 mg, 1 mg, and then 3 mg	8	5
21) 13C210	OBD non-cancer	Placebo Alvimopan 0.5 mg, 1.5 mg, 3 mg and then 4.5 mg	26	4
22) 13C208	OBD non-cancer	Placebo Alvimopan 0.5 mg Alvimopan 1.5 mg Alvimopan 3 mg	62	1

Reference: Adapted from Volume 133, Table 1, Pages 1-6

Table 56 Continued: A summary of the 36 alvimopan studies that comprise the entire safety population

23) 13C209	OBD non-cancer	Placebo Alvimopan 0.5 mg Alvimopan 1.5 mg Alvimopan 3 mg	13	1
24) 13C217	OBD non-cancer	Placebo Alvimopan 0.5 mg Alvimopan 1 mg	20	21
25) 13C304	OBD non-cancer	Placebo Alvimopan 0.5 mg Alvimopan 1 mg	168	21
26) 13CL223	OBD cancer	Alvimopan 0.25 mg to 1 mg prn	16	Up to 21
27) 13CL224	OBD cancer	Alvimopan 0.25 mg to 1 mg prn	7	Up to 21
28) 13C206*	**POI**	**Placebo Alvimopan 1 mg Alvimopan 6 mg**	**79**	**Up to 8**
29) 13C213*	**POI**	**Placebo Alvimopan 3 mg Alvimopan 6 mg Alvimopan 12 mg**	**153**	**Up to 8**
30) 13C214*	**POI**	**Placebo Alvimopan 12 mg**	**65**	**Up to 8**
31) 13C302* (302)	**POI**	**Placebo Alvimopan 6 mg Alvimopan 12 mg**	**451**	**Up to 8**
32) 13C306* (306)	**POI**	**Placebo Alvimopan 12 mg**	**519**	**Up to 8**
33) 13C308* (308)	**POI**	**Placebo Alvimopan 6 mg Alvimopan 12 mg**	**666**	**Up to 8**
34) 13C313* (313)	**POI**	**Placebo Alvimopan 6 mg Alvimopan 12 mg**	**510**	**Up to 8**
35) SB-767905/001* (001)	**POI**	**Placebo Alvimopan 6 mg Alvimopan 12 mg**	**911**	**Up to 8**
36) SB-767905/016**	QT Study in Healthy Patients	Placebo Alvimopan 6 mg BID Alvimopan 12 BID Moxifloxacin 400 mg q day	162	7

***The eight studies (the POI studies in the U.S. and in Europe) in bold and 12 point represent the most important studies for the safety review.**

** The 36th study (Study SB-767905/016) is the QT safety study in healthy subjects, submitted in the safety update in 10/04

Reference: Adapted from Volume 133, Table 1, Pages 1-6

7.2.1.1 Study type and design/patient enumeration

Please see Table 56 in Section 7.2.1 for a summary of the 36 alvimopan studies that comprise of the entire safety population. Additionally, the following Tables in Section 4.2 contain more detailed information about the 36 studies:

- Table 2 lists the 6 single-dose studies in healthy subjects (14C114, 14CL115, RC99-CP006, 13C111, 14CL124, and 14CL127)
- Table 3 lists the 8 multiple-dose studies in healthy subjects (H3G-LC-BGGA, 14CL118, 14CL119, RC99-CP007, 13C109, RC98-CP001, H3G-LC-BGGC, and SB-767905/016)
- Table 4 lists the 5 studies in special populations (14CL116, 14CL117, 14CL123, 14CL125, 14CL126)
- Table 5 lists the 7 opioid bowel dysfunction (OBD) studies in chronic (non-cancer) pain patients (RC99-CT001, RC99-CT002, 13C210, 13C208, 13C209, 13C217, and 13C304)
- Table 6 lists the 2 OBD studies in chronic cancer pain patients (13CL223 and 13CL224)
- Table 7 lists the 8 POI studies in surgery patients in the United States and Europe (13C206, 13C213, 13C214, 302 , 306, 308, 313, and 001)

7.2.1.2 Demographics

Table 57 lists the demographics (including age, race, gender, weight, and height) of the U.S. POI population (Studies 13C206, 13C213, 13C214, 302 , 306, 308, and 313). Table 58 lists the demographics (including the age, race, gender, weight, and BMI) in the European POI population (Study 001). In the U.S. POI studies, the racial demographics, the heights, and the weights were similar among the alvimopan and placebo treatment groups. In the U.S. studies the median age for the placebo treatment group, the 6 mg alvimopan treatment group, and the 12 mg alvimopan treatment group was 54, 56, and 49, respectively. In the U.S. studies, the percentages of female patients for the placebo group, the 6 mg group, and the 12 mg alvimopan group were 71%, 60%, and 78%, respectively.

In the European study, all three groups had similar demographics. Compared to the U.S. POI population, the European POI population was older, more homogeneous (99% Caucasian), and thinner (lower weight).

Medial Reviewer's Comments: Study 306 accounts for the different ages and gender characteristics of the treatment groups in the U.S. POI population. The population of Study 306 (which included only sTAH patients) was 100% female and had a younger median age than the other POI studies (sTAH patients tend to be younger than rTAH and/or BR patients). Study 306 included 413 patients on 12 mg of alvimopan and 103 patients on placebo due to a 4:1 randomization.

In the entire U.S. POI population, women were more common than men because only women receive rTAH/sTAH surgery and both women and men have BR surgery. The 12 mg alvimopan group had a higher percentage of women (compared to the 6 mg

alvimopan group and the placebo group) because of the 4:1 randomization in Study 306.

Some of the demographic differences between the European and U.S. POI populations can be explained by the disparities in surgical subgroups (the European POI patients were less likely to have gynecologic surgery than the U.S. POI patients).

Table 57: Summary of the demographics in the U.S. POI Studies (13C206, 13C213, 13C214, 302, 306, 308, and 313)

		Alvimopan		
	Placebo (N=748)	6 mg (N=604)	12 mg (N=1024)	Total (N=1690)
Demographic Parameter	N (%)	N (%)	N (%)	N (%)
Age, n (%)				
N	748	604	1024	1690
Mean (yrs)	55.4	57.2	52.4	54.1
SD	14.87	14.85	14.22	14.55
Median	54	56	49	52
Min	20	19	20	19
Max	93	91	93	93
< 65 Years, n (%)	524 (70.1)	395 (65.4)	789 (77.1)	1232 (72.9)
≥ 65 Years, n (%)	224 (29.9)	209 (34.6)	235 (22.9)	458 (27.1)
> 75 Years, n (%)	85 (11.4)	80 (13.2)	76 (7.4)	159 (9.4)
Race, n (%)				
Caucasian	592 (79.1)	493 (81.6)	812 (79.3)	1354 (80.1)
Black	102 (13.6)	74 (12.3)	116 (11.3)	200 (11.8)
Asian	12 (1.6)	5 (0.8)	24 (2.3)	30 (1.8)
Hispanic	35 (4.7)	28 (4.6)	57 (5.6)	87 (5.1)
Other	7 (0.9)	4 (0.7)	15 (1.5)	19 (1.1)
Gender, n (%)				
Female	530 (70.9)	361 (59.8)	800 (78.1)	1212 (71.7)
Male	218 (29.1)	243 (40.2)	224 (21.9)	478 (28.3)
Weight (kg)				
N	746	601	1022	1684
Mean	80.6	80.3	78.8	79.5
SD	20.13	18.77	19.13	19.13
Median	78.2	79	75.8	77.3
Min	37.7	39.5	38.6	38.6
Max	188.2	180.5	167.7	180.5
Height (cm)				
N	744	598	1018	1677
Mean	166.9	168.7	166	166.9
SD	9.77	10.3	9.44	9.81
Median	165.1	167.6	165.1	165.1
Min	134.6	124.5	139.7	124.5
Max	198.1	198.1	200.7	200.7

Reference: Adapted from the ISS, Table 25, Page 72

Table 58: Summary of the demographics in the European POI Study (001)

	Placebo (N=292)	Alvimopan 6mg (N=294)	Alvimopan 12mg (N=297)
Age (years)			
Mean (SD)	62.8 (12.35)	64.0 (12.84)	63.1 (13.52)
Range	24 to 90	21 to 89	20 to 97
Sex [n (%) of subjects]			
Male	137 (47)	143 (49)	144 (48)
Female	155 (53)	151 (51)	153 (52)
Race [n (%) of subjects]			
White/Caucasian	289 (99)	289 (98)	292 (98)
Arabic/North African	1 (<1)	2 (<1)	2 (<1)
Black	0	1 (<1)	1 (<1)
Other	2 (<1)	2 (<1)	2 (<1)
Weight (kg)	n=291	n=292	n=292
Mean (SD)	73.3 (15.03)	73.1 (13.95)	73.4 (15.37)
Range	39 to 160	41 to 130	38 to 132
BMI (kg/m²)	n=285	n=287	n=287
Mean (SD)	26.42 (4.522)	26.33 (4.406)	26.53 (4.908)
Range	15.4 to 46.5	15.1 to 46.1	14.7 to 46.1
BMI Category	n=285	n=287	n=287
<30 kg/m² (%)	237 (83)	237 (83)	226 (79)
≥30 kg/m² (%)	48 (17)	50 (17)	61 (21)

Reference: Study Report for 001, Table 9, Page 69

7.2.1.3 Extent of exposure (dose/duration)

Table 59 and Table 60 list the extent of exposure for the U.S. and European POI populations, respectively.

Table 59: Extent of exposure for the U.S. POI population (Studies 13C206, 13C213, 13C214, 302, 306, 308, and 313)

Parameter/Statistics	Placebo (N=748)	Alvimopan 6 mg (N=604)	Alvimopan 12 mg (N=1024)	Alvimopan Total (N=1690)
Total No. of Doses Received, N (%)				
1	54 (7.2)	42 (7.0)	49 (4.8)	96 (5.7)
2	14 (1.9)	9 (1.5)	13 (1.3)	26 (1.5)
3	11 (1.5)	11 (1.8)	15 (1.5)	27 (1.6)
4	39 (5.2)	41 (6.8)	43 (4.2)	93 (5.5)
5	43 (5.7)	31 (5.1)	36 (3.5)	71 (4.2)
6	96 (12.8)	86 (14.2)	93 (9.1)	195 (11.5)
7	36 (4.8)	35 (5.8)	37 (3.6)	79 (4.7)
8	95 (12.7)	88 (14.6)	102 (10.0)	197 (11.7)
9	32 (4.3)	28 (4.6)	28 (2.7)	59 (3.5)
10	70 (9.4)	101 (16.7)	94 (9.2)	197 (11.7)
11	17 (2.3)	22 (3.6)	25 (2.4)	48 (2.8)
12	59 (7.9)	50 (8.3)	64 (6.3)	117 (6.9)
13	9 (1.2)	9 (1.5)	14 (1.4)	23 (1.4)
14	39 (5.2)	27 (4.5)	53 (5.2)	80 (4.7)
15	134 (17.9)	24 (4.0)	358 (35.0)	382 (22.6)
Total No. of Doses, N				
N	748	604	1024	1690
Mean	8.9	8.0	10.4	9.4
SD	4.31	3.59	4.45	4.32
Median	8.0	8.0	11.0	10.0
Min	1.0	1.0	1.0	1.0
Max	15.0	15.0	15.0	15.0
Treatment Period (Days)				
N	748	604	1024	1690
Mean	5.3	4.9	6.0	5.5
SD	2.15	1.88	2.16	2.12
Median	5.0	5.0	6.0	6.0
Min	1.0	1.0	1.0	1.0
Max	8.0	8.0	9.0[a]	9.0
Total Exposure to alvimopan (mg)				
N	748	604	1024	1690
Mean	0.0	48.0	124.6	93.2
SD	0.00	21.54	53.45	58.83
Median	0.0	48.0	132.0	72.0
Min	0.0	6.0	12.0	1.0
Max	0.0	90.0	180.0	180.0

Reference: ISS, Table 28, Page 80

Table 60: Extent of exposure for the European POI population (Study 001)

		PLACEBO (N=292)	ALVIMOPAN 6MG (N=294)	ALVIMOPAN 12MG (N=297)
Cumulative dose	n	292	294	297
	Mean	0.0	67.4	134.0
	SD	0.00	27.50	58.92
	Median	0.0	78.0	168.0
	Min.	0	6	12
	Max.	0	102	192
Days on study drug	n	292	294	297
	Mean	6.2	6.4	6.3
	SD	2.50	2.30	2.47
	Median	8.0	8.0	8.0
	Min.	1	1	1
	Max.	9	10	9
Doses of study drug	n	292	294	297
	Mean	10.9	11.2	11.2
	SD	4.99	4.58	4.91
	Median	13.5	13.0	14.0
	Min.	1	1	1
	Max.	17	17	16
>15 doses taken	n	2 (<1%)	1 (<1%)	3 (1%)

Reference: Study Report for 001, Table 12.8, Page 578

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

This NDA does not contain secondary clinical data sources.

7.2.2.1 Postmarketing experience

Alvimopan has never been approved in the United States or any foreign country; therefore, no post-marketing data is available.

7.2.2.2 Literature

The most relevant studies found in the literature were studies performed by the sponsor that are part of the primary data source containing 36 studies.

7.2.3 Adequacy of Overall Clinical Experience

Medical Reviewer's Comments: The well-designed trials (randomized, double-blind, placebo-controlled) were adequate to answer critical questions in this NDA.

Since the intended use of alvimopan for the treatment of POI is for short-term (≤ 7.5 days), long-term exposure to alvimopan is not needed. [redacted] are not likely to be used for other indications such as the treatment of OBD. Initial OBD trials have demonstrated (at this early stage) that the most favorable dose is 0.5 mg BID. [redacted] The duration of alvimopan exposure was adequate for the short-term POI indication.

This medical officer asserts that an adequate number of geriatric patients were exposed to alvimopan in the entire alvimopan program. Of the 1690 patients in the U.S. POI studies, 458 (27%) patients were over 65 years old and 175 (9%) patients were over 75 years old. Additionally, the mean age in the European POI study was over 63 years old.

Patients who were excluded from the major phase 3 efficacy BR trials (such as patients who were scheduled for a total colectomy, colostomy, and ileostomy) should not limit the relevance of the safety database. However, physicians should be informed about the lack of demonstrated efficacy in this subgroup of surgery patients (in the investigator brochure or in a future label).

Patients on concomitant opioid analgesics should be contraindicated to use alvimopan because these patients were excluded from the major phase 3 efficacy BR trials. Additionally, alvimopan studies demonstrated a higher incidence of abdominal pain, nausea, and vomiting in patients on concomitant opioids.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

According to Dr. Tamal Chakraborti, the pharmacology/toxicology reviewer, the non-clinical testing was adequate to explore possible AEs from an opioid antagonist. Please see his November 4, 2004 review for more details.

The in vitro assays for cardiovascular effects including the effect of alvimopan and its metabolite (ADL 08-0011) on cloned hERG channels expressed in mammalian cells and isolated dog Purkinje fibers were completely negative for any significant cardiovascular pharmacologic effect.

7.2.5 Adequacy of Routine Clinical Testing

Medical Reviewer's Comments: **The alvimopan POI development program included adequate types of clinical testing including blood tests, vital signs, ECGs. The clinical safety tests performed at baseline and at the end of study drug administration were acceptable.**

However, the alvimopan program was deficient in follow-up testing (testing 7 days after the last dose of study medication). Only one study (Study 306) out of a total of eight POI studies conducted clinical tests 7-10 days after the last dose of study drug administration. Thus, only 519 patients in Study 306 (16%) received adequate follow-up clinical testing out of the total POI population of 3326. Since alvimopan's metabolite (ADL 08-0011) has a long-half life – it takes at least five days after the last alvimopan dose for 95% of ADL 08-001 to be cleared from the body – follow-up clinical testing (about seven days after the last alvimopan dose) is necessary.

Since there are demographics disparities between Study 306 and the rest of the POI population, extrapolation of the follow-up safety data may not be possible to the rest of the POI population. The following are some demographic differences of Study 306 (compared to the rest of the POI population):

- **The mean age in Study 306 was 44; in contrast, the mean age in the entire POI population was 57.**
- **In Study 306, about 5% of the population had an underlying malignancy; in contrast, about 62% of the entire POI population had an underlying malignancy.**

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Please see Dr. Sue Chih Lee's review for details regarding drug-drug interaction assessments, the effects of alvimopan on CYP450 enzymes, and identification of enzymatic pathways responsible for alvimopan clearance.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The sponsor's efforts to detect specific cardiac and hepatic AEs were adequate.

7.2.8 Assessment of Quality and Completeness of Data

The overall quality and completeness of data was acceptable. The sponsor appropriately divided the entire alvimopan safety population into the following groups: healthy subjects, OBD cancer patients, OBD non-cancer patients, POI patients, patients with hepatic insufficiency, patients with renal insufficiency, Crohn's disease patients, and geriatric patients. However, the sponsor did not combine the subgroup data sets into one comprehensive population. Additionally, the sponsor did not analyze this complete population (containing all of the above subpopulations).

The sponsor divided the POI safety population into two groups: the seven U.S. POI trials and the one European trial. The sponsor did not analyze pooled safety data from the U.S. and European POI populations. Additionally, some of the safety data from the European POI trial were in different units than the data in the U.S. POI trials and this made it difficult to interpret the entire data set.

7.2.9 Additional Submissions, Including Safety Update

On October 22, 2004, the sponsor submitted a 120-day safety update report. The safety update contained the results of the QT study (Study SB-767905/016), a list of recently initiated studies, a list of ongoing studies, and blinded SAE data from the ongoing studies through August 20, 2004 (the original safety cut-off date was March 15, 2004). Please see Dr. Sue Chih Lee's review for a full evaluation of Study SB-767905/016.

On April 8, 2005, the sponsor submitted the results of their phase 3 POI study in European patients (Study 001). Since this important phase 3 safety/efficacy study was considered a

major amendment, the Prescription Drug User Fee Act (PDUFA) goal date was extended for three months to July 25, 2005. The results of Study 001 were incorporated into the major sections of this review. Unfortunately, the sponsor did not pool the safety results of the four U.S. POI studies with Study 001.

7.3 Summary of Selected Drug-Related AEs, Important Data Limitations, and Conclusions

Compared to the placebo treatment group, both alvimopan treatment groups had similar rates of the following events: deaths; SAEs; discontinuations due to AEs; common AEs; uncommon AEs; and laboratory, ECG, and vital sign abnormalities. There were no significant drug-related adverse events in the POI population.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Deaths and SAEs were pooled from all 36 alvimopan studies. Discontinuations, common AEs, less common AEs, laboratory findings, vital signs, and ECGs were obtained for two populations: the pooled results from the seven U.S. POI studies (Studies 13C206, 13C213, 13C214, 302 , 306, 308, and 313) and the single European POI study (Study 001).

7.4.1.2 Combining data

In pooling data for this review, the numerator events of the selected studies were combined and the denominator events of the selected studies were combined. Weighting methods were not used in this review because the POI studies were very similar in design.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

This is not applicable.

7.4.2.2 Explorations for time dependency for adverse findings

This is not applicable.

7.4.2.3 Explorations for drug-demographic interactions

This is not applicable.

7.4.2.4 Explorations for drug-disease interactions

This is not applicable.

7.4.2.5 Explorations for drug-drug interactions

This is not applicable.

7.4.3 Causality Determination

This is not applicable.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Medical Reviewer's Comments: **Given the efficacy deficiencies of both doses (alvimopan 6 mg and alvimopan 12 mg) in the treatment of POI, this medical officer cannot recommend a specific alvimopan dose at this time. Neither dose has demonstrated superior efficacy compared to placebo in the treatment of POI.**

From a safety perspective, both the 6 mg and 12 mg alvimopan doses appeared safe in the dosage regimen. The alvimopan treatment groups did not demonstrate a higher incidence of death, SAEs, study discontinuation, or common AEs compared to the placebo treatment group. Additionally, both doses demonstrated equivalent safety — to one another — in the alvimopan development program.

In the sponsor's proposed dosing regimen (which is very similar to the dosing in the four important phase 3 efficacy trials), patients receive the first alvimopan dose 0.5 to 5 hours prior to the scheduled start of surgery. Thus, if surgery is canceled, patients may be exposed to one unnecessary alvimopan dose. Therefore, this medical officer will encourage the sponsor to consider alternative dosing regimens in their future POI trials. For example: If the first alvimopan dose is administered after surgery on POD 0, then the former situation could be prevented.

In summary, since the efficacy of neither of the two alvimopan doses was demonstrated, this medical officer cannot recommend an alvimopan dosing regimen.

8.2 Drug-Drug Interactions

According to Dr. Sue Chih Lee, alvimopan has no significant drug-drug interactions.

8.3 Special Populations

Gender: From the safety perspective, males and females had similar percentages of treatment-related AEs, SAEs, and discontinuations from AEs in the U.S. POI population.

Race: From the safety perspective, Caucasians and African-Americans had similar percentages of treatment-related AEs, SAEs, and discontinuations from AEs in the U.S. POI population.

Geriatrics: From the safety perspective, geriatric patients (compared to patients under 65 years old) were more likely to have slightly higher treatment-related AEs, SAEs, and discontinuations from AEs in the U.S. POI population. However, the death rate was similar in the two groups.

Hepatic insufficiency: In Study 14C126, out of the three severe hepatic insufficiency patients who received alvimopan, one patient developed very high alvimopan blood levels and two patients had only slightly higher alvimopan levels (compared to patients without hepatic disease). Patients with mild to moderate hepatic insufficiency had similar alvimopan pharmacokinetics compared to patients without hepatic disease.

Renal insufficiency: In Study 14CL116, out of the six patients with severe renal insufficiency who received alvimopan, two patients developed high ADL 08-0011 blood levels (alvimopan's metabolite). Mild and moderate renal insufficiency patients did not have significant differences in alvimopan or ADL 08-0011 blood levels compared to patients without renal insufficiency. Alvimopan was not studied in end-stage renal disease patients or dialysis patients.

Medical Reviewer's Comments: Gender, Race, and Geriatrics: This medical officer believes that the differences in AE rates between geriatric patients and patients less than 65 years old are likely to higher surgery morbidity associated with increased age and not due to alvimopan effects on geriatric patients.

In summary, there are no special dosing considerations for gender, race, or age.

Hepatic and renal insufficiency: Since the exposure of alvimopan in severe hepatic insufficiency patients is limited, these patients should not receive alvimopan. Patients with mild to moderate hepatic impairment should be closely monitored for AEs (e.g. diarrhea, abdominal pain). Dosage adjustments based solely on mild to moderate hepatic insufficiency are not required.

Patients with severe renal disease should be closely monitored for AEs that could indicate higher metabolite levels. Dosage adjustments based solely on mild to moderate renal insufficiency are not required.

8.4 Pediatrics

During the pre-NDA meeting, the DGICDP agreed with the sponsor that all pediatric studies will be deferred until the NDA is approved in adults. No consultations with the Division of Pediatric Drug Development have taken place for this NDA.

8.5 Advisory Committee Meeting

After the original assessment of this NDA submission by the DGICDP, the clinical meaningfulness of the efficacy of alvimopan in the treatment of POI appeared equivocal. The DGICDP communicated to the sponsor that an Advisory Committee (AC) Meeting may help elucidate the clinical value of alvimopan in the treatment of POI since this was the first proposed drug product in the treatment of POI. Subsequently, the DGICDP and the sponsor began to prepare for an AC Meeting on the efficacy of alvimopan in the treatment of POI.

Afterward, the DGICDP learned of a fourth efficacy POI study (001). After initial review of Study 001 and a detailed review of the original three efficacy studies, the DGICDP found that both alvimopan treatment groups only demonstrated statistical significance (over placebo) in one out of the four important efficacy studies. Given the lack of efficacy of alvimopan and the knowledge that a fifth phase 3 efficacy study (14CL314) was ongoing and would be unavailable for an AC Meeting, the DGICDP canceled the AC Meeting (the meeting was canceled prior to a public announcement). In addition, the DGICDP informed the sponsor that the AC Meeting was cancelled and the DGICDP outlined efficacy deficiencies in their NDA submission.

8.6 Literature Review

Literature in this review is referenced throughout the review.

8.7 Postmarketing Risk Management Plan

No post-marketing risk management plan was needed and no plan was submitted.

8.8 Other Relevant Materials

There are no additional relevant materials.

9 OVERALL ASSESSMENT

9.1 Conclusions

In summary, both alvimopan doses demonstrated a good safety profile. However, the efficacy of both alvimopan doses in the treatment of postoperative ileus was not demonstrated. In the gynecologic subpopulation, both alvimopan doses did not demonstrate efficacy in the treatment of postoperative ileus. In the GI subpopulation, each alvimopan dose demonstrated statistical significance in only one out of four studies for the primary efficacy endpoint (recovery of both upper and lower GI tract motility). The clinical meaningfulness of the positive statistical results is questionable. Additionally, both alvimopan doses demonstrated poor concordance of positive efficacy results. It remains unclear why the higher alvimopan dose (12 mg) was ineffective in the study that demonstrated some efficacy in the lower alvimopan dose (6 mg).

9.2 Recommendation on Regulatory Action

This medical officer recommends an **approvable** action for the 12 mg dose of Entereg™ (alvimopan) Capsules to accelerate the time to recovery of upper and lower gastrointestinal tract motility following partial large or partial small bowel resection surgery with anastomosis.

[redacted]

To obtain approval of the 12 mg dose of alvimopan for this postoperative ileus indication, the sponsor must:

1) Provide at least one additional adequate and well-controlled study (in patients scheduled to have partial large or partial small bowel resection surgery with anastomosis) that demonstrates statistical significance and clinical meaningfulness of the 12 mg alvimopan dose.
2) Demonstrate the clinical meaningfulness of the results of the 12 mg alvimopan dose in Studies 313 and 308. This medical officer believes that an Advisory Committee Meeting will be required to recommend the clinical meaningfulness of these results.

9.3 Recommendation on Postmarketing Actions

Post-marketing actions are not applicable.

9.3.1 Risk Management Activity

Risk management activity is not applicable.

9.3.2 Required Phase 4 Commitments

Phase 4 commitments are not applicable.

9.3.3 Other Phase 4 Requests

Other phase 4 requests are not applicable.

9.4 Labeling Review

Since this medical officer believes that the efficacy of alvimopan in the treatment of POI is equivocal, a labeling review will not be performed.

9.5 Comments to Applicant

Please see Section 1.3.2 (the Efficacy subsection of the Executive Summary) for the major deficiencies in this NDA.

10 APPENDICES

10.1 Review of Individual Study Reports

The individual study reports are included in Section 6.1.3.

10.2 Line-by-Line Labeling Review

This section is not applicable.

10.3 Abbreviations

Please see Table 61 for a list of abbreviations and definitions used in this review.

Table 61: List of abbreviations and definitions

AEs	adverse drug events
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BID	two times a day
BM	Bowel Movement
BMI	Body mass index
BR	Bowel Resection
CI	Confidence Interval
C_{max}	Maximum observed plasma concentration
COSTART	Coding Symbols for a Thesaurus of Adverse Reactions Terms
CYP	Cytochrome
DB	Double-blind
DGICDP	Division of GI and Coagulation Drug Products
EPSBO	Early post-operative small bowel dysfunction
EE	Efficacy evaluable (per protocol)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI^2	Time to recovery of GI function as determined by a 2-component composite endpoint (time to first BM and toleration of first solid food). Mathematically represented by GI^2 = max (BM, solids)
GI^3	Time to recovery of GI function as determined by a 3-component composite endpoint (flatus, BM, and solid food). Mathematically represented by GI^3 = max (min (flatus, BM), solids)
HR	Hazard Ratio
lbs	Pounds
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	Intent-to-treat
LDH	Lactate Dehydrogenase
LOCF	Last Observation Carried Forward
Max	Maximum
MC	Multi-centered
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
Min	Minimum

Table 61 Continued: List of abbreviations and definitions

MITT	Modified Intent-To-Treat
mL	Milliliter
mm	Millimeters
ng	Nanogram
NGT	Nasogastric tube
NSAID	non-steroidal anti-inflammatory drug
OBD	Opioid Bowel Dysfunction
PC	Placebo-controlled
PCA	Patient-controlled analgesia
PD	Pharmacodynamic
PK	Pharmacokinetic
POD	Postoperative day is based on a calendar day. POD 0 was the date when a patient had his/her surgery regardless of when the surgery was completed. POD 1 was the next calendar date.
POI	postoperative ileus
prn	As needed
PSD	Post-surgery day — A 24-hour period after the end of surgery, not based on the calendar date.
q d	Once daily
R	Randomized
rTAH	radical total abdominal hysterectomy — complete removal of the uterus, upper vagina, parametrium through an incision in the abdominal wall with lymph node excision and/or exploration of the retroperitoneal space.
SAE	Serious adverse event
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
sTAH	simple total abdominal hysterectomy
SOC	System Organ Class
TAH	total abdominal hysterectomy
TEAE	Treatment Emergent Adverse Event — An AE that had an onset date/time on or after the day/time of the first dose of study medication administration, and up to 7 days after the last dose of study medication, and was not present at baseline, or was present at baseline, but increased in severity after the start of study medication treatment.
T_{max}	Time to reach the observed maximum plasma concentration
VAS	Visual Analog Scale

11 REFERENCES

Please see each Table in the document for all the references.

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/s/

Eric Brodsky
7/12/05 09:49:50 AM
MEDICAL OFFICER

Ruyi He
7/12/05 09:59:48 AM
MEDICAL OFFICER

08/10/04

MEMORANDUM

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

DATE: August 10, 2004

TO: NDA 21-775/S-000

THROUGH: Robert Justice, MD, Division Director
Division of Gastrointestinal and Coagulation Drug Products
HFD-180

FROM: Eric Brodsky, MD, Medical officer
Division of Gastrointestinal and Coagulation Drug Products
HFD-180

SUBJECT: **Review Classification of Entereg™ (Alvimopan, ADL 8-2698)**
NDA 21-775/S-000

Adolor Corporation (Adolor) submitted the complete New Drug Application for Entereg™ (Alvimopan, ADL 8-2698) Capsules on June 25, 2004 for the prevention of postoperative ileus in patients who have elective gastrointestinal (small or large bowel resection with primary anastomosis) or pelvic surgery (total abdominal hysterectomy). Adolor requests a priority review classification for Entereg because "Entereg will provide a significant improvement in the management of postoperative ileus ... following abdominal or pelvic surgery."

During the Entereg filing meeting on August 6, 2004, the clinical review team decided that a priority review classification should be denied for the following reasons:

1) For the proposed 12 mg Entereg dose, the efficacy results from the four Phase III post-operative ileus trials (302, 308, 313, and 306) are not impressive. For the 12 mg proposed dose, only one of the four Phase III efficacy trials (313) had a statistically significant positive primary endpoint [the time to tolerate the first solid meal and (the time to the first bowel movement or first flatus)] and only two of the four Phase III trials (313 and 308) had a statistically significant important secondary endpoint (time to discharge written).

2) The demonstration of a positive primary efficacy endpoint for the 12 mg Entereg dose in trial 313 may have been due to the poor placebo response.

Therefore from our preliminary evaluation, the proposed 12 mg Entereg dose may not provide a significant improvement in the management of post-operative ileus following abdominal or pelvic surgery.

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/s/

Eric Brodsky
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Ruyi He
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