ADOLOR CORPORATION

ENTEREG® (alvimopan) Capsules

for

Postoperative Ileus (POI)

Gastrointestinal Drugs Advisory Committee

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1. EXECUTIVE SUMMARY

The purpose of this Gastrointestinal Drugs Advisory Committee Meeting is to discuss the safety and efficacy of the new drug application (NDA) 21–775, Entereg® (alvimopan) Capsules, for the proposed indication of acceleration of time to upper and lower gastrointestinal (GI) recovery following partial large or small bowel resection (BR) surgery with primary anastomosis. This Briefing Document has been prepared for members of Advisory Committee to support use of Entereg (alvimopan) for the management of postoperative ileus (POI) and as such, includes a summary of the efficacy and safety of alvimopan in the POI population. In addition, the document summarizes safety findings from clinical studies evaluating the potential long-term, chronic use of alvimopan for treatment of opioid-induced bowel dysfunction (OBD).

Alvimopan is an orally administered, peripherally-acting µ-opioid receptor antagonist that reverses opioid-induced changes in the GI tract without affecting opioid-induced analgesia. Alvimopan is the first compound of this class to be considered for the treatment of POI. Alvimopan has been in clinical development since 1999. There are currently two alvimopan development programs. Adolor is developing alvimopan for the indication of POI (acute, in-patient use), while GlaxoSmithKline (GSK) is developing alvimopan for the treatment of OBD (chronic, out-patient use). Alvimopan received Fast Track Status in February 2004 for the proposed use in the management of POI. The basis for this designation was that POI is a serious condition for which no drugs have been approved and alvimopan appeared to be a safe and effective treatment for this unmet medical need.

The NDA for POI was submitted in June 2004. During the time of the NDA review, Adolor began a new Phase 3 study of alvimopan, 12 mg, twice daily (BID), in BR patients only (Study 14CL314) and GSK initiated the Phase 3 program for OBD. In July 2005 the FDA issued a NDA "Approvable Letter" requesting additional POI efficacy data (i.e., 14CL314). The final data from 14CL314 were submitted by Adolor in May 2006.

During the FDA's review of 14CL314, interim data from a 12-month GSK safety study in OBD (GSK014) revealed an imbalance in the number of myocardial infarctions (MIs). The findings were discussed with the FDA and the study continued with increased safety monitoring. In November 2006, the FDA issued a second "Approvable Letter" for POI, requesting final safety data in OBD from Study GSK014. Final data revealed no additional events of MI; however, 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 GSK014 led to an interim analysis of the ongoing extension study in cancer pain (GSK684) 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 to allow further statistical evaluation of the data and a clinical evaluation of the reported events. Investigators and regulatory authorities were promptly notified. The final safety data from the OBD studies was submitted in August 2007.

The data presented in this briefing document support the following statements:

- POI occurs in all patients following BR and remains a serious condition with an unmet medical need

- POI increases patient risk for postoperative complications following BR

- Alvimopan 12 mg, administered as a single dose preoperatively and BID for up to 7 days postoperatively in patients undergoing BR with primary anastomosis, significantly accelerates GI recovery, leading to shortened length of hospital stay (LOS) and a reduction in morbidity related to POI.

- The improvement in patient recovery milestones demonstrated with alvimopan treatment in BR patients occurred in the presence of standardized accelerated care pathway.

- The benefits associated with alvimopan treatment in patients undergoing BR are clinically meaningful.

- Alvimopan is well tolerated with no evidence of increased cardiovascular risk in patients undergoing BR.

- The numeric imbalance in reports of MI, neoplasm, and bone fracture adverse events (AEs) in the long-term OBD study (GSK014) likely represent an isolated finding; a causal relationship with alvimopan has not been established. Prospective evaluation in the OBD population will be required to further evaluate these findings.

- Stratified and multivariate analysis suggest that the imbalance in reported deaths observed in GSK008 and GSK684 may have been largely due to the selection of sicker patients with poorer prognosis into the alvimopan treatment group.

- The overall benefit/risk profile for alvimopan in patients undergoing BR is positive and supports use in this population for the management of POI.

1.1   Postoperative Ileus (POI)

Although there is no universally accepted definition of POI, it is characterized by a transient cessation of bowel function with a variable reduction in motility sufficient to prevent effective transit of intestinal contents. Patients undergoing BR are at highest risk for developing POI, occurring in all cases. Signs and symptoms of POI correlate with a lack of normal GI function and may include abdominal distention and bloating, persistent abdominal pain, nausea, vomiting, variable reduction of bowel sounds, delayed passage of or inability to pass flatus or stool, and inability to tolerate oral intake or progress to a solid diet.

While these symptoms are inherently undesirable, the physiologic complications of ileus include substantial morbidity. Atelectasis associated with abdominal distention as well as pain preventing deep inspiration carry the risk of pneumonia. Vomiting in the postoperative period, when patients are frequently reclining and under the effect of the sedative properties of narcotics, is a significant risk factor for aspiration and pneumonia. The need to place a nasogastric (NG) tube once nausea and vomiting have become manifest carries its own risks,

including gastroesophageal reflux, atelectasis, and pneumonia, as well as universally experienced intense discomfort and attendant immobility.

From "simple" POI to complicated/prolonged POI, there is an associated morbidity of temporary malnutrition, be it minimal (i.e., 1 to 2 days) or prolonged (i.e., over the course of 4 to 5 days or more). Daily nitrogen loss is common following laparotomy due to the stress associated with surgery and the inability to tolerate adequate enteral nutrition until resolution of POI, which often takes 5 days or longer. Maintenance of oral feeding high enough in caloric content to result in positive nitrogen balance is therefore a clinical challenge following laparotomy for BR and fails in up to 25% of patients. As a result, these patients are at risk for slipping into a state of negative nitrogen balance, which may lead to weight loss, fatigue, deconditioning, and compromised immunity.

Opioids are the mainstay for postoperative pain management. However, they are a known and significant contributing factor to the pathogenesis of POI. Although highly effective analgesics, opioids bind to μ receptors in the GI tract, disrupting normal GI motility and prolonging the duration of POI. This physiologic effect of opioids on the GI tract may lead many physicians to wean or taper analgesia prematurely.

Despite the recognition that POI represents a serious medical condition, there is no approved treatment. The impact of POI is substantial and clinically serious. The effective management of POI, while maintaining effective postoperative analgesia, represents a continuing unmet medical need, the satisfaction of which will represent a major advance in postoperative patient care.

1.2   Summary of Major Efficacy Findings

A total of five Phase 3 studies (four in North America [NA] and one outside of NA) have been conducted in patients at risk of developing POI. These studies included patients undergoing laparotomy for BR with primary anastomosis or total abdominal hysterectomy (TAH) and scheduled to receive opioid-based, intravenous (IV), patient-controlled analgesia (PCA) for postoperative pain management. All five studies were randomized, double-blind, placebo-controlled, parallel studies of alvimopan versus placebo in hospitalized patients. All Phase 3 POI studies utilized a standardized accelerated postoperative care pathway consisting of early NG tube removal, early ambulation, and early diet advancement. Studies 14CL302 and 14CL308 enrolled patients either undergoing TAH or partial BR with primary anastomosis. Studies 14CL313 and GSK001 (ex-NA study) consisted primarily of BR patients. Doses of 6 and 12 mg were evaluated. In these four trials, clinical benefit was demonstrated only in the BR population; therefore, the final NA study (14CL314) enrolled only BR patients comparing 12 mg alvimopan to placebo.

Based on the results of the Phase 3 studies, data presented in the efficacy section of this document will be limited to the BR population, the indication for which an approval is requested. Additionally, the efficacy data in this document are focused on the results of the 12 mg dose group vs. placebo, as this is the proposed dose for approval.

Although POI is widely recognized as a significant medical concern following BR surgery, an established clinical trial endpoint that measures patient benefit was not available when the clinical development program began. This is frequently the case for innovative therapies when establishing the first effective treatment for a condition. There is, however, general agreement that providing a reduction in the time to GI recovery following BR surgery is clinically meaningful to the patient. The multiple other endpoints (i.e., discharge from the hospital and postoperative NG tube insertion), characterize further the benefits of accelerated GI recovery following BR surgery. Additionally, consistent trends in the reduction of complications associated with POI are another way to confirm the clinical relevance of earlier GI recovery following BR surgery.

The following criteria demonstrate robust, reproducible, and clinically meaningful patient benefits achieved with alvimopan in the Phase 3 efficacy studies:

- Accelerated upper and lower GI recovery (i.e. earlier resolution of POI)

- Earlier discharge from the hospital

- Reduction in complications associated with POI

1.2.1   GI Recovery

In order to have a single measure that indicates the recovery of both upper and lower GI function, a composite endpoint was derived from the individual GI events (solids, bowel movement [BM] and flatus). This composite measure was expressed in one of two ways: as GI-3—defined as the last to occur of the following events: time to first solids and either BM or flatus (which ever occurred first)—and GI-2—which excludes flatus. By the prespecified primary analysis method, the Cox Proportional Hazards (Cox PH) model; the hazard ratios (HRs) for each of the individual GI recovery events in all five studies were always greater than one when comparing alvimopan 12 mg with placebo, indicating a higher probability of achieving GI recovery during the study period with alvimopan treatment.

The HRs and 95% confidence intervals (CIs) from the Cox PH model analysis of GI-3 and GI-2 are presented in Figure 1. Three of the five studies (14CL313, 14CL314, and GSK001) were composed of primarily or exclusively BR patients (87% to 100% of modified intent-to-treat [MITT] patients). The treatment effect for GI recovery indicated by the primary endpoint (GI-3 for 14CL313 and GSK001; GI-2 for 14CL314) was statistically significant in two of the three studies: 14CL313 (HR = 1.494, p = 0.001) and 14CL314 (HR = 1.533, p < 0.001). However, statistical significance was not achieved in GSK001 (HR = 1.132, p = 0.200).

The remaining two NA studies (14CL302 and 14CL308) comprised approximately 70% BR patients; therefore, the results were based on subgroup analyses. Treatment effect for GI recovery, as represented by GI-3, in these two studies did not achieve statistical significance: 14CL302 (HR = 1.295, p = 0.086) and 14CL308 (HR = 1.317, p = 0.029, not significant after adjustment for multiple comparisons). GI-2 was statistically significant (p < 0.05) in all five studies, and HRs ranged from 1.299 to 1.625.

Figure 1   Hazard Ratios and 95% CIs for GI-2 and GI-3 by Individual Study
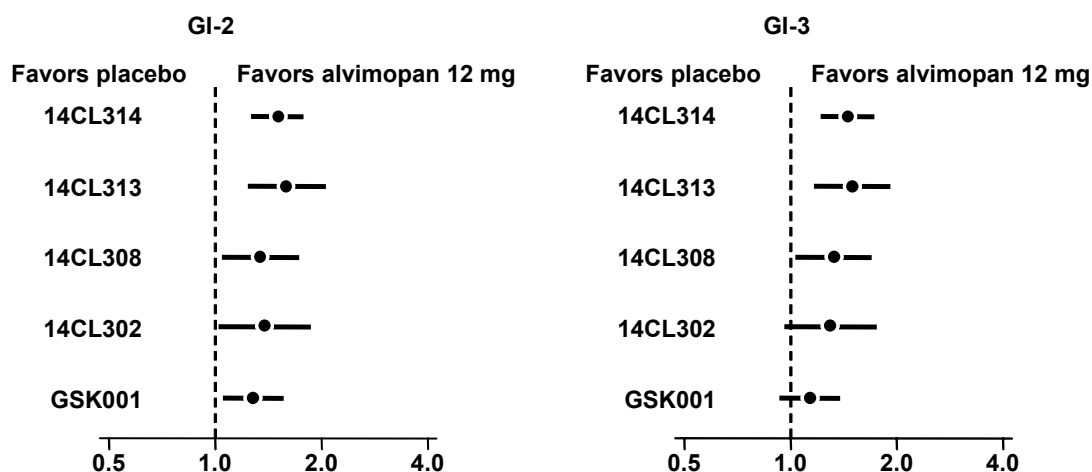
Note: HR and 95% CI were plotted on a log (2) scale. HR = hazard ratio; CIs = confidence intervals.

1.2.2   *Hospital Discharge*

The time from the end of surgery to when the patient was ready for discharge based on GI recovery (READY) and when the discharge order was written (DOW) represented the length of hospital stay (LOS). Using the Cox PH model for time to READY and DOW, the HR was always greater than one when comparing alvimopan 12 mg with placebo in all five studies, indicating a higher probability of achieving the event during the study period with alvimopan 12 mg than with placebo. The HRs and 95% CIs from the Cox PH model analysis of READY and DOW are presented in Figure 2.

Figure 2   Hazard Ratios and 95% CIs for Time to READY and DOW
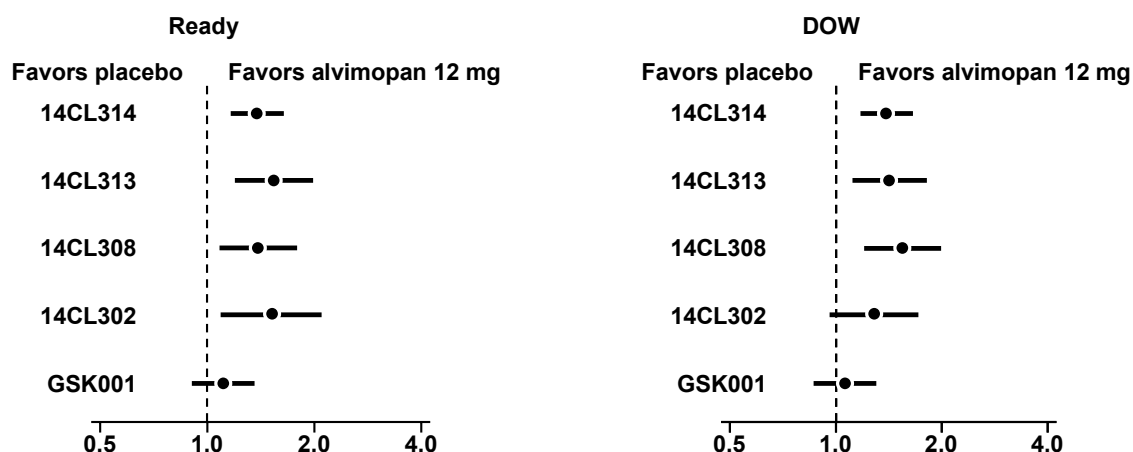
Note: HR and 95% CI were plotted on a log (2) scale. HR = hazard ratio; CIs = confidence intervals.

The average LOS (day of surgery to the day of DOW) for patients who received alvimopan 12 mg or placebo in each of the five studies is presented in Table 1. In three of the five studies, patients who received alvimopan 12 mg had shorter average LOS than those who received placebo, with an average difference of approximately one day.

Table 1   Average Length of Stay (Days) by Study

Treatment	Study 14CL314	Study 14CL313	Study 14CL308	Study 14CL302	Study GSK001
Placebo	6.2	7.4	6.6	6.4	9.2
Alvimopan 12 mg	5.2	6.1	5.7	6.1	8.9
Difference	1.0	1.3	0.9	0.3	0.2

1.2.3   Early Morbidity Related to POI

A patient was considered as having postoperative morbidity (POM) related to POI if either of the following conditions was met: (1) postoperative NG tube insertion, or (2) complications of POI resulting in prolonged hospital stay or readmission within 7 days of actual discharge as measured by serious adverse event (SAE) reports. As shown in Figure 3, each of the five individual studies shows a lower proportion of patients with POM in the alvimopan 12 mg group compared with the placebo group.

Figure 3   Proportion of Patients With Postoperative Morbidity by Study
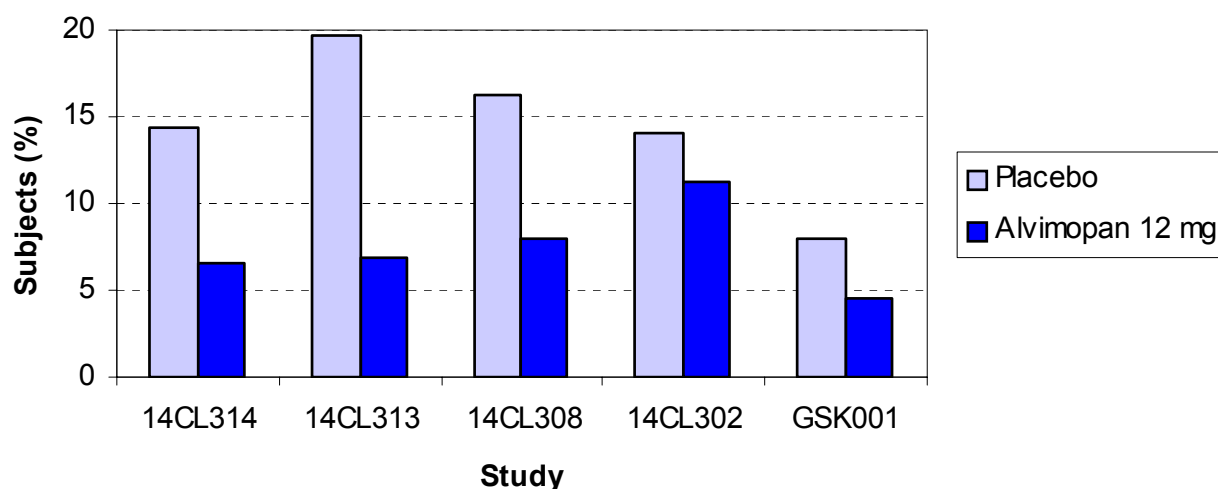
1.3   Summary of Major Safety Findings

1.3.1   Postoperative Ileus

Nine POI studies in patients scheduled to receive opioid-based IV PCA for postoperative pain management after either segmental BR with primary anastomosis or TAH have been

completed. A total of 3975 patients are included in the worldwide POI safety database, 1365 patients received placebo and 2610 patients received alvimopan. A total of 2667 BR patients are included in the BR safety database, 986 received placebo and 1681 received alvimopan. The dosing regimen for all studies was the following: one dose preoperatively followed by BID starting on postoperative day (POD) 1 until discharge or up to a maximum of 7 days. POI patients in the worldwide safety database received a median of 9 to 10 doses of study drug over a median duration of 6 days.

As shown in Table 2, the incidence of nausea and vomiting were lower in both alvimopan groups compared with the placebo group among patients who underwent BR. The incidence of all other treatment-emergent adverse events (TEAEs) among BR patients was similar across treatment groups.

Table 2   Most Common Treatment-Emergent Adverse Events Reported in the BR Population

	Placebo N=986 n (%)	Alvimopan		
		6 mg N=663 n (%)	12 mg N=999 n (%)	Total[b] N=1681 n (%)
Preferred Term[a]				
Nausea	491 (49.8)	246 (37.1)	433 (43.3)	691 (41.1)
Vomiting	209 (21.2)	111 (16.7)	141 (14.1)	256 (15.2)
Hypertension	117 (11.9)	84 (12.7)	126 (12.6)	213 (12.7)
Abdominal distension	137 (13.9)	59 (8.9)	120 (12.0)	183 (10.9)
Pyrexia	144 (14.6)	64 (9.7)	102 (10.2)	168 (10.0)

a A patient who had more than one AE in the same category was counted only once.

b The 19 BR patients in the alvimopan 1- to 3-mg group are included in the alvimopan total.

The percentage of patients who reported SAEs was lower in the alvimopan treatment groups than in the placebo group. The incidence of POI reported as an SAE was 4- and 5-fold lower in the alvimopan 6 mg and alvimopan 12 mg groups, respectively, compared with the placebo group. All other SAEs were reported at similar rates across the three treatment groups. A total of 22 (9 placebo and 13 alvimopan) deaths were reported in the POI safety database. No SAE leading to death occurred at a frequency of $\geq 1\%$.

Nausea, vomiting, and POI were the most common TEAEs leading to discontinuation in any treatment group. The percentage of patients who discontinued due to vomiting or POI was somewhat lower in the alvimopan treatment groups than in the placebo groups.

Overall, the AE profile for alvimopan was consistent with what would be expected in patients undergoing abdominal surgery. Alvimopan was well tolerated in all studies. The incidence of AEs in the alvimopan treatment groups was comparable to that reported in the placebo groups.

The mortality rate in all POI studies combined was less than 1% in both the alvimopan and placebo treatment groups, with no treatment-related, treatment-emergent deaths as determined by the investigator (with the exception of one placebo patient in a non-US site whose cause of

death and relationship to treatment was not determined by the investigator and therefore was included per convention in the treatment-related category).

The incidence of MI as determined both by AE reporting from clinical trials and by independent blinded adjudication based on patient-level data (Duke Clinical Research Institute) is consistent with expected rates in the POI population and was comparable between alvimopan and placebo treatment groups.

Anastomotic leak is one of the most serious complications after BR surgery and significantly increases patient morbidity and mortality. In the Phase 3 studies, no evidence was found that the risk for anastomotic leak was increased with alvimopan treatment. The incidence of anastomotic leak was low and similar in patients receiving either 12 mg alvimopan (0.8%) or placebo (0.8%).

1.3.2   *Chronic Opioid-Induced Bowel Dysfunction*

Evidence of the safety of alvimopan in OBD patients is drawn from more than 1800 patients who received alvimopan in eight clinical studies conducted in the US and elsewhere.

In May 2006 during the course of the 12-month safety study, GSK014, GSK noted an imbalance of MIs in this study. Seven events occurred in the alvimopan arm and none in the placebo arm These events occurred in patients with pre-existing CV disease or underlying CV risk factors. GSK concluded that while the difference in rates of MIs and related SAEs in GSK014 compared to other OBD studies remained unexplained, the imbalance of events observed on alvimopan vs. placebo in GSK014 was not supported by the incidence of events in all OBD studies.

As the increased number of total MIs and related events in GSK014 could have been due to chance, GSK Global Safety Board determined that the study should continue with appropriate safeguards put in place to assure patient safety. Subsequently, GSK convened an Independent Data Monitoring Committee (IDMC) to ensure uniform evaluation of CV AEs and to make recommendations appropriate to protect patient safety in studies with alvimopan for the treatment of OBD.

Following the completion of GSK014 and the unblinding of data in March 2007, the initial analysis of the frequency of AEs by MedDRA (Medical Dictionary for Regulatory Activities) system organ class showed a numerical imbalance in the reports of benign and malignant neoplasms in the alvimopan treatment arm as well as an increase in the incidence of bone fractures compared to placebo. The identification of the imbalance in neoplasms in GSK014 led to an interim analysis of the ongoing extension study in cancer pain (GSK684) 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 to allow further statistical evaluation of the data and a clinical evaluation of the reported events. Investigators and regulatory authorities were promptly notified and in response to GSK's voluntary actions, FDA placed the alvimopan development program on clinical hold.

During the interval between unblinding of the final data from GSK014 and submission of the POI Complete Response (approximately 5 months), GSK has performed an extensive evaluation of the safety data from all studies across the OBD program. This included additional posthoc analyses, internal clinical and scientific review, adjudication of CV events by the IDMC and review of the neoplasia data by an independent Oncology Advisory Board consisting of medical oncologists, epidemiologists and statisticians. A summary of the results from these analyses and outcomes of the independent external review for CV and Neoplasia Adverse Events follows within this section. A more comprehensive review of the OBD safety findings, including data related to adverse events within the category of fracture, along with overall conclusions can be found in section 7.2.

1.3.2.1   Non-Cancer OBD Studies

CV Events

CV events of interest for GSK014 and all studies conducted in the non-cancer OBD population, according to categories requested by FDA, are summarized in Table 3 and Table 4, respectively. Table 4 shows a numerical imbalance in MIs and othe CV adverse events, although less pronounced than that observed in study 014, reflecting the fact that there was no imbalance in these events in other studies. Narratives for patients diagnosed with MI appear in Appendix 12.7.

Table 3   **CV Events of Interest—GSK014**

CV Event Category	Placebo Group N=267 n (%)	Alvimopan Group[a] 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)

a Alvimopan dose regimen was 0.5 mg BID.

Table 4   CV Events of Interest— 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.

For its review, the IDMC considered of primary importance all confirmed SAEs that met the criteria of CV ischemia such as MI. Definitions and diagnostic criteria for other CV AEs of special interest were discussed in collaboration with the GSK study team to allow for the identification and independent adjudication of all major cardiac events. Adjudication was based primarily on source documents requested by the IDMC. GSK, in a blinded fashion, collected and collated the source documents and other information necessary for case extraction and adjudication from each of the OBD studies (GSK011, GSK012, GSK013 and GSK014), which account for substantially all of the patients in the non-cancer OBD program.. The IDMC reviewed these blinded cases of CV interest for clinical significance, attribution, and impact on the safety profile of alvimopan and determined whether they met the criteria for "Adjudicated Major Cardiac Events (AMCEs)." The IDMC then evaluated the totality of unblinded AMCEs in its evaluation of the benefit/risk balance of alvimopan therapy and on this basis provided recommendations to GSK. For their review, the IDMC specified that adjudicated CV events were to be categorized as follows:

- ▪ All CV events

- ▪ Ischemic CV events: acute MI, new onset/unstable angina, congestive cardiac failure, cerebrovascular accident (CVA)/transient ischemic attack (TIA), cardiac arrest, sudden death

- ▪ Other CV events: bradycardia, atrial fibrillation, supraventricular tachycardia, hypotension, venous thrombosis, pulmonary embolism, syncope

Summary statistics derived from the adjudication database are presented Table 5.

Table 5   CV Event Summary—IDMC Adjudication Database

	Placebo N=817 n (%)	Alvimopan N=1807 n (%)	Relative Risk Alv/Pla (95% CI)
Adjudicated cases	21	63	--
Any CV event[a]	9 (1.1%)	26 (1.4%)	1.30 (0.61,2.77)
Ischemic CV events	6 (0.7%)	13 (0.7%)	0.98 (0.37,2.57)
Other CV events	3 (0.4%)	14 (0.8%)	2.11 (0.61,7.32)

a Study GSK014 / Patient 807 had both ischemic and Other CV events.

Final summary recommendations from the IDMC regarding CV safety data generated by the OBD clinical development program are as follows:

- The risk of ischemic heart disease had been largely discharged

- The incidence of other CV events with alvimopan vs. placebo was not statistically significant

- Further studies should confirm these conclusions if it is decided to pursue the indication for OBD.

Based on the conclusions reached by the IDMC and an analysis of all available data, the imbalance in GSK014 appears to represent an isolated observation. The sponsor's conclusion is that the observed imbalance is more consistent with a chance finding than with a causal relationship to alvimopan.

Malignant Neoplasms

Table 6 summarizes the incidence of all malignant neoplasia events reported in GSK011, GSK012, GSK013, and GSK014, along with estimates of the relative risk and HR calculations. Results from GSK014 alone are also depicted.

Following the initial finding of the numerical imbalance of malignant neoplasm, GSK communicated with site investigators concerning these malignant events. During the course of that interaction, GSK became aware of an additional case of neoplasm for a placebo patient (#7846) in GSK014. This report was unsolicited and GSK did not systematically screen all investigators for additional cases of neoplasia.

Table 6   Neoplasia Event Summary—All Malignant Neoplasms

	Placebo n/N (%)	Alvimopan n/N (%)	Rel Risk (Alv/Pla)	Hazard Ratio (Alv/Pla)	p value**
Initial Analysis					
Non-cancer pain studies*	2/732 (0.3%)	10[b]/1598 (0.6%)	2.3 (0.50, 10.43)	2.4 (0.52, 10.83)	0.250
GSK014	1/267 (0.4%)	5/538 (0.9%)	2.5 (0.29, 21.13)	2.3 (0.27, 20.04)	0.424
Including Additional Patient[a]					
Non-cancer pain studies*	3/732 (0.4%)	10[b]/1598 (0.6%)	1.5 (0.42, 5.53)	1.6 (0.43, 5.72)	0.487
Study GSK014	2/267 (0.7%)	5/538 (0.9%)	1.2 (0.24, 6.35)	1.2 (0.23, 5.99)	0.858

* Non-cancer pain studies: GSK011, GSK012, GSK013, GSK014.

** Log-rank test.

a Patient #7846 was randomized to placebo in GSK014. Patient identified following post-analysis communication with study investigators. This report was unsolicited and GSK did not systematically screen all investigators for additional cases of neoplasia.

b Includes a case reported 6 months after study completion, patient 2077 (GSK011) with adenocarcinoma of the lung.

There was a numerical imbalance in reported malignant neoplasia in the non-cancer OBD studies. This imbalance of 10:3 (alvimopan: placebo) represented a relative imbalance of 1.5 to 1 given the unequal randomization in the studies. Given the low incidence of events and wide confidence intervals, a statistical analysis in not instructive in explaining the observed difference. An examination of the patient narratives together with additional information available from investigators suggests that most if not all of these were present at baseline. It is important to note the preclinical carcinogenicity studies of alvimopan in two species were negative. Furthermore, alvimopan did not produce any significant genotoxicity or mutagenicity in animals. The extensive review of clinical data along with preclinical findings does not support a causal relationship between alvimopan and the induction or progression of malignant neoplasia. Narratives for all malignancies in the non-cancer OBD studies are presented in Appendix 12.7.

1.3.2.2   Cancer Related Pain Studies (GSK008 and GSK684)

GSK008 and its long-term extension, GSK684, were conducted separately from the non-cancer pain OBD trials to eliminate the potentially confounding factors inherent in the underlying cancer disease state. Enrollment criteria required that subjects have pain due to cancer, and a minimum three month life expectancy. For the most part, patients had existing malignancies however disease type or status were not considered in the randomization of patients. Study duration in GSK008 was 3 to 6 weeks. If a patient elected to participant in the extension study, they continued on the same treatment as they were randomized to in GSK008. There was no designated end date or time for treatment duration in GSK684. As the cumulative person-time for alvimopan-treated patients who progressed into the extension study was much greater than

that for the placebo-treated patients who progressed into the extension study, incidence rates and the incidence density ratio (IDR) were used initially to assess the risk of death. Incidence rates and the IDR use person-time rather than number of patients and therefore can account for differences in exposure. The IDR for all deaths in the cancer pain studies is listed in Table 7.

Table 7   Patients With a Malignant Neoplasm—GSK014

	Placebo (N=70)	Alvimopan (N=160)	IDR (Alv/Pla)
Patient years	11.2	43.3	
All-cause death	3 (26.8/100 pt-yrs)	20 (46.2/100 pt-yrs)	1.72 (0.51, 9.06)

There was a numerical imbalance in deaths on alvimopan compared to placebo in GSK008 and GSK684. Multivariate modeling demonstrated that disease type, extent of disease (i.e. number of metastases) and functional status (Karnofsky score) likely accounted for the numerical differences observed in reported deaths. While a causal relationship can not be ruled out, the totality of these data do not suggest the observed imbalance is drug related.

1.4   Risk Management Proposal

A risk management plan has been proposed that will communicate the possible CV risk of longer-term alvimopan exposure as well as minimize off-label use.

To meet these objectives, Adolor is committed to a number of activities to promote use consistent with product labeling and minimization of the potential risks. Risk minimization proposals include a comprehensive set of activities to communicate data regarding use of the drug consistent with product labeling and patient populations, including educational, communication, and promotional activities, as described hereunder:

- Proposed professional labeling includes language that will communicate:
  - the imbalance of reports of MI between alvimopan 0.5 mg BID and placebo treatment groups in a 12-month safety study of patients taking opioids for treatment of chronic non-cancer pain, GSK014.
  - Entereg is contraindicated in patients who have taken therapeutic doses of opioids for more than 7 consecutive days immediately prior to taking Entereg.
  - Entereg is for hospital use only.
- Education of healthcare providers: Educational efforts will be directed to healthcare providers involved in the care of BR surgery patients, including surgeons, anesthesiologists, hospitalists, nurse anesthetists, hospital nurses, and hospital pharmacists. These educational pieces will communicate the approved patient population, key safety sections of the labeling (including the section related to GSK014), and the approved dosing regimen—particularly a maximum of 15 total doses administered in the hospital only.

- The Patient Counseling Information in the package insert provides the information needed by the patient. Because Entereg Capsules are administered in the hospital by a health professional, the information can be verbally given to the patient. In this manner, the health professional can ensure the patient understands the benefits and risks of Entereg. It may be better understood by the patient prior to surgery than an insert given to the patient for the patient to read.

- Targeted Sales Force: Selling efforts will be directed only to surgeons and other hospital-based personnel involved in or who influence the management of patients undergoing large or small BR, such as anesthesiologists, hospitalists, nurse anesthetists, hospital nurses, and hospital pharmacists.

- Targeted Promotion: Advertisements will be limited to journals associated with surgeons and other hospital personnel who manage patients undergoing BR as mentioned above. Commercial booths will be limited to professional meetings attended by these healthcare professionals. There will be no direct-to-consumer advertising for this hospital-use-only product.

- Samples: No samples will be provided for this product.

- The hospital cost for Entereg 12 mg will be covered under the diagnosis-related group (DRG) payment for BR surgery, i.e., a lump sum payment from the payer directly to the hospital. Therefore, Adolor and GSK will not seek outpatient managed care coverage for Entereg 12 mg capsules, which has the potential to discourage use out of the hospital setting.

- "Hospital Use Only" will be printed on the outer packaging carton and between the rows of blistered capsules on the front of the blister card. Blister cards showing the "Hospital Use Only" are also attached.

- Wholesale Distribution Agreement will specify that 12 mg Entereg capsules should be distributed only to hospitals.

- An electronic notice will be established in retail pharmacy drug information systems to alert community pharmacists not to dispense 12 mg Entereg.

1.5   Conclusions

The results achieved with alvimopan in the NA studies clearly demonstrate both statistical superiority and clinically meaningful patient benefit without added risk of AEs (including CV events, fractures, or neoplasia) or reversal of opioid analgesia. Treatment with alvimopan represents a significant advance in the practice of medicine and standard of care for patients undergoing BR surgery.

The higher reported incidence of CV, neoplasia, and bone fracture events in the alvimopan treatment group observed during initial review of the data in the long-term OBD study, were unexpected based on the preclinical and clinical safety data across all indications. A comprehensive clinical and scientific review of the OBD clinical database along with additional

patient-level data suggests that GSK014 represents an isolated observation and supports a conclusion that these imbalances more likely represent a chance finding or an unidentified disproportionate patient risk prior to randomization as opposed to a causal relationship with alvimopan. Additionally, GSK014 was not prospectively designed or powered to provide an evaluation of the rates of CV, neoplastic or bone fracture events in the OBD population. In addition, the events observed in the OBD long-term study occurred within a timeframe not relevant to the duration of treatment in the acute POI setting.

Stratified and multivariate analysis suggest that the imbalance in reported deaths observed in GSK008 and GSK684 may have been largely due to the selection of sicker patients with poorer prognosis into the alvimopan treatment group.

Furthermore, no numerical imbalances were observed in the Worldwide POI Safety Database within the AE categories of CV, neoplasm, or bone fracture. Therefore safety findings in the OBD program do not alter the favorable benefit/risk profile of alvimopan in patients undergoing BR.

The impact of POI on patients remains substantial and clinically serious. Alvimopan has demonstrated clinically meaningful benefits in the management of POI for patients undergoing BR surgery. These benefits were achieved without increased risk of AEs or reversal of opioid analgesia. Additionally, the proposed risk management plan will further optimize the benefit/risk balance.

2. INTRODUCTION AND BACKGROUND

Alvimopan is being jointly developed by Adolor Corporation and GlaxoSmithKline (GSK). Adolor is developing alvimopan for acute use in the management of postoperative ileus (POI), while GSK is developing alvimopan for the chronic treatment of opioid-induced bowel dysfunction (OBD). NDA 21-775 provides data to support the proposed use of alvimopan in the management of POI in patients undergoing bowel resection (BR) surgery. This represents the first proposed use of alvimopan.

This Briefing Document will provide members of FDA's Gastrointestinal Drugs Advisory Committee with efficacy and safety data describing the benefits and risks of alvimopan for the management of POI following BR surgery. Although clinical studies included patients undergoing BR as well as patients undergoing total abdominal hysterectomy (TAH), clinical benefit in the hospital setting was demonstrated only in patients with BR. This is very likely due to the relatively short hospital stay in TAH compared with BR that resulted in high censoring rates for gastrointestinal (GI) recovery endpoints in patients undergoing TAH, i.e. time to first bowel movement (BM).

This Briefing Document presents a clinical overview of POI (Section 2.2); a summary of the non-clinical data available for alvimopan (Section 4); the clinical data demonstrating the efficacy of alvimopan as treatment for patients with POI (Section 6.2.7); the clinical trial safety data for POI (Section 7.1) as well as the safety data in patients being treated for OBD (Section 7.2); and, the benefits and risks of alvimopan for POI (Section 8).

2.1   Product Description

Alvimopan is an orally administered, potent, selective, and competitive, peripherally-acting μ-opioid receptor (PAM-OR) antagonist (Figure 4). The potency and specificity of alvimopan as a selective PAM-OR antagonist have been investigated and confirmed in numerous in vitro and in vivo experimental preclinical procedures. The primary metabolite, a product of intestinal flora metabolism, is also a potent μ-opioid receptor antagonist with a K_i of 0.8 nM (0.3 ng/mL). The potential for alvimopan to be effective in managing POI and opioid-induced bowel dysfunction (OBD) has been confirmed in a series of in vivo animal studies, with results confirming the absence of central effects at therapeutic doses for these indications. Alvimopan has a low potential for producing any secondary pharmacological effects at intended clinical doses.

Figure 4   Structural Formula of Alvimopan
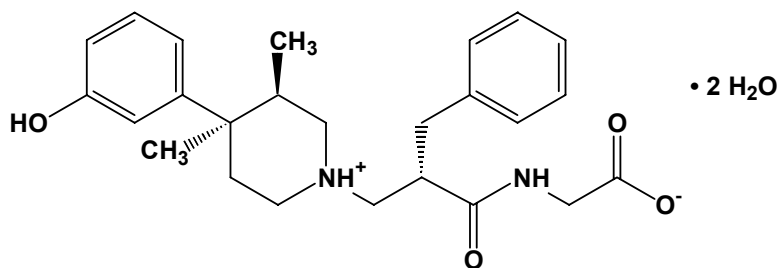
2.1.1   How Supplied

Entereg® (alvimopan) Capsules, 12 mg, are blue, hard gelatin capsules printed with "ADL2698" on both the body and the cap of the capsule. Entereg Capsules are available in unit dose packs of 30 capsules (30 doses) for hospital use only.

2.1.2   Dosage and Administration

For hospital use only. The recommended adult dosage of Entereg is 12 mg administered 30 minutes to 5 hours prior to surgery followed by 12 mg twice daily (BID) beginning the day after surgery for a maximum of 7 days or until discharge. Patients should not receive more than 15 doses of Entereg.

2.2   Postoperative Ileus (POI)

2.2.1   Clinical Course

Although there is no universally accepted definition of POI, it is characterized by a transient cessation of bowel function with a variable reduction in motility sufficient to prevent effective transit of intestinal contents (Livingston and Passaro, 1990; Resnick et al, 1997; Holte and Kehlet, 2000; Woods, 2000; Kehlet and Holte, 2001; Behm and Stollman, 2003). Patients undergoing BR are at highest risk for developing POI, occurring in nearly all cases (Woods, 2000; Saclarides, 2006). Signs and symptoms of POI correlate with a lack of normal GI function and may include abdominal distention and bloating, persistent abdominal pain, nausea, vomiting, variable reduction of bowel sounds, delayed passage of or inability to pass flatus or stool, and inability to tolerate oral intake or progress to a solid diet (Holte and Kehlet, 2000; Woods, 2000; Kehlet and Holte, 2001; Luckey et al, 2003; Clevers and Smout, 1989; Petros et al, 1995).

While these symptoms are inherently undesirable, the physiologic complications of POI include substantial morbidity. Atelectasis associated with abdominal distention as well as pain preventing deep inspiration carry the risk of pneumonia. Vomiting in the postoperative period, when patients are frequently reclining and under the effect of the sedative properties of narcotics, is a significant risk factor for aspiration and pneumonia (Holte and Kehlet, 2000; Woods, 2000; Kehlet and Holte, 2001; Luckey et al, 2003; Clevers and Smout, 1989; Petros et al, 1995). The need to place a nasogastric (NG) tube once nausea and vomiting have become manifest carries its own risks, including gastroesophageal reflux, atelectasis, and pneumonia, as well as universally experienced intense discomfort and attendant immobility (Platell and Hall, 1997; Manning et al, 2001).

From "simple" POI to complicated/prolonged POI, there is an associated morbidity of temporary malnutrition, be it minimal (i.e., 1 to 2 days) or prolonged (i.e., over the course of 4 to 5 days or more). Daily nitrogen loss is common following laparotomy due to the stress associated with surgery and the inability to tolerate adequate enteral nutrition until resolution of POI, which often takes 5 days or longer. Maintenance of oral feeding high enough in caloric content to result in positive nitrogen balance is therefore a clinical challenge following

laparotomy for BR and fails in up to 25% of patients. As a result, these patients are at risk for slipping into a state of negative nitrogen balance, which may lead to weight loss, fatigue, deconditioning, and compromised immunity (Kurz and Sessler, 2003; Senagore et al, 1995).

Opioids are the mainstay for postoperative pain management (Austrup and Korean, 1999; Person and Wexner, 2006). However, they are a known and significant contributing factor to the pathogenesis of POI. Although highly effective analgesics, opioids bind to μ receptors in the GI tract disrupting normal GI motility and prolonging the duration of POI (Luckey et al, 2003; Kurz and Sessler, 2003; Kalff et al, 2003). This physiologic effect of opioids on the GI tract may lead many physicians to wean or taper analgesia prematurely.

Clinical studies have attempted to find correlations between the duration of POI and preoperative comorbidities such as surgical history (especially prior abdominal surgery), extent of bowel manipulation or resection, duration of surgery, length of incision, and other factors. However, the results have been inconsistent, with no single factor or group of factors consistently identified (Livingston and Passaro, 1990;Behm and Stollman, 2003; Graber et al, 1982; Condon et al, 1986; Collins et al, 1999; Cali et al, 2000; Longo et al, 2000). Prolonged POI always begins the same way as "expected" ileus following abdominal surgery. However, the unpredictable course of POI presents a significant clinical dilemma to surgeons and their patients.

More than 70 years after the introduction of routine NG tube decompression, and despite the more recent introduction of multimodal postoperative care pathways, physicians continue to search for effective methods to manage POI (Kehlet and Holte, 2001; Paine et al, 1933; Delaney et al, 2001; Kehlet et al, 2006).

2.2.2   Outcome Measures

2.2.2.1   GI Recovery

GI recovery is a key clinical milestone after BR and serves as the barometer of patient progress during the critical period of in-hospital postoperative recovery. The clinical events that characterize upper and lower GI recovery (i.e., the passage of flatus or BM and the ability to tolerate a solid diet) are the primary factors in determining hospital discharge after BR (Delaney et al, 2001; Gervaz et al, 2005). GI recovery occurring within 5 days of BR is generally expected and considered "physiologic" (Person and Wexner, 2006; Kehlet et al, 2006; Miedema and Johnson, 2003). A delay beyond 5 days increases both patient risk and the probability of extending length of hospital stay (LOS) and may be considered prolonged POI (Kehlet and Holte, 2001; Collins et al, 1999; Prasad and Matthews, 1999; Aydin et al, 2005).

2.2.2.2   Length of Hospital Stay

In a 2006 review article on the current management of POI by colorectal surgeons at the Cleveland Clinic (Person and Wexner, 2006), the authors noted, "The duration of POI is the most important factor in determining the length of hospitalization [after bowel resection]" and "After abdominal surgery, POI is the most common cause of and a significant risk factor for

delaying discharge and extending length of hospital stay." In a study of more than 2,000 patients undergoing partial colectomy (Collins et al, 1999), POI (delayed GI recovery) was one of the most common risk factors associated with prolonged LOS. Prolonged LOS may increase the risk for nosocomial complications (Buchner and Sonnenberg, 2002; Barbut and Petit, 2001; Thompson et al, 2006; Alizadeh and Hyman, 2005; Borly et al, 2005; Gillis and MacDonald, 2005; Mallery et al, 2003). According to Health Care Financing Administration (HCFA) data for the years 1999 to 2000 in more than 160,000 cases of major intestinal resection from 150 US hospitals, mean hospital stay in patients with coded POI was 11.5 days, as compared with 6.5 days in those without this complication.

2.2.2.3   Morbidity Related to POI

As recently as 2003, a survey of 39 US hospitals that evaluated postoperative clinical practice management in patients undergoing BR revealed that, when an NG tube was used, its removal occurred on average approximately 3 days after surgery in 41% of the 232 patients studied (Kehlet et al, 2006).

Recent studies indicate that NG tube decompression does not shorten the duration of POI and may, in fact, contribute to postoperative complications such as nasal and pharyngeal injury, fever, atelectasis, increased gastric reflux and regurgitation, and pneumonia (Luckey et al, 2003; Platell and Hall, 1997; Manning et al, 2001; Sagar et al, 1992). It is now well recognized that NG tubes cause significant patient discomfort; therefore, routine use after abdominal surgery is no longer recommended (Cheatham et al, 1995).

2.2.3   The Unmet Medical Need

More than 70 years after the introduction of routine NG tube decompression, and despite the more recent introduction of multimodal postoperative care pathways, physicians continue to search for effective methods to manage POI (Kehlet and Holte, 2001; Paine et al, 1933; Delaney et al, 2001; Kehlet et al, 2006).

Despite the recognition that POI represents a serious medical condition, there is still no approved treatment. The impact of POI is substantial and clinically serious. The effective management of POI represents a continuing unmet medical need, the satisfaction of which will represent a major advance in postoperative patient care.

2.3   Overview of Clinical Development Program for Alvimopan

Alvimopan demonstrated appropriate activity in preclinical models and was therefore developed as a therapeutic agent to treat patients recovering from surgery who are suffering from POI and patients with bowel dysfunction associated with chronic opioid use (OBD) while preserving the desired, centrally mediated, analgesia. Given the significant differences in these populations (POI and OBD), two separate development programs were initiated. Figure 5 provides a schematic outlining the POI and OBD studies supporting each indication.

Figure 5   Alvimopan Phase 2/3 Clinical Studies

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                    ┌─────────────────────────┐
                    │        Alvimopan         │
                    │    Phase 2 & 3 Studies   │
                    └─────────────────────────┘
                              │
              ┌───────────────┴───────────────────┐
    ┌──────────────────────┐        ┌──────────────────────┐
    │  Post Operative Ileus │        │      Chronic OBD      │
    │        Program        │        │        Program        │
    └──────────────────────┘        └──────────────────────┘
              │                          ┌───────┴────────┐
    ┌──────────────┐         ┌──────────────────┐   ┌──────────────┐
    │   13C206     │         │ Non-Cancer Pain  │   │ Cancer Pain  │
    │   13C213     │         │   RC 99CT001     │   │   13CL223    │
    │   13C214     │         │   RC 99CT002     │   │   13CL224    │
    │   14CL302    │         │     13C208       │   │    GSK008    │
    │   14CL306    │         │     13C209       │   │    GSK684    │
    │   14CL308    │         │     13C210       │   │    GSK965    │
    │   14CL313    │         │     12C217       │   └──────────────┘
    │   14CL314    │         │     13C304       │
    │   GSK001     │         │    GSK011        │
    └──────────────┘         │    GSK012        │
                             │    GSK013        │
                             │    GSK014        │
                             └──────────────────┘
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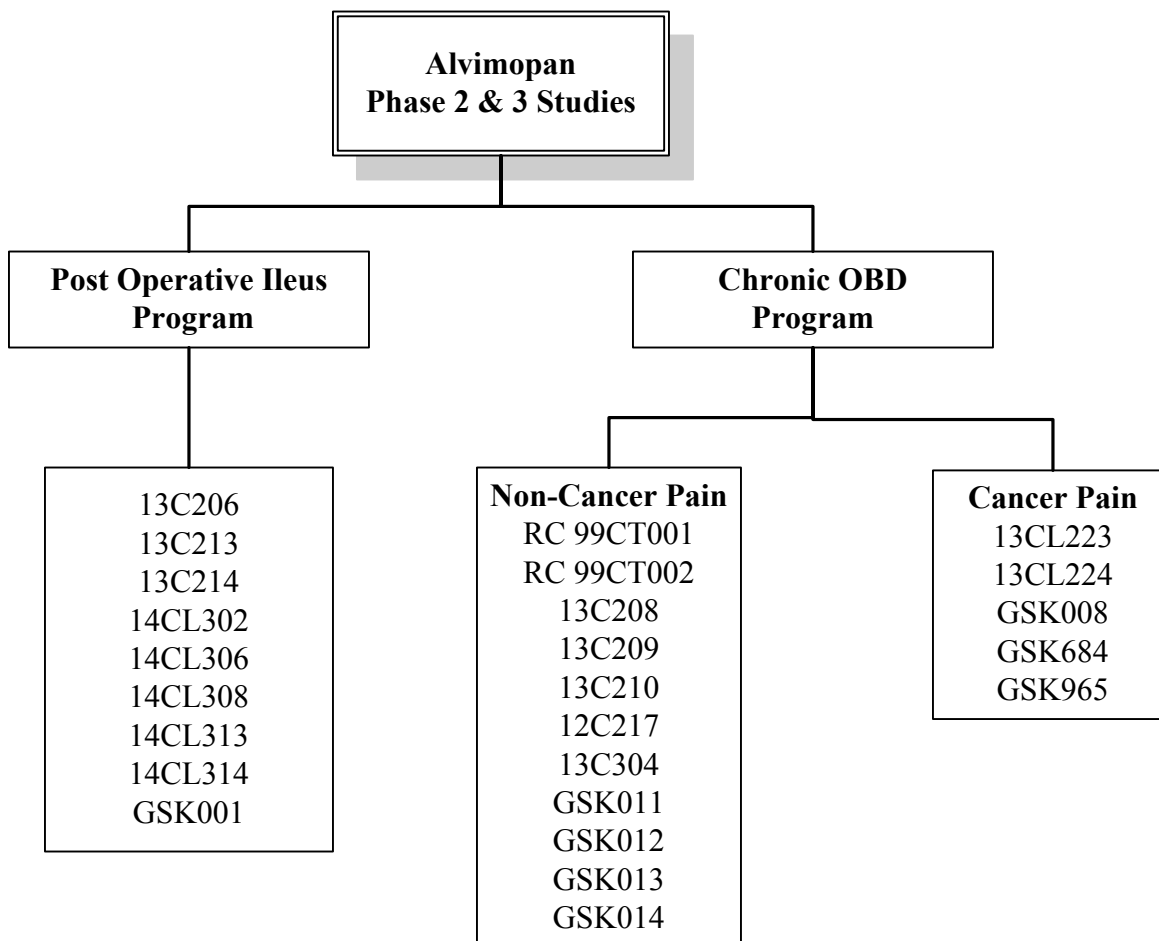
2.3.1   POI Program

A total of nine Phase 2 and 3 studies have been conducted in patients at risk of developing POI. The three Phase 2 studies explored different doses of alvimopan in TAH and BR patients. Study 14CL306 was a Phase 3 safety study conducted in TAH patients only. The five Phase 3 efficacy studies included patients undergoing laparotomy for BR with primary anastomosis or TAH and scheduled to receive opioid-based, intravenous (IV), patient-controlled analgesia (PCA) for postoperative pain management. All five studies were randomized, double-blind, placebo-controlled, parallel studies of alvimopan vs. placebo in hospitalized patients. All studies except for GSK001 were conducted in North America (NA). Studies 14CL302 and 14CL308 enrolled patients either undergoing TAH or partial BR with primary anastomosis. Study 14CL313 consisted primarily of BR patients, and GSK001 was amended to include primarily BR patients. Study 14CL314 enrolled only BR patients. A total of 2,610 patients have received treatment with alvimopan, and 1365 patients received placebo in the POI studies.

2.3.1.1   Dose Selection

The selection of doses for use in the management of POI was driven by clinical and pharmacokinetics data. Early studies demonstrated that alvimopan was well tolerated when studied as repeat doses up to 120 mg once daily (QD) for 3 days, 18 mg three times daily (TID) for 4 days, or 24 mg BID for 7 days in healthy volunteers. Phase 2, dose-ranging studies in POI demonstrated a clinically meaningful effect when alvimopan was given BID in doses ranging from 3 to 12 mg to patients undergoing abdominal and pelvic surgery. Alvimopan was well tolerated at all doses, and there were no data to suggest an increased incidence of treatment-emergent adverse events (TEAEs) with increasing doses of alvimopan in these studies.

Clinical pharmacology and clinical study data indicated that alvimopan has limited oral bioavailability and a margin of safety that covers all doses in the range of clinical interest (i.e., up to 12 mg BID). The safety margin allowed the opportunity to select doses based on the goal of ensuring optimum efficacy, i.e., a significant acceleration of GI recovery to as large a portion of the patient population as possible.

The ability to titrate dose within this surgical setting is very limited as the effect of early intervention may be critical to reducing the duration and severity of POI. From a practical standpoint, therefore, the window of opportunity perioperatively in these surgical populations is short, requiring a dose that, during the entire course of treatment, is optimized for both efficacy and safety. Hence, alvimopan doses at the higher end of the dose range shown to be well-tolerated and effective in Phase 2 studies (6 mg and 12 mg) were selected for the Phase 3 studies.

The pharmacokinetics of alvimopan in normal subjects and special populations have been well characterized. Alvimopan is a low-solubility drug with low permeability and an absolute bioavailability of 6% (range, 1% to 19%). This leads to a wide variation of plasma levels at any given dose. A linear dose-concentration relationship has been established between doses of 6 to 18 mg BID, with apparent dose-limited absorption at higher doses (24 mg BID produced similar plasma levels to 18 mg BID).

The receptor kinetics of alvimopan have been characterized, and inferences based on plasma concentrations and effective receptor concentrations can be proposed. In vitro immunohistochemistry studies have demonstrated that μ-opioid receptors in the human small and large intestine are located on nerve cells in the submucosal plexus as well as in the myenteric plexus. While concentrations at these receptors are not known, the GI tract is highly vascular and well perfused. Concentrations at or above the K_i for alvimopan are presumed to provide adequate exposure to effectively antagonize the potential effect of μ-opioids in the GI tract. The time that concentrations are above the K_i of alvimopan at the μ-opioid receptor after alvimopan doses of 6 and 12 mg BID are illustrated in Figure 6. As shown, alvimopan plasma levels achieved after 6 or 12 mg BID orally appear to be sufficient to exceed the K_i in 95% of the subjects for 6 and 12 hours, respectively. Thus, the 12 mg dose gives a more optimal chance of reaching adequate concentrations in all patients.

Figure 6 **Alvimopan Concentrations Relative to K_i for μ-Opioid Receptors**

Alvimopan 6 mg BID   Alvimopan 12 mg BID
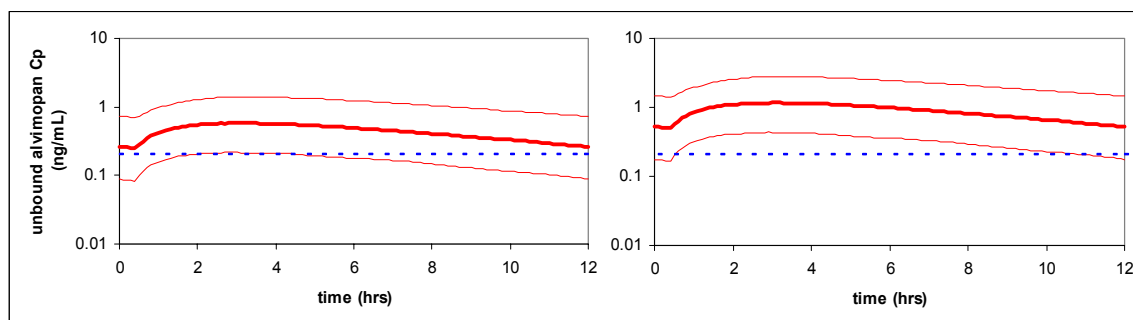
Note: The median (thick red line) and 5th and 95th percentile (thin red lines) plasma unbound concentration-vs.-time profile in POI patients receiving 6 or 12 mg BID. The blue dotted line represents the K_i of alvimopan for μ-opioid receptors.

2.3.1.2   Timing and Frequency of Dose Administration

Initially, alvimopan was believed to act via delivery of high intraluminal concentrations of unabsorbed drug to the colon, concentrations that would be sufficient to produce local receptor blockade and hence release the colon from the inhibitory effects of opioids on motility. Data from animal model studies were consistent with this hypothesis. Additionally, several clinical studies demonstrated that oral-cecal transit time in fasted volunteers is approximately 90 to 100 minutes (Yuan 2000). It was therefore believed that alvimopan would need to be dosed at least 90 minutes prior to surgery to ensure delivery of unabsorbed alvimopan to the colon. As such, BID dosing postoperatively was chosen based on the results of the Phase 2 program and the desire to maintain a steady delivery of unabsorbed drug to the colon. Results from other Phase 2 clinical studies confirmed that this was an effective dosing regimen. Therefore, the regimen of one preoperative dose followed by postoperative BID dosing was implemented in the Phase 3 studies.

Further studies revealed that a single oral dose of alvimopan 12 mg produces systemic free (unbound) plasma concentrations that meet or exceed the K_i for μ-receptor antagonism within 30 minutes in 75% of subjects and within 40 minutes in 95% of the subjects. In addition, many subjects, especially those undergoing BR, will have an NG tube placed after induction of anesthesia. Therefore, the initial dose should be administered at least 30 minutes prior to the scheduled start of surgery (time of induction) to prevent aspiration by the NG tube. Dosing 30 minutes to 5 hours before the scheduled start of surgery (93% of the patients receiving 12 mg alvimopan in the NA Phase 3 studies received the preoperative dose within this range) provides plasma levels of alvimopan in a range above that which is anticipated to be required to antagonize the receptors.

2.3.1.3   Study Population Evolution

Initially, in order to study the efficacy and safety of alvimopan for the management of POI, it was necessary to identify surgical populations at risk for this condition and/or its associated symptoms (e.g., nausea, vomiting, abdominal bloating/distension). Additional factors that were considered in identifying the study populations included those undergoing a more common elective surgery with relatively standardized surgical approaches where the standard of care for postoperative pain management is predominantly IV PCA opioids. Two populations at risk were identified: (1) patients undergoing laparotomy for BR, with primary anastomosis; and (2) patients undergoing laparotomy for hysterectomy (simple or radical).

The Phase 2 program was then initiated with a randomized clinical study (13C206) in 79 patients undergoing simple hysterectomy (sTAH), radical hysterectomy (rTAH), or partial colectomy. This study evaluated 1 mg and 6 mg alvimopan vs. placebo and demonstrated that alvimopan produced statistically significant and clinically meaningful improvements in time to achieve first flatus, first BM, tolerance of solid food, readiness for hospital discharge, and actual hospital discharge. Two additional Phase 2 POI studies were completed (Studies 13C213 and 13C214). Study 13C213 was a multicenter study that evaluated the efficacy and safety of alvimopan at 3, 6, and 12 mg BID vs. placebo in 153 patients undergoing partial BR, sTAH, or rTAH. Study 13C214 included 65 patients and evaluated the efficacy and safety of 12 mg alvimopan vs. with placebo in abdominal surgery (excluding planned BR), primarily sTAH and rTAH. The data from these studies demonstrated that alvimopan 3, 6, and 12 mg regimens accelerated recovery of GI function and that increased surgical severity (increased length and complexity of surgery) was associated with increased treatment benefit, in terms of rapidity of recovery of GI function postoperatively.

Based on these results, it was decided to evaluate BR patients as well as abdominal hysterectomy patients in the Phase 3 program. The BR population was chosen as the primary population due to higher risk of POI and associated morbidity along with a longer hospital stay. Benefit in the abdominal hysterectomy population was also observed in the Phase 2 studies; however, due to a shorter LOS (as compared to BR patients) and therefore a greater potential for censoring in this population, a smaller number of abdominal hysterectomy patients were enrolled when compared to the BR population.

Data from the first three Phase 3 studies demonstrated a clear treatment effect in BR patients. For patients undergoing TAH, positive trends were observed; however, none were statistically significant. This is likely due to short LOS (~3 days) and aggressive discharge criteria, often not driven by occurrence of a BM. When patients undergoing sTAH were sent home with alvimopan following discharge and GI endpoints were monitored via diary after hospital discharge for a total of 7 days in Study 14CL306, a statistically significant difference in time to first BM was observed for the alvimopan 12 mg treatment group vs. placebo. These data resulted in the design of the final Phase 3 study, Study 14CL314, where only BR patients were enrolled.

2.3.1.4   Endpoint Evolution

At the initiation of the development program for POI, no standards existed in the assessment of GI recovery. In discussions with FDA, it was agreed that efficacy in POI required demonstration of both upper and lower GI recovery. Therefore, time to first toleration of solid food after surgery was used to indicate the recovery of upper GI function, and time to first flatus or time to first BM were used to indicate the recovery of lower GI function. Collectively, these represent resolution of POI. These three individual time to GI recovery events were collected in all studies.

In order to have a single measure that indicates the recovery of both upper and lower GI function, a composite endpoint was derived from the individual GI events. This composite measure was expressed in one of two ways: as GI-3, which uses times to all three components (BM, solids, and flatus) to calculate the endpoint; and GI-2, which uses times to two components (BM and solids) in the calculation. See Appendix 12.2 for a precise definition of these endpoints.

In the initial Phase 3 studies (14CL302, 14CL308, 14CL313, and GSK001), GI-3 was the primary efficacy endpoint and GI-2 was a secondary endpoint. Following the completion of the initial studies, a review of the data demonstrated that GI-2 was a more appropriate assessment of GI function in BR patients. Compared with GI-3, GI-2 excludes time to first flatus, a clinical event that is subject to greater variability as compared to BM. This is likely due to the fact that flatus is subjective endpoint reported by the patient. As a result, GI-2 is likely the more objective composite endpoint for measuring alvimopan treatment effect on GI recovery, especially in BR patients. Subsequently GI-2 was the primary efficacy endpoint in the final Phase 3 study (Study 14CL314).

2.3.2   OBD Program

To date, 2008 patients with OBD have received treatment with alvimopan in 16 completed clinical trials. An additional 895 patients with OBD have served as placebo controls. Eleven of the studies evaluated alvimopan in patients receiving chronic opioids (Studies RC 99-CT001, RC 99-CT002, 13C208, 13C209, 13C210, 13C217, 13C304, GSK011, GSK012, GSK013 and GSK014), and five studies evaluated alvimopan in cancer pain patients taking opioids (Studies 13CL223, 13CL224, GSK965, GSK008 and GSK684). Of these studies, non-cancer studies GSK011, GSK012, GSK13 and GSK014 as well as cancer studies GSK008 and GSK684 make up the vast majority of exposures in the population.

2.3.3   POI vs. OBD Population Comparison

Surgical patients studied in the POI clinical program differ significantly from the chronic pain population included in the OBD studies, from both a physiologic and clinical perspective.

2.3.3.1   Physiologic—Opioid Tolerance and μ-Receptor Sensitivity

Tolerance is a well known physiologic response to chronic opioid use. In patients who have developed tolerance, small doses of a μ-opioid antagonist can precipitate a moderate to severe

withdrawal syndrome comparable to that seen after abrupt cessation of opioid use.
The difference, however, is that signs and symptoms of withdrawal often begin minutes after administration of the antagonist, with the duration and severity related to dose and degree of tolerance (Goodman and Gilman's 9th Edition pp. 550). This heightened "sensitivity" to a μ-opioid antagonist in an opioid-tolerant patient is not well understood; however, it is thought to be related to physiologic changes at the cellular/receptor level.

Tolerance development with chronic opioid use may occur at different rates within different tissues. The development of tolerance to specific opioid effects is unequal, and the rate of tolerance development depends on the pattern of opioid use (Jaffe, 1985). Although patients become tolerant to the analgesia, emesis, euphoria, sedation, and respiratory depression resulting from chronic administration of μ-opioid agonists, the presence of miosis and constipation has been reported in users tolerant to opioid-induced respiratory depressant effects (Jaffe, 1985). In addition, although tolerance to most opioid-induced side effects is observed with chronic administration, constipation is the exception and remains a problem for the patient (Ballantyne, 2006).

Phase 1 and 2 studies in opioid-tolerant patients have established that there is a difference in the tolerability of alvimopan in patients on chronic opioid use vs. that in opioid-naive patients. Opioid-tolerant subjects experienced dose-limiting GI AEs at 3-mg doses of alvimopan, while doses up to 120 mg QD for 3 days, 18 mg TID for 4 days, or 24 mg BID for 7 days have been well tolerated with no dose-related toxicities in opioid-naive patients. In opioid-tolerant subjects, dose-limited AEs included abdominal cramps and pain, nausea, diarrhea, and vomiting.

2.3.3.2   Clinical

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 (6 or 12 mg BID) are required to antagonize opioid effects on bowel motility in order to shorten the duration of POI.

Chronic pain patients are managed as outpatients via primary care providers, specialists, or within a pain clinical setting. As mentioned above, these patients have been on opioids for many years, particularly those with non-cancer–related pain, and require chronic treatment for management of OBD. Patients enrolled in the OBD clinical studies had a high incidence of baseline cardiovascular (CV) comorbidity (e.g., obesity, smoking [incidence approximately double that of the US adult population], hyperlipidemia, hypertension).

In contrast, patients undergoing elective major abdominal surgery undergo extensive preoperative screening. These screening assessments help to identify patients at high surgical

risk resulting in either implementation of non-surgical alternatives or medical intervention to reduce the risk for perioperative complications. Furthermore, unlike the outpatient setting of the OBD population, the level of patient monitoring and medical oversight is high within the inpatient setting of patients undergoing major intestinal surgery.

2.4   Regulatory Interactions

Adolor has collaborated closely with the FDA during the development process. Alvimopan for the management of POI received Fast Track Status as FDA recognized that POI is a serious condition with no approved pharmacological therapy.

An End-of-Phase 2 meeting was held in March 2001. Agreement was reached that achievement of time to recovery of both upper and lower GI function would be necessary to demonstrate efficacy. FDA stressed that the reduction in the time to return of GI function must be clinically significant and lead to the patient being ready for discharge based on recovery of GI function. An endpoint was included in the POI studies to assess when the investigator felt the patient was ready for discharge from a GI recovery perspective; this endpoint was referred to as Ready for Discharge (READY).

A pre-NDA meeting was held in February 2004. Agreement was reached on the preclinical and clinical studies to be included in the NDA as well as a deferral of pediatric studies until post approval. There was also agreement that nonclinical carcinogenicity studies would not be required for the proposed acute use of alvimopan in POI.

The NDA for POI was submitted in June 2004 and subsequently accepted for filing by the FDA. During the time of the regulatory review, Adolor began a new Phase 3 study of alvimopan, 12 mg BID, in BR patients only, Study 14CL314. The Phase 3 studies submitted with the NDA had included both 6-mg and 12 mg BID doses of alvimopan in BR and hysterectomy patients. After review of those studies, Adolor proposed the 12-mg BID dose for approval due to greater consistency in benefit/response and no increased risk of AEs seen with the 12-mg dose compared with the 6-mg dose.

Study GSK001 was completed during the NDA review, and FDA requested the results of this study. FDA extended the review clock 3 months to provide time to review the results of that study. At the end of its review FDA issued an "Approvable Letter" on July 21, 2005, which included a request for additional efficacy data as well as support for the conclusion that the median reduction in time to GI recovery relative to placebo treatment seen in the POI studies was clinically meaningful. After consultation with the FDA, agreement was reached that ongoing study 14CL314 could provide the requested additional efficacy data if the results of that study were both statistically significant and clinically meaningful. The FDA and Adolor agreed on the statistical analysis plan (SAP) for that study, which prespecified GI-2 as the primary efficacy endpoint and "Discharge Order Written" (DOW) as a key secondary endpoint assessing efficacy.

The primary endpoint of Study 14CL314 was statistically significant, and the difference compared with placebo considered clinically meaningful. Based on these results, a Complete Response to the NDA approvable letter was submitted on May 9, 2006. During the review of

the Complete Response, interim data from a GSK study (GSK014), a 12-month safety study in non-cancer pain patients with OBD, revealed an imbalance in the number of myocardial infarctions (MIs). The findings and subsequent results of a detailed evaluation of those findings were discussed with the FDA, and the study continued uninterrupted with an Independent Data Monitoring Committee (IDMC) to assess CV-related safety during the trial.

On November 3, 2006, the FDA issued a second "Approvable Letter" to NDA 21-775 requesting final safety data from the now-completed OBD Study GSK014, the final reports for two carcinogenicity studies (mouse and rat) conducted by GSK to support long-term treatment with alvimopan, and a Risk Management Plan for POI.

An imbalance in reports of neoplasms and bone fractures was noted when the final safety data from GSK014 were analyzed in March 2007. No further MIs were reported since the interim findings, although there was still an imbalance in reports of MIs with proportionally more reports in the alvimopan arm vs. placebo. As a precautionary measure to these unexpected findings, GSK and Adolor voluntarily stopped all ongoing studies with alvimopan and initiated a detailed follow-up investigation. Regulators worldwide, including FDA, and investigators were expeditiously notified of the unexpected findings. FDA subsequently placed alvimopan investigational studies on full clinical hold and that hold remains in place at this time.

After investigations into the unexpected safety findings of GSK014 and consultation with internal and external experts, Adolor submitted a Complete Response to the second NDA approvable letter on August 9, 2007, with the data requested by the FDA. An action date of February 10, 2008, was assigned by the FDA for the NDA and the decision on the clinical hold remains outstanding. Figure 7 summarizes all key regulatory events.

Figure 7   Regulatory Event Timeline
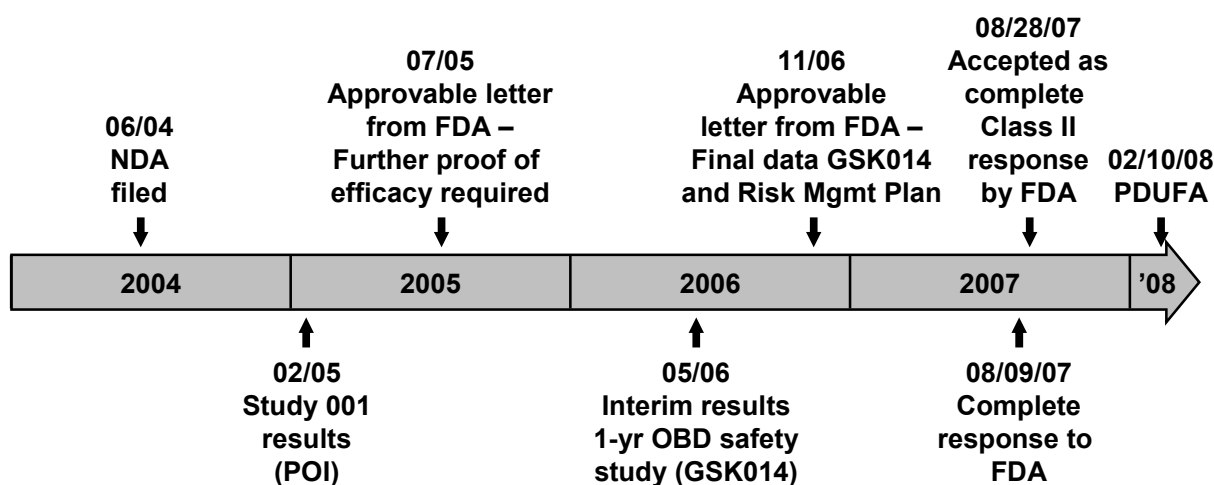
3. OPIOID RECEPTOR PHARMACOLOGY AND PHYSIOLOGY

Endogenous opioid peptides and opiate drugs modulate a variety of biological processes, including stress response, immunity, analgesia, motor activity, and autonomic functions. Endogenous opioids are generated from three different genes, the pro-opiomelanocortin, proenkephalin, and prodynorphin genes, which give rise to several biologically active peptides, including β-endorphin, enkephalin, and dynorphin. These genes and their products have a broad distribution in the central nervous system (CNS) and periphery, including the GI tract. The information presented in this section is excerpted from three review publications (DeHaven-Hudkins, et al., 2007; Greenwood-Van Meerveld, et al., 2004; Sternini et al., 2004).

Three distinct opioid receptors (μ, κ and δ) are expressed throughout the CNS and in peripheral regions, including the GI tract. The receptors consist of seven helical regions in the cell membrane and an intracellular region that couples G-proteins. They bind alkaloid opiates (morphine) and endogenous opioid peptides (enkephalins, endorphins, dynorphins). The three opioid receptor types have been cloned in the mouse, rat, and man.

The diverse effects of opioids and opiates are mediated by the activation of these multiple membrane receptors, which belong to the super family of seven transmembrane G-protein–coupled receptors. These μ-, κ−, and δ-opioid receptors partly overlap in their distribution and function, but maintain a certain degree of selectivity for the three families of endogenous opioids and differ in their pharmacological profiles. For instance, enkephalins are the preferred ligands for δ-opioid receptors, but they also have affinity for μ-opioid receptors. Dynorphins display some selectivity for κ-opioid receptors, whereas endorphins bind to μ-opioid receptors and δ-opioid receptors with similar affinity, having only low affinity for κ−opioid receptor sites. However, endogenous opioids bind all opioid receptor subtypes with moderate selectivity.

Animal studies have revealed that endogenous opioids released peripherally can modulate GI motor and secretory functions, and the effects depend on the nature of the subclass of receptor involved. Agonist and antagonist drugs that possess selectivity for the individual subtypes of opioid receptors have been used in vivo and in vitro to determine the effects of opioids on GI functions. Exogenous opioid receptor ligands, with different affinities for the opioid receptor subtypes, have been used effectively to modify and normalize altered gut functions. Morphine, a μ-opioid receptor agonist, slows GI transit in vivo by its effect on neurons innervating the circular and longitudinal muscle of the intestine. This delay in GI transit occurs following treatment with other μ-opioid receptor agonists as well.

Opioid pathways have also been implicated in the adaptation response to stress-induced mucosal pathophysiology, colonic ion secretion and permeability, and the effects of intestinal inflammation.

Systemic opioids have shown a greater slowing of GI transit in a mouse model of chronic intestinal inflammation along with decreases in intestinal secretion and inhibition of intestinal permeability.

The clinical use of opioid analgesics in acute or chronic settings contributes to the severity of POI and OBD, respectively. POI is a condition resulting from the combination of surgical trauma, psychological stress, and administration of opioids for pain management that commonly follows a variety of surgical procedures. POI is most common after abdominal or pelvic surgery, but can occur following other major nonabdominal surgery. Other factors such as sympathetic activation and inflammation also impact the development of POI. Endogenous opioids may also play an important role in the development of and recovery from ileus due to the localization of opioid receptors in the gut and their role in coordination of GI motility. POI is generally characterized as a temporary period of cessation of bowel function, accompanied by ineffective transit of bowel contents. POI is manifested as a dysregulation of GI motility that can take up to a week to resolve and is poorly treated by most of the pharmacological and procedural interventions that are currently available.

Chronic use of μ-opioid receptor agonists such as morphine to treat pain also results in stimulation of μ-opioid receptors in the periphery, including the GI tract. This chronic use often results in opioid bowel dysfunction. The symptoms of OBD include severe constipation, hard stools, straining, incomplete evacuation, bloating, abdominal distension, and increased gastroesophageal reflux.

Recent research in the field of gastroenterology has concentrated on the design of opioid molecules that do not pass the blood-brain barrier and thus have selectivity for the peripheral opioid receptors. Opioid receptor antagonists with limited brain penetration after systemic or central administration may be therapeutically useful in reversing the unwanted side effects of opiate analgesics such as POI and OBD while preserving centrally mediated analgesia.

4. NONCLINICAL DEVELOPMENT SUMMARY

4.1   General Pharmacology

Alvimopan and its metabolite were evaluated across a broad in vitro selectivity panel that included adrenergic, muscarinic and nicotinic cholinergic, dopaminergic, and serotonergic receptors, various ion channels, and peptidergic receptors and their subtypes. Both alvimopan and its metabolite failed to demonstrate activity at more than 70 non-opioid receptors and enzymes at a concentration of 1 or 10 μM. A complete list of the receptor binding and enzyme assays performed is presented in Appendix 12.4.

A summary of the findings of studies in receptor binding and functional assays in vitro, and in animal models of GI function, physical dependence, and analgesia, are as follows:

- Alvimopan and its metabolite are highly potent, selective, competitive, peripherally acting μ-opioid receptor antagonists.

- Oral administration of either alvimopan or its metabolite results in long-acting and potent antagonism of morphine-induced inhibition of GI transit in mouse models.

- Oral administration of alvimopan reverses the delay in GI transit induced by intestinal manipulation alone, or intestinal manipulation and morphine administration, in a rat model of ileus.

- Alvimopan selectively antagonizes the peripheral effects of morphine in mice that are physically dependent on morphine.

- Alvimopan's metabolite antagonizes the peripheral effects of morphine in mice that are physically dependent on morphine at low doses and antagonizes the central effects of morphine at higher doses.

- Alvimopan antagonizes morphine-induced analgesia only after oral doses that are 10- to 30-fold higher than the effective doses to antagonize the effects of opioid agonists on measures of GI function.

- Alvimopan's metabolite antagonizes morphine-induced inhibition of GI transit at doses approximately 10-fold lower than those required to antagonize morphine induced analgesia.

4.2   Safety Pharmacology

A number of safety pharmacology studies have been conducted to date with alvimopan. The following is a summary of those findings:

- Alvimopan, given IV to anesthetized guinea pigs at doses up to 2.72 mg/kg, had no adverse effects on respiratory system function.

- Alvimopan at single oral doses of 100 and 200 mg/kg decreased sensorimotor reactivity in mice.

- In rats given alvimopan for 3 days IV at doses of 1, 5, and 10 mg/kg, no significant treatment-related effects were observed on neurobehavioral endpoints.

- Alvimopan, administered orally to rats at single doses up to 200 mg/kg, did not produce any adverse effects on renal function.

- Alvimopan or its metabolite did not produce any adverse effects on the CV system in the dog Purkinje fiber assay.

- Alvimopan and its metabolite did not produce major inhibition of the cloned human cardiac potassium channel (hERG).

- Alvimopan did not cause any adverse CV effects after administration of single oral doses up to 200 mg/kg in rats or single IV doses up to 2.5 mg/kg in dogs.

4.3   General Toxicology

A total of 26 in vivo toxicology studies, ranging from single-dose studies to two-year carcinogenicity studies, have been conducted with alvimopan and its metabolite. These acute and multiple-dose animal studies demonstrate that alvimopan has a low order of toxicity by the oral and IV routes.

In the subchronic repeat-dose toxicity studies conducted in mice, rats, and dogs, there was no evidence of any overt toxicity associated with administration of alvimopan. Effects that were noted are likely associated with the known mode of pharmacological action of the compound (i.e., modification of the motility of the GI tract). These manifestations include emesis, loose or soft stools, and minor effects on food consumption and food utilization, especially in dogs after oral administration.

Alvimopan did not produce any significant genotoxicity or reproductive toxicity in animals.

Alvimopan's metabolite was also shown to have a low order of toxicity, based on multiple-dose IV toxicity studies in two species, and to be devoid of any genotoxicity.

4.4   Carcinogenicity Studies

Carcinogenicity studies in the mouse and rat were conducted to support potential long-term use of alvimopan in humans for treatment of chronic medical conditions, such as OBD. These studies have been completed, and both studies concluded that were no adverse findings and there were no neoplastic findings of an unusual incidence or nature suggestive of a carcinogenic effect of alvimopan. Thus the no observed adverse effect levels (NOAELs) were the highest doses used in each study: 500 mg/kg/day in rats and 4000 mg/kg/day in mice. Carcinogenicity studies were not required by FDA or other regulatory agencies to support potential acute use of alvimopan in conditions such as POI. More information regarding the carcinogenicity studies can be found in Appendix 12.4.

5. HUMAN PHARMACOLOGY

5.1   GI Transit

The effect of alvimopan on opioid-induced changes in GI transit were evaluated in four studies in healthy volunteers and is summarized in Table 8. These four studies provided early evidence of a human pharmacodynamic effect arising from alvimopan's basic pharmacologic mechanism, selective μ-opioid antagonism. These studies consistently demonstrate the effect of opioids on the GI tract to inhibit motility and the ability of alvimopan to restore GI motility in this setting.

Table 8   Summary of Clinical Pharmacology Studies Evaluating the Reversal of Opioid-Induced Changes in GI Transit

Study	Conclusion
Study of the reversal of loperamide-induced constipation	The number of episodes of constipation reported as AEs decreased with increasing dose of alvimopan. Loperamide-induced constipation symptoms were reversed by alvimopan at doses of 2.4 and 24 mg TID.
Study of the reversal of morphine-induced delayed GI transit	Morphine increased oral-cecal transit time from a mean of 68.5 to 102.8 min. When alvimopan was given in conjunction with morphine, the mean oral-cecal transit time was 75.5 min. This transit time was not statistically different from that of saline/placebo (68.5 min; $p > 0.3$) but was significantly less than the transit time after morphine/placebo (102.8 min; $p = 0.0064$).
Study of the reversal of morphine-induced delay in GI transit	Alvimopan significantly enhanced GI transit when administered with MS CONTIN compared to placebo. In addition, compared to placebo, subjects treated with alvimopan had more stools at a greater weight. This effect was achieved without apparent interference with the analgesic or centrally mediated changes in pupil size due to morphine.
Study of the reversal of codeine-induced delay on gastric, small bowel, and colonic transit	Codeine significantly delayed small bowel transit times and colonic transit. Alvimopan completely reversed the slowing effect of codeine on small and large bowel transit. Alvimopan accelerated colonic transit in the absence of codeine. Alvimopan did not affect gastric emptying.

5.2   Opioid-Induced Analgesia

In nonclinical models, administration of alvimopan during opioid therapy did not antagonize morphine-induced analgesia at doses that normalized bowel motility and GI transit time. The ability of alvimopan to reverse morphine-induced delays in lower GI transit without antagonizing opioid effects in the CNS was evaluated in a Phase 1, randomized, placebo-controlled, crossover trial involving 13 normal subjects. Subjects received either placebo or alvimopan 3 mg orally TID and morphine 30 mg orally BID for 4 days. This was followed by a washout period of 1 week, and then 4 days of the crossover treatment. Co-administration of

alvimopan did not antagonize the central effects of morphine as shown by its failure to change the magnitude of pupil constriction with morphine administration.

Another Phase 1 study assessed the effects of alvimopan on morphine-induced analgesia and pupillary constriction in 45 subjects who underwent dental surgery. Subjects were randomly assigned in a double-blind fashion to one of three treatment groups (n = 15 per group): oral alvimopan (total = 4 mg) and IV morphine 0.1 or 0.15 mg/kg, oral placebo and IV morphine 0.1 or 0.15 mg/kg, or oral placebo and IV placebo. Morphine significantly reduced visual analogue scale (VAS) pain scores and categorical pain scores, and increased pain relief scores. Administration of alvimopan before and after surgery did not affect either pain scores or morphine-induced pupillary constriction (Liu, 2001).

Additional data on the lack of effect of alvimopan on opioid-induced analgesia in Phase 3 studies of POI subjects are presented in Section 6.2.7.4.

5.3   Pharmacokinetics

The PK of alvimopan were studied after single and multiple oral dosages ranging from 6 to 24 mg BID in healthy volunteers and in other populations. The primary metabolite, a product of intestinal flora metabolism, is also a potent μ-opioid receptor antagonist with a K_i of 0.8 nM (0.3 ng/mL). This metabolite is not required for efficacy.

5.3.1   Absorption

Alvimopan is rapidly absorbed after oral administration, with a median time to observed maximum plasma concentration (T_{max}) of 2 hours and an absolute bioavailability of 6% (range; 1% to 19%). Mean peak plasma concentrations (C_{max}) of 9 ng/mL were observed after administration of alvimopan 12 mg BID for 5 days. There is a delay in the appearance of metabolite, which has a median T_{max} of 36 hours following the administration of a single dose of alvimopan. The mean C_{max} for the metabolite after alvimopan 12 mg BID is 24 ng/mL.

A high-fat meal decreased the rate and extent of absorption of alvimopan. The C_{max} was decreased by 37%, the area under the curve from time zero to infinity ($AUC_{0-\infty}$) was decreased by 19%, and T_{max} was approximately 1 hour later in the presence of a high-fat meal. This food effect is not clinically relevant in POI subjects.

5.3.2   Distribution

The average volume of distribution of alvimopan ranged from 11 to 98 L (0.24 to 2 L/kg). Plasma protein binding of alvimopan and its metabolite is independent of concentration over ranges observed clinically and averages 70% to 80% and 95%, respectively. Both alvimopan and the metabolite are bound to albumin and not to alpha 1 acid glycoprotein.

5.3.3   Metabolism and Elimination

Alvimopan is a moderate clearance drug, with the average plasma clearance ranging from 325 to 401 mL/min. Alvimopan is eliminated primarily (~65%) through biliary excretion; renal excretion accounts for approximately 35% of total clearance. Unabsorbed drug and unchanged

alvimopan resulting from biliary excretion are then hydrolyzed to its metabolite by gut microflora. The metabolite is eliminated in the feces and in the urine as unchanged metabolite, the glucuronide conjugate of the metabolite, and other minor metabolites.

Plasma concentrations of alvimopan increase proportionally with increasing doses between 6 and 18 mg, but increase less than proportionally from 18 to 24 mg. There is little or no accumulation of alvimopan at steady state following BID administration of 6, 12, 18, or 24 mg. The mean terminal phase half life of alvimopan after multiple oral doses of alvimopan ranged from 4 to17 hours.

Concentrations of the metabolite are highly variable between patients and within a patient. The metabolite accumulates after multiple doses of alvimopan, but the magnitude of accumulation varies widely, with an average accumulation ratio of 6 to 9 on Day 5. Concentrations of the metabolite in plasma remain relatively constant for 60 to 96 hours after the last dose of alvimopan, and then decline with a half-life of 10 to 20 hours.

The lack of clinically significant drug interactions with alvimopan are summarized in Appendices 12.5.1.1 and 12.5.1.2. The PK of alvimopan and metabolite in special populations are described in Appendix 12.5.1.3.

5.4   Pharmacokinetics and Exposure Response—POI

Population PK showed that the bioavailability of alvimopan is higher (~1.9-fold) and the bioavailability of metabolite is slightly higher (~1.4-fold) in BR patients than in healthy volunteers. In addition, the rate of alvimopan absorption and the rate of formation/absorption of metabolite is slowed in BR patients. Concentrations of metabolite are much lower (81%) in patients with POI who receive preoperative oral antibiotics (85% of patients). The observed median C_{min} of alvimopan on Day 3 of dosing in POI patients is much higher than that of metabolite (3 and 0.1 ng/mL, respectively, see Appendix 12.5.2.1, Figure 12.5-1).

The pharmacokinetic/pharmacodynamic analysis following oral dosing of alvimopan demonstrated there was no clear relationship between alvimopan or metabolite exposure and response (the time to first BM) in subjects with POI after BR or TAH (see Appendix 12.5.2.2).

The contribution of the metabolite to the efficacy in POI is likely negligible during the first 3 days of dosing. During later days of dosing, when recolonization of the colon and accumulation of the metabolite have begun, the contribution of the metabolite is unclear. It is clear that the metabolite is not needed for efficacy based on clinical pharmacology studies of single-dose alvimopan and based on the low trough concentrations on Day 3 in POI patients. In addition, efficacy is maintained in surgical patients receiving antibiotics that have markedly lower concentrations of metabolite.

5.5   Exposure Response for AEs of Special Interest

For the AEs of special interest discussed in Sections 7.1.5.3 and 7.2, the potential for an exposure-response relationship was evaluated. There did not appear to be any relationship between alvimopan or metabolite exposure and the occurrence of CV-AEs, neoplasm, or

fractures. The relationships between exposure to alvimopan and/or metabolite and the incidence of AEs of special interest (e.g., CV-AEs, neoplasm, and fractures) are presented in detail in Appendix 12.5.3.

5.6   Effects of Alvimopan on Cardiac Conduction

A Thorough QT Study was conducted at oral doses up to 24 mg alvimopan BID for 7 days. The results from this study demonstrated that alvimopan did not cause clinically significant QTc prolongation and, therefore, within this dose range, has a low risk of affecting cardiac conduction. The methods and results from this study, including exposure-response analyses, are summarized in Appendix 12.6.

6. SUMMARY OF CLINICAL EFFICACY

As discussed in Section 2.3.1.1, Dose Selection, the Phase 3 studies evaluated both a 6 mg and 12 mg dosage regimen. However, the data presented in the efficacy section of this document are focused on the results of the 12 mg dose group vs. placebo as this is the only dose level for which an indication is requested. In addition, the efficacy data presented are from the MITT BR population only. Appendix 12.3 provides an overview of the results of the 12 mg dose studied in the five Phase 3 studies.

6.1   Exposure

A total of 953 BR patients have received alvimopan 12 mg in the five Phase 3 efficacy studies. An addition 924 BR patients received placebo.

6.2   Phase 3 Studies in POI

All five studies were randomized, double-blind, placebo-controlled, parallel studies of alvimopan vs. placebo in hospitalized patients undergoing major abdominal surgery. Studies 14CL302 and 14CL308 enrolled patients either undergoing TAH or partial small/large BR with primary anastomosis. Study 14CL313 consisted primarily of BR patients, and Study GSK001 was amended to include primarily BR patients. Study 14CL314 enrolled only BR patients. Surgery characteristics for each of the five studies are summarized in Table 9.

Table 9   Surgery Characteristics of the Population in the POI Program

Surgery Characteristics	Study					All
	14CL302	14CL308	14CL313	14CL314	GSK001	
Placebo, n						
Bowel resection	99	142	142	312	229	924
Total abdominal hysterectomy	46	65	8	0	38	157
Alvimopan 12 mg, n						
Bowel resection	98	139	160	317	239	953
Total abdominal hysterectomy	40	65	6	0	32	143

All surgical procedures in the five studies were performed by open laparotomy. In Studies 14CL302, 14CL308, 14CL313, and GSK001, alvimopan or matching placebo was administered at least 2 hours prior to the scheduled start of surgery, and then BID beginning on Postsurgical Day (PSD) 1 until hospital discharge or for a maximum of 7 days of postoperative treatment. Alvimopan was administered closer to the scheduled start of surgery in Study 14CL314 than in the other studies as the protocol specified that study drug be administered 30 to 90 minutes prior to the scheduled start of surgery.

All patients in the NA studies were scheduled to receive IV PCA. In the non-NA study (GSK001), patients were scheduled to receive opioids either by IV PCA or bolus parenteral

administration (IV or intramuscular [IM]). This was intentionally planned in Study GSK001 so that the participating hospitals could implement their usual pain management protocols. In all studies, there was no restriction on the type of opioid used or the duration of PCA. A standardized accelerated postoperative care pathway was implemented for all protocols: early NG tube removal (end of surgery); early ambulation (Day 1); and early diet advancement (liquids offered by Day 1 and solids by Day 2, as tolerated).

Methodology in GSK001, which was conducted mainly in Europe, was designed to be similar to that of the three completed NA studies. The protocol, however, did not prohibit the use of concomitant non-opioid analgesics (nonsteroidal anti-inflammatory drugs [NSAIDs] or others) for opioid-sparing technique in this study compared with the NA Phase 3 studies. Additionally, the duration of the post surgery, in-hospital observation period was longer: GSK001 had a 14-day period whereas the four NA studies had a 10-day period.

6.2.1   Methods and Endpoints

6.2.1.1   Gastrointestinal Recovery-Related Endpoints

Time to first toleration of solid food after surgery was used to indicate the recovery of upper GI function, and time to first flatus and time to first BM were used to indicate the recovery of lower GI function. Collectively, these represent resolution of POI. These three individual time to GI recovery events were collected in all studies. The end of surgery time was used as the reference point for calculating the time to a GI recovery event.

In order to have a single measure that indicates the recovery of both upper and lower GI function, a composite endpoint was derived from the individual GI events. This composite measure was expressed in one of two ways:

- GI-3, which uses times to all three components (BM, solids, and flatus) to calculate the endpoint (see Appendix 12.1 for a precise definition),
- GI-2, which uses times to two components (BM and solids) in the calculation.

GI-3 was the primary efficacy endpoint for four studies (14CL302, 14CL308, 14CL313, and GSK001) while GI-2 was the primary efficacy endpoint in one study (14CL314). Compared with GI-3, GI-2 excludes time to first flatus, a clinical event that is subject to greater patient-reported variability compared to BM. As a result, GI-2 is likely the more objective composite endpoint for measuring alvimopan treatment effect on GI recovery in the BR patients.

6.2.1.2   Hospital Discharge-Related Endpoints

To assess the effect of alvimopan on patient discharge, two events were collected on case report forms (CRFs) in all studies: time to patient ready for discharge based solely on GI recovery as determined by the surgeon (referred to as READY), and time that the discharge order was written (referred to as DOW). The time to actual hospital Departure was collected in 14CL314 only. The end of surgery time was used as the reference point for calculating the time to a discharge-related event.

6.2.1.3   Responder Analysis Endpoints

A cumulative responder analysis was conducted in each of the studies. However, the definition of a responder evolved during the POI program. In 14CL302, 14CL308, and 14CL313, a BR patient was considered a responder if the patient achieved GI-3 by 108 hours following the end of surgery. GSK001 expanded this analysis to five cut-off time points (96, 108, 120, 144, or 168 hours post surgery), and a BR patient was considered a responder if GI-3 was achieved by the cut-off time points. GSK001 also expanded the responder analysis for DOW by two cut-off time points: a patient was considered a responder if the patient had DOW by 120 or 168 hours after surgery.

In 14CL314, the definition of a responder was modified based on discussions with FDA. In this study, a responder was defined as any patient who achieved the event by the cut-off point and subsequently did not develop complications of POI. The responder analysis was applied to each of the following events: GI-3, GI-2, time to BM, READY, DOW, and Departure; and each was summarized by 6 cut-off time points: 72, 96, 120, 144, 168, and 192 hours post surgery.

Although the definition of a responder did evolve over the Phase 3 program, the 14CL314 analysis is thought to be the most clinically relevant based on the population (BR) and condition (POI) under study. Therefore, it was used not only for 14CL314, but also applied retrospectively to the other Phase 3 trials. Furthermore, the results of this analysis will be used, in part, to support the clinical relevance of alvimopan's treatment effect in the BR population.

6.2.1.4   Postoperative Morbidity Endpoint (Early Morbidity Related to POI)

Postoperative morbidity (POM) is a composite endpoint derived from two components: a patient was considered as having POM if the patient either required a postoperative NG tube insertion or had developed complications of POI. This endpoint is an attempt to characterize early POM directly to POI in the Phase 3 NA clinical studies. The component of "need for postoperative NG tube insertion" was captured directly on the CRFs as an efficacy endpoint. However, the component of "complications of POI" was not captured directly as an efficacy endpoint on the CRFs, but the data used to derive "complications of POI" were prospectively collected in the four NA studies as safety data on the CRFs. That is, a patient was considered to have an event of complications of POI if the patient had any of the following serious adverse events (SAEs) resulting in prolonged hospital stay (as determined solely by the investigator) or re-admission $\geq$ 7 days of the initial hospital discharge:

- Postoperative ileus

- Ileus paralytic

- Small intestinal obstruction

6.2.1.5   Number Needed to Treat (NNT) Estimates

The NNT provides an estimate of the number of patients who need to be treated to attain an additional favorable outcome, or to prevent an additional adverse outcome, and is the reciprocal of the absolute risk reduction. The closer the NNT is to 1, the greater the probability that every

patient treated achieves treatment benefit. This measure has the advantage of direct applicability to clinical practice as it demonstrates the effort required to achieve a particular therapeutic target, e.g., achieving GI recovery within 5 days or discharge from the hospital within 1 week after surgery for BR (McQuay and Moore, 1997). The NNT is used by clinicians to help determine the relative benefit of a treatment for the individual patient or a population and to assist in the decision regarding incorporating a preventative therapy or treatment into standard clinical practice.

This concept was applied to the Phase 3 study results (where appropriate) by using the reciprocal of the absolute difference in proportions to provide an additional dimension for determining clinically meaningful patient benefit of treatment with alvimopan as compared with placebo. A perspective for the interpretation of the NNTs achieved in the Phase 3 program can be provided from examples of several preventative therapies for acute postoperative conditions (Song, 1998; Anderson et al, 1993; Wells et al, 1994) such as deep vein thrombosis (i.e., the use of graduated compression stockings or low molecular weight heparin in patients undergoing orthopedic or major abdominal surgery) and wound infection (i.e., the use of IV antibiotics in patients undergoing open colorectal surgery). The NNTs calculated from the results of meta-analyses for these preventative therapies ranged from 4 to 17 (calculated using absolute risk reduction). These preventative therapies have been incorporated into standard clinical practice based on the benefits they have demonstrated in randomized, controlled clinical trials. The NNTs for these preventative therapies provide support that a therapy (i.e., alvimopan) for an acute postoperative condition of similar importance and potential sequelae (i.e., POI), demonstrating NNTs of comparable magnitude and without increased risk, would represent meaningful patient benefit and should be incorporated into standard clinical practice.

6.2.1.6   Analysis Methods for Endpoints

Analyses presented are for the MITT analysis set. Details of analysis methods used for the above endpoints are presented in Appendix 12.2.

6.2.2   Major Entry Criteria

The relevant inclusion and exclusion criteria for the Phase 3 trials are summarized below:

6.2.2.1   Inclusion

- Patients had to be at least 18 years of age

- Patients had to have an ASA Score of I to III

- Patients had to be scheduled for partial small or large BR with primary anastomosis performed by laparotomy

- Postoperative pain management to be controlled with opioid-based IV PCA

6.2.2.2   Exclusion

- Patients could not be scheduled for total colectomy, colostomy, ileostomy

- Patients could not have a complete bowel obstruction

- Patients could not have received more than three doses of opioid analgesics within 7 days of surgery

6.2.3   Patient Disposition—BR Population

Disposition was generally similar among the BR populations for the five Phase 3 POI studies (Table 10).

6.2.4   Demographic Characteristics—BR Population

Demographic characteristics were generally similar among the BR populations for the five studies, with the exception of race (Table 11). Few Black patients, and no Hispanic or Asian patients were enrolled in GSK001, and a lower proportion of patients in GSK001 had body mass index (BMI) $\geq$ 30 kg/m^2 compared with the four NA studies.

6.2.5   Surgery Characteristics—BR Population

Surgery characteristics were generally similar among the BR populations for the five studies (Table 12).

6.2.6   Extent of Exposure—BR Population

Extent of exposure by number of doses was generally similar among the five studies, but some variation existed since, by protocol, patients could take study medication until discharge or for up to 7 days BID while hospitalized. Hence, the LOS confounded the number of days on study medication. The mean and median numbers of doses taken by patients were higher for GSK001 compared to the four NA studies.

Table 10   Patient Disposition—BR Population

Characteristic	14CL302		14CL308		14CL313		14CL314		GSK001	
	Placebo n (%)	12 mg n (%)	Placebo n (%)	12 mg n (%)	Placebo n (%)	12 mg n (%)	Placebo n (%)	12 mg n (%)	Placebo n (%)	12 mg n (%)
Total number of patients, n	99	98	142	139	142	160	312	317	229	239
Completed treatment, n (%)	82 (82.8)	74 (75.5)	113 (79.6)	120 (86.3)	109 (76.8)	136 (85.0)	253 (81.1)	266 (83.9)	178 (77.7)	197 (82.4)
Discontinued from treatment, n (%)	17 (17.2)	24 (24.5)	29 (20.4)	19 (13.7)	33 (23.2)	24 (15.0)	59 (18.9)	51 (16.1)	51 (22.3)	42 (17.6)
Adverse event, n	15	20	25	14	25	14	43	31	7	11
Other[a], n	2	4	4	5	8	10	16	20	44	31
Completed study, n (%)	94 (94.9)	88 (89.8)	113 (79.6)	120 (86.3)	134 (94.4)	153 (95.6)	303 (97.1)	305 (96.2)	187 (81.7)	198 (82.8)

a Additional reasons were added together to obtain the total number of "other." These included administrative reasons, lost to follow-up, withdrawn consent & protocol violations.

Table 11   Demographic Characteristics—BR Population

Characteristic	14CL302 Placebo n (%)	14CL302 12 mg n (%)	14CL308 Placebo n (%)	14CL308 12 mg n (%)	14CL313 Placebo n (%)	14CL313 12 mg n (%)	14CL314 Placebo n (%)	14CL314 12 mg n (%)	GSK001 Placebo n (%)	GSK001 12 mg n (%)
Total BR patients	99	98	142	139	142	160	312	317	229	239
Age, years										
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)
Sex										
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

| Characteristic | 14CL302 | | 14CL308 | | 14CL313 | | 14CL314 | | GSK001 | |
	Placebo n (%)	12 mg n (%)	Placebo n (%)	12 mg n (%)	Placebo n (%)	12 mg n (%)	Placebo n (%)	12 mg n (%)	Placebo n (%)	12 mg n (%)
(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/m², 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/m², 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)

BR = bowel resection; SD = standard deviation; BMI = body mass index; min = minimum; max = maximum.

Table 12   Surgery Characteristics—BR Population

Characteristic	14CL302		14CL308		14CL313		14CL314		GSK001a	
	Placebo n (%)	12 mg n (%)	Placebo n (%)	12 mg n (%)	Placebo n (%)	12 mg n (%)	Placebo n (%)	12 mg n (%)	Placebo n (%)	12 mg n (%)
Total patients	99	98	142	139	142	160	312	317	229	239
Surgery category, n (%)										
Small BR	NA	NA	16 (11.3)	11 (7.9)	12 (8.5)	23 (14.4)	22 (7.1)	31 (9.8)	12 (5.2)	9 (3.8)
Large BR	99 (100.0)	98 (100.0)	126 (88.7)	128 (92.1)	130 (91.5)	137 (85.6)	290 (92.9)	286 (90.2)	217 (94.8)	230 (96.2)
Left	48 (48.5)	52 (53.1)	77 (54.2)	78 (56.1)	81 (57.0)	80 (50.0)	185 (59.3)	174 (54.9)	99 (43.2)	112 (46.9)
Right	51 (51.5)	46 (46.9)	49 (34.5)	50 (36.0)	49 (34.5)	57 (35.6)	105 (33.7)	112 (35.3)	80 (34.9)	87 (36.4)
Other	0	0	0	0	0	0	0	0	38 (16.6)[a]	31 (13.0)[a]
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 (min-max)	1.9 (0.5-5.1)	1.6 (0.5-7.8)	2.2 (0.9-8.4)	2.2 (0.8-6.6)	1.9 (0.4-5.8)	1.8 (0.3-7.2)	1.8 (0.4-5.9)	1.7 (0.4-6.9)	2.5 (0.3-5.8)	2.5 (0.7-7.3)
Elapsed time between 1st dose & surgery, hours										
Mean (SD)	3.2 (1.62)	3.0 (0.89)	3.6 (1.55)	3.6 (1.46)	3.3 (1.28)	3.4 (1.45)	1.4 (0.58)	1.4 (0.68)	2.4 (1.53)	2.3 (0.62)
Median (min-max)	2.8 (1.3-9.6)	2.8 (1.1-6.2)	3.2 (1.5-11.8)	3.1 (1.4-9.0)	3.0 (1.0-10.6)	2.9 (1.1-10.5)	1.3 (0.2-4.8)	1.3 (0.3-4.8)	2.3 (-14.8-12.5)	2.3 (1.0-4.4)
Number of doses of study drug										

Characteristic	14CL302		14CL308		14CL313		14CL314		GSK001a	
	Placebo n (%)	12 mg n (%)	Placebo n (%)	12 mg n (%)	Placebo n (%)	12 mg n (%)	Placebo n (%)	12 mg n (%)	Placebo n (%)	12 mg n (%)
Mean (SD)	10.1 (3.13)	9.0 (3.01)	10.2 (3.54)	9.5 (2.80)	9.2 (3.44)	9.1 (3.10)	9.1 (3.31)	8.5 (3.20)	11.8 (4.15)	12.0 (4.02)
Median (min-max)	10.0 (2-15)	9.0 (1-15)	10.0 (1-15)	10.0 (1-15)	9.0 (1-15)	9.0 (1-15)	9.0 (1-15)	8.0 (1-15)	14.0 (1-17)	14.0 (1-16)

a In Study GSK001, transverse BR was captured as "other" versus large left BR.

BR = bowel resection; min = minimum; max = maximum; SD = standard deviation.

6.2.7   Summary of Efficacy Results in POI

This efficacy section presents data from the MITT BR population only.

6.2.7.1   Gastrointestinal Recovery-Related Endpoints

6.2.7.1.1   Endpoint Analysis

Using the Cox Proportional Hazards (Cox PH) model, the hazard ratios (HRs) for each of the individual GI recovery events in all five studies were always greater than one when comparing alvimopan 12 mg with placebo, indicating a higher probability of achieving GI recovery during the study period with alvimopan treatment.

The HRs and 95% confidence intervals (CIs) from the Cox PH model analysis of GI-3 and GI-2 are presented in Figure 8. Three of the five studies (14CL313, 14CL314, and GSK001) were composed of primarily or exclusively BR patients (87% to 100% of MITT patients). The treatment effect for GI recovery indicated by the primary endpoint (GI-3 for 14CL313 and GSK001; GI-2 for 14CL314) was statistically significant in two of the three studies: 14CL313 (HR = 1.494, p = 0.001) and 14CL314 (HR = 1.533, p ≤ 0.001). However, statistical significance was not achieved in GSK001 (HR = 1.132, p = 0.200).

The remaining two NA studies (14CL302 and 14CL308) comprised approximately 70% BR patients; therefore, the results were based on subgroup analyses. Treatment effect for GI recovery in these two studies did not achieve statistical significance: 14CL302 (HR = 1.295, p = 0.086) and 14CL308 (HR = 1.317, p = 0.029, not significant after adjustment for multiple comparison). GI-2 was statistically significant (p < 0.05) in all five studies, and HRs ranged from 1.299 to 1.625.

Figure 8   Hazard Ratios and 95% CIs for GI-2 and GI-3 by Individual Study
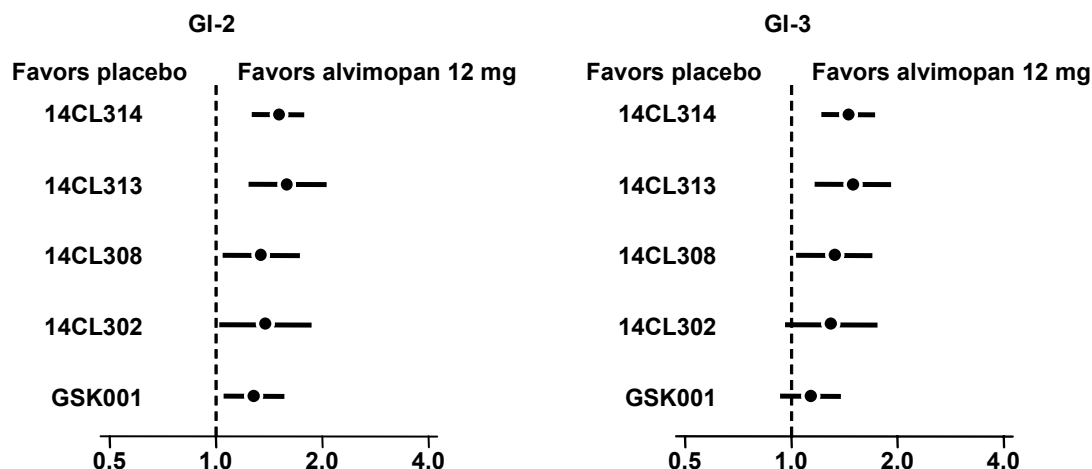
Note: HR and 95% CI were plotted on a log (2) scale. HR = hazard ratio; CIs = confidence intervals.

Kaplan-Meier (KM) survival curve analysis results for all GI recovery events showed a higher proportion of patients in the alvimopan 12-mg group achieving an event earlier throughout the entire observation period than patients who received placebo. The curves generally separated from one another as early as PSD 3 and maintained a separation throughout the remainder of the observation period.

Kaplan-Meier estimates for the median and mean differences in GI-3 and GI-2, respectively, according to each individual study are illustrated in Figure 9. The median and mean differences in KM estimates between the treatment groups for each study favored alvimopan. The median differences in KM estimates for GI-3 and GI-2 among the five studies ranged from approximately 3 hours to 12 hours and 3 hours to 17 hours, respectively. The mean differences in KM estimates for GI-3 and GI-2 ranged from 5 hours to 20 hours and 11 hours to 26 hours, respectively. Appendix 12.2 provides details regarding the KM estimates.

Figure 9   Difference in KM Estimates: Median and Mean Time to GI-3 and GI-2
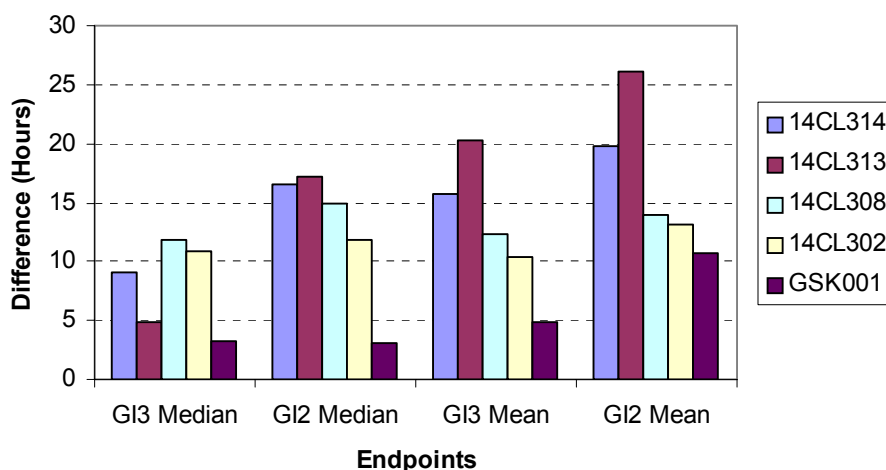
In all five Phase 3 studies, the 75th percentile on the placebo KM survival curves for GI-2 and GI-3 generally corresponded to the higher risk period for prolonged POI Figure 10. Differences favoring alvimopan observed at or beyond the 75th percentile ranged from 15 to 39 hours for GI recovery (GI-2 and GI-3) in the NA Phase 3 studies.

**Figure 10   Differences in KM Estimates: Median, Mean, and the 75th Percentile
                     for GI-3 and GI-2**
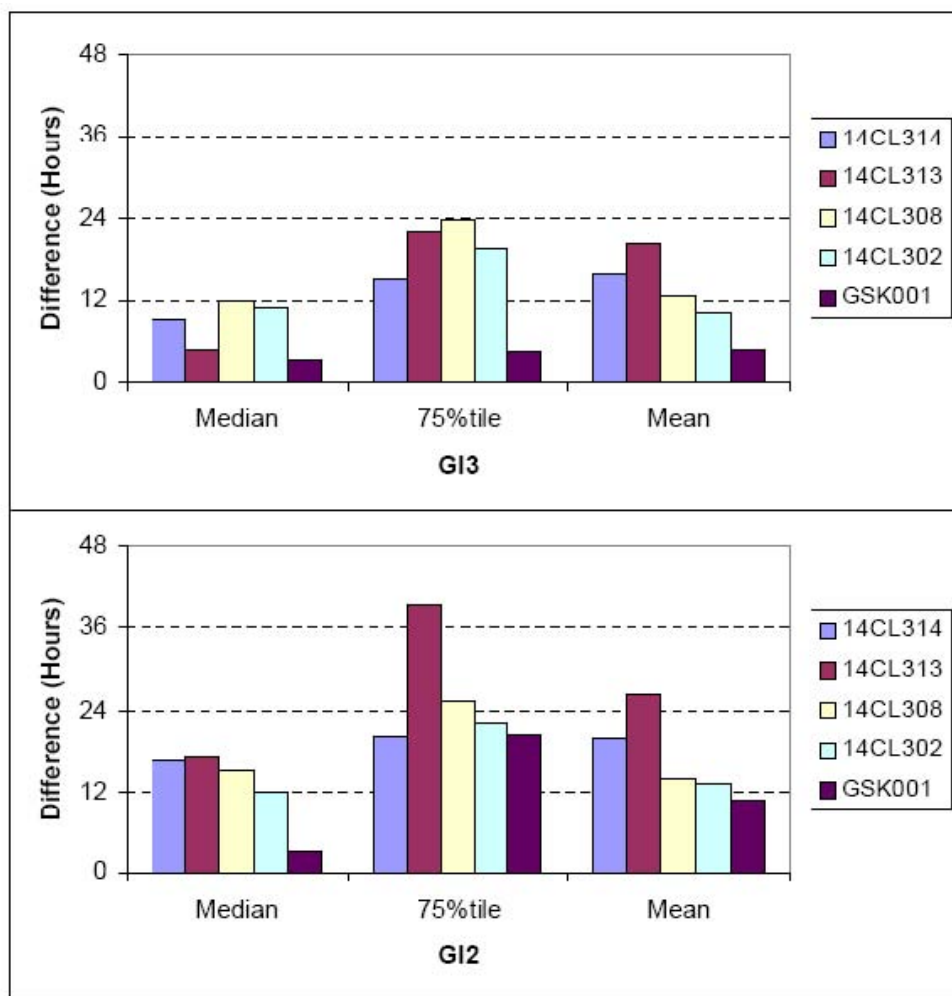
6.2.7.1.2   *Responder Analysis*

Responder analysis results for the GI recovery composite endpoint GI-3 for each of the five studies generally show the highest difference in proportion of responders by PSD 4 (Figure 11). The alvimopan 12-mg group had a higher proportion of responders by each PSD compared with placebo, with the exception of Study GSK001 on PSD 3.

Results for the responder analysis of the GI recovery composite endpoint GI-2 generally show the highest difference in proportion of responders by PSD 4 (Figure 12). The alvimopan 12-mg group had a higher proportion of responders by each PSD compared with placebo.

Figure 11   **Difference in Responders Analysis for GI-3 by PSD**
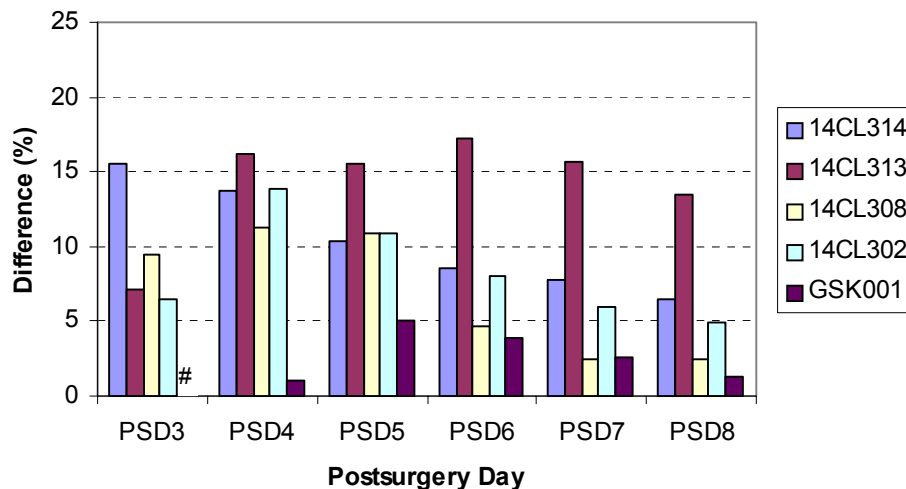
= Difference (%) of -1.5% in GSK001.

Figure 12   **Difference in Responders Analysis for GI-2 by PSD**
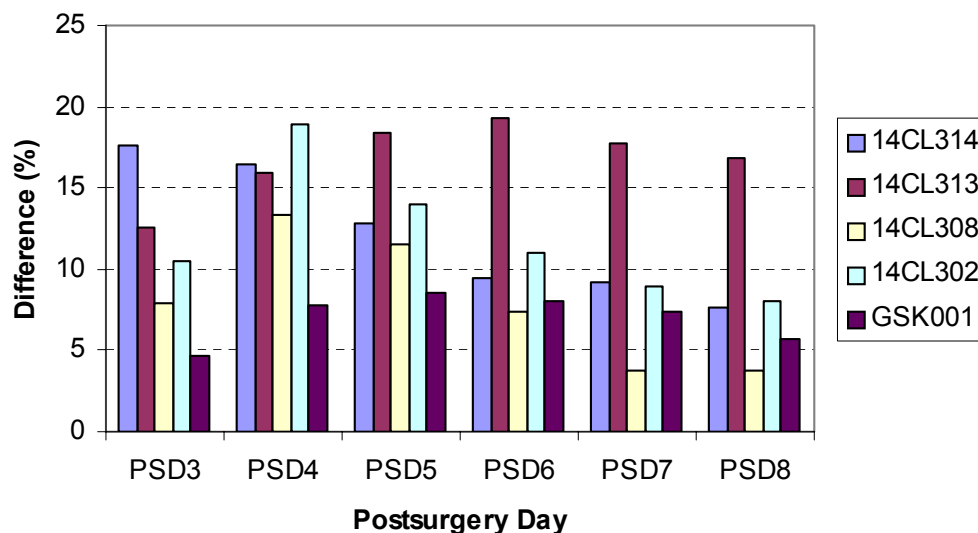
The proportion of responders was higher in the alvimopan treatment group than in the placebo treatment group for both GI-2 and GI-3 at each period (PSDs 3 through 8) across all five of the Phase 3 studies (with the exception of GI-3 by PSD 3 in the non-NA study, GSK001).

In the NA Phase 3 studies, the percentage difference between the alvimopan and placebo treatment groups in the proportion of responders measured by GI-2 or GI-3 ranged from 10% to 18% by PSD 5. This corresponds to NNTs ranging from 6 to 10. The differences in the

proportion of responders by PSDs 6, 7, and 8 for GI-2 and GI-3 continued to favor alvimopan. In the non-NA study, the percentage difference between the alvimopan and placebo treatment groups for GI recovery ranged from 5% to 9% by PSD 5 for GI-2 and GI-3, respectively.

6.2.7.1.3   Evaluating GI Recovery Data in GSK001

The results with alvimopan obtained in GSK001 raised a number of questions regarding the comparability of this study to those conducted in North America. A review of the data was directed towards clarifying major differences between this non-NA study and the NA Phase 3 efficacy trials (Table 13).

Table 13   Overview of Results of Cox PH Analysis for GI-2 and GI-3

	Hazard Ratio (95% CI)
GI-3	
14CL302	1.295 (0.964, 1.741)
14CL308	1.317 (1.029, 1.686)
14CL313	1.494 (1.167, 1.914)
14CL314	1.452 (1.233, 1.710)
GSK001	1.132 (0.936, 1.370)
GSK001 (Non-PCA Users)	1.01 (0.76, 1.34)
GSK001 (PCA Users)	1.18 (0.90, 1.56)
GI-2	
14CL302	1.400 (1.035, 1.894)
14CL308	1.365 (1.057, 1.764)
14CL313	1.625 (1.256, 2.102)
14CL314	1.533 (1.293, 1.816)
GSK001	1.299 (1.070, 1.575)
GSK001 (Non-PCA Users)	1.17 (0.88, 1.56)
GSK001 (PCA Users)	1.39 (1.05, 1.84)

The dominant focus was on postoperative analgesia where there were substantial differences in the patterns and practices of pain management that, as a consequence, had a major impact on the outcome of GSK001 as it relates to those studies conducted in the NA. The major findings and implications of these analyses are summarized below with respect to the BR population.

There were significant differences in the extent of IV PCA use for delivery of opioid analgesics between GSK001 (used in 45% of patients) and the NA studies (used in 99% of patients) providing evidence of different practice in GSK001.

There was a slower recovery of GI function in the GSK001 PCA placebo population as compared with the non-PCA placebo population (approximately 12, 19, and 24 hours difference for GI-3, GI-2 and first BM, respectively) providing evidence of an impact of route of opioid administration on underlying recovery of GI function in GSK001.

The magnitude of treatment response in the GSK001 PCA cohort was similar to that seen in the NA studies with respect to time to GI-3 and GI-2, with limited efficacy demonstrated in the GSK001 non-PCA cohort. This provides evidence of a consistent pharmacological effect and clinical benefit of alvimopan when similar patient populations in GSK001 and NA studies were compared.

There was a significantly higher use of non-opioid analgesics in GSK001 patients overall (69%) compared with the NA studies (< 4%), particularly during the early period of most intense postoperative pain (first 48 hours), which supports evidence of opioid-sparing approach in GSK001.

These important and significant differences are most likely responsible for the overall earlier recovery of GI function in GSK001 (as seen in placebo-treated patients) compared with those in NA studies, and the related impact on the magnitude of alvimopan treatment effect.

6.2.7.1.4   Summary for Gastrointestinal Recovery

Given that the clinical objective is GI recovery by the critical time point of PSD 5, the KM estimate median and mean differences demonstrated that treatment with alvimopan resulted in earlier GI recovery, with more patients achieving GI recovery within 5 PSDs. The associated NNTs supported a meaningful individual patient benefit with alvimopan. Treatment with alvimopan also provided benefit to those patients at both the median and at the higher risk period for prolonged POI (i.e., at or beyond the 75th percentile). Additional support for clinical benefit with alvimopan was demonstrated by a higher proportion of responders who achieved GI recovery without subsequent relapse due to complications of POI.

6.2.7.2   Hospital Discharge-Related Endpoints

6.2.7.2.1   Endpoint Analysis

The time from the end of surgery to when the discharge order was written (DOW) represented the length of hospital stay (LOS). Support for the use of DOW to represent LOS was provided in Study 14CL314 where Actual Departure was collected. In that study, the difference in mean DOW and mean Actual Discharge was only 4 hours for both treatments.

Using the Cox PH model for time to READY and DOW, the HR was always greater than one when comparing alvimopan 12 mg with placebo in all five studies, indicating a higher probability of achieving the event during the study period with alvimopan 12 mg than with placebo. The HRs and 95% CIs from the Cox PH model analysis of READY and DOW are presented in Figure 13.

Figure 13   Hazard Ratios and 95% CIs for Time to READY and DOW
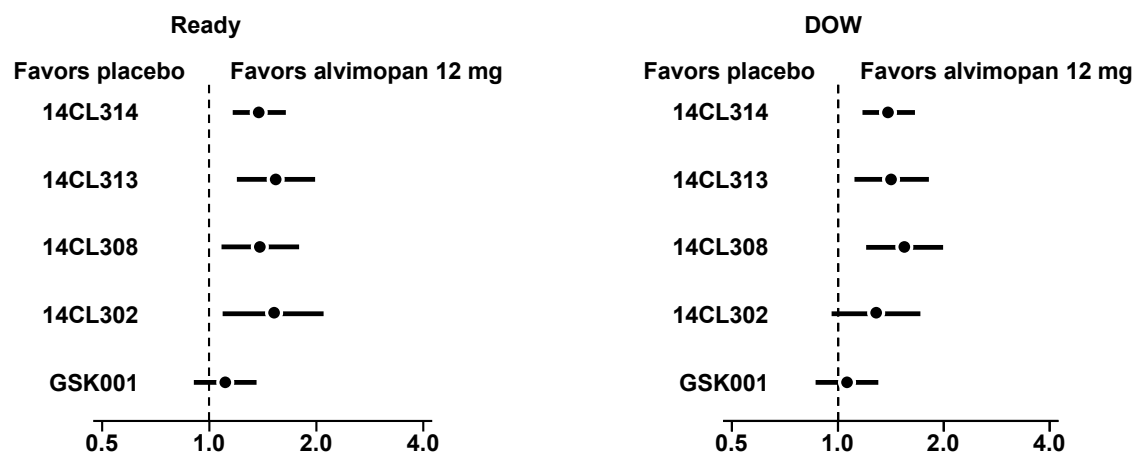
Note: HR and 95% CI were plotted on a log (2) scale. HR = hazard ratio; CIs = confidence intervals.

Treatment with alvimopan 12 mg compared with placebo was statistically significant in each of the four NA studies for READY, and in three of the four NA studies for DOW. The treatment effect on both discharge-related endpoints was not significant in GSK001. These findings are not unexpected due to differences in clinical practice regarding hospital discharge in Europe and other countries worldwide compared with NA as described above.

In the four NA studies, the accelerated time to GI recovery led to earlier time to READY and DOW, with KM median differences ranging from 11 to 16 hours for READY and from 6 to 22 hours for DOW; KM mean differences for READY and DOW ranged from approximately 13 to 21 hours. For GSK001, KM median differences for time to READY and DOW were 12 and 14 hours, respectively; mean differences for READY and DOW were each approximately 6 hours. The discrepancy between median and mean differences is likely explained by the stepwise or cyclical characteristic for discharge-related endpoints (less often reflected in the continuous variables representing times to GI recovery and first flatus, BM, or toleration of solid foods) and is consistent with clinical practice (i.e., surgical rounds and associated orders for discharge primarily occur within a 12-hour period during a hospital day). In fact, across the NA Phase 3 studies, approximately 90% of the discharge orders were written between 7 AM and 7 PM for each postoperative day. Therefore, the difference between placebo and alvimopan in the KM medians can be misleading if used as the only descriptive statistic with respect to these curves because the median may coincidentally occur at a point at which the curves are either narrowly or widely separated.

In the NA Phase 3 studies, the 75th percentile in the KM survival curves in the placebo population generally occurred by PSD 7. At or beyond the 75th percentile, time to READY or DOW for patients treated with alvimopan was reduced by 21 to 45 hours when compared with placebo (Figure 14). This analysis demonstrates a meaningful reduction in LOS to an important subset of patients.

Figure 14   Difference in KM Estimates of the Median, Mean, and 75th Percentile for READY and DOW
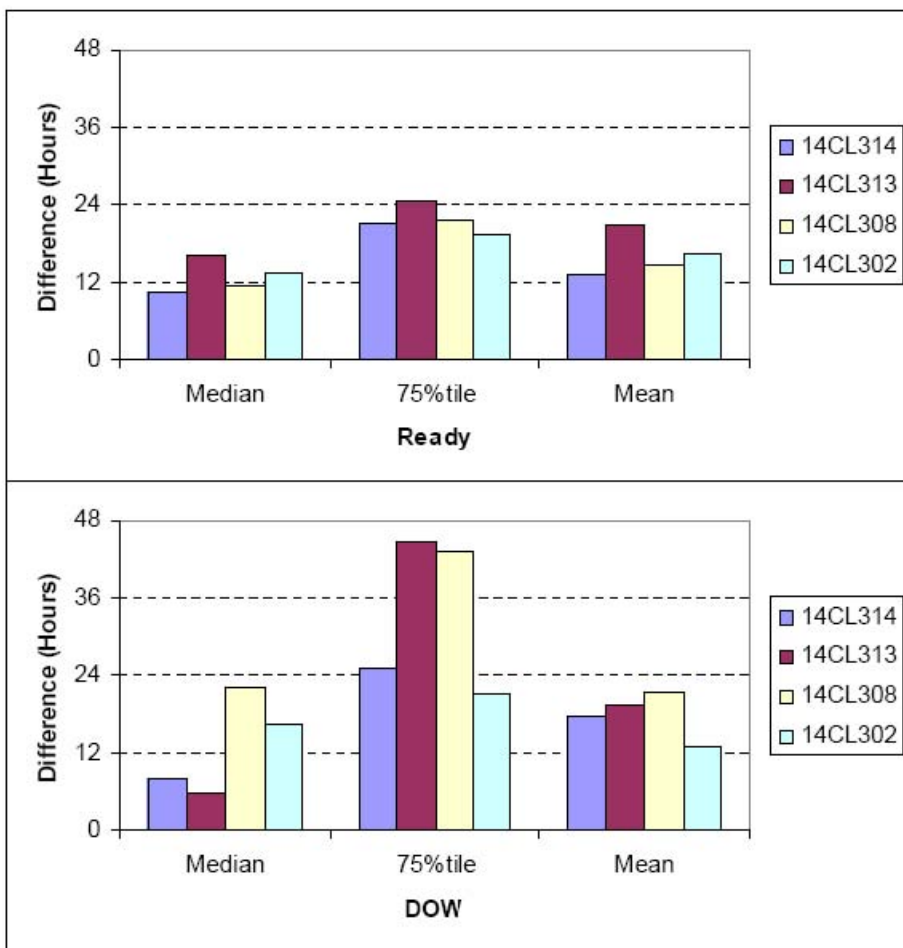
6.2.7.2.2   Responder Analysis

Across the NA Phase 3 studies, the proportion of responders for PSDs 3 through 8 was consistently higher in the alvimopan-treated patients than in placebo-treated patients for times to READY and DOW (Figure 15 and Figure 16). Importantly, there were 11% to 22% more responders in the alvimopan treatment group than in the placebo treatment group for time to DOW before PSD 7. This corresponded to NNTs ranging from 5 to 9.

Figure 15   Difference in Responders Analysis for READY
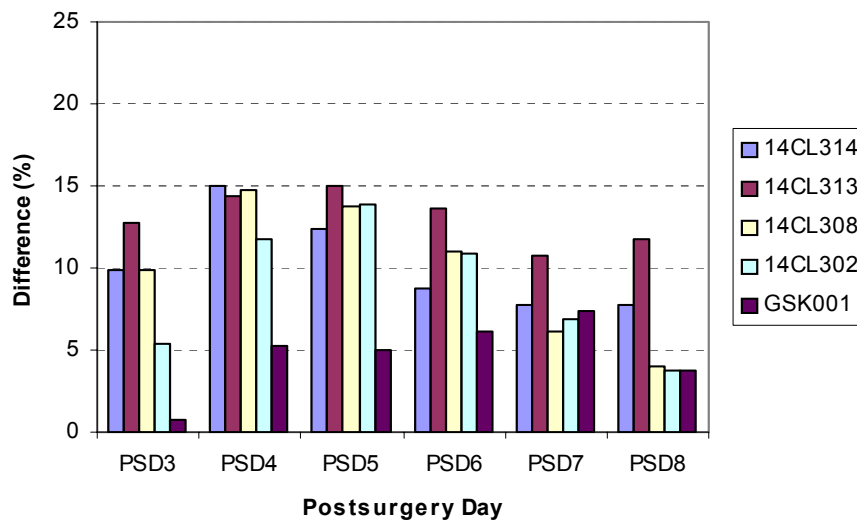
Figure 16   Difference in Responders Analysis for DOW
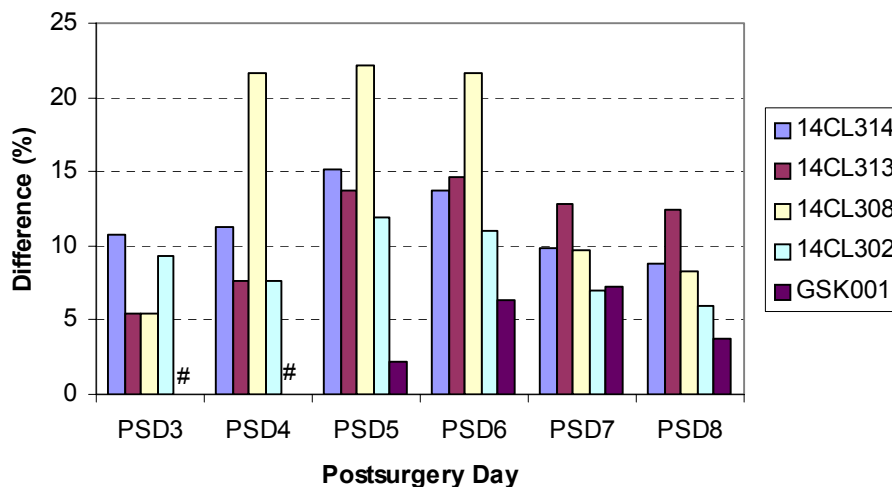
= Difference (%) of –0.1% on PSD 3 and –0.8% on PSD4 for Study GSK001.

FDA suggested that another clinically meaningful responder analysis would include the difference between the alvimopan and placebo treatment groups in the proportion of patients who had DOW on or after POD 7. The analysis demonstrated that the proportion of patients who had DOW on or after POD 7 was 13% to 24 % lower in the alvimopan treatment group than in the placebo treatment group across all NA Phase 3 studies. This corresponded to NNTs ranging from 4 to 8.

Consistent with the expected demography of colorectal cancer, 47% of the BR patients across all POI clinical trials were at least 65 years old, a population known to be at higher risk for postoperative mortality and morbidity in the hospital after BR.

When data from the NA Studies were pooled, the proportion of older patients who had DOW on or after POD 7 was lower in the alvimopan treatment groups than in the placebo treatment groups: 17% lower in patients who were at least 65 years old and 24% lower in patients who were at least 75 years old (Figure 17).

Figure 17   DOW on Postoperative Day 7 or Later in the Four Pooled NA Studies
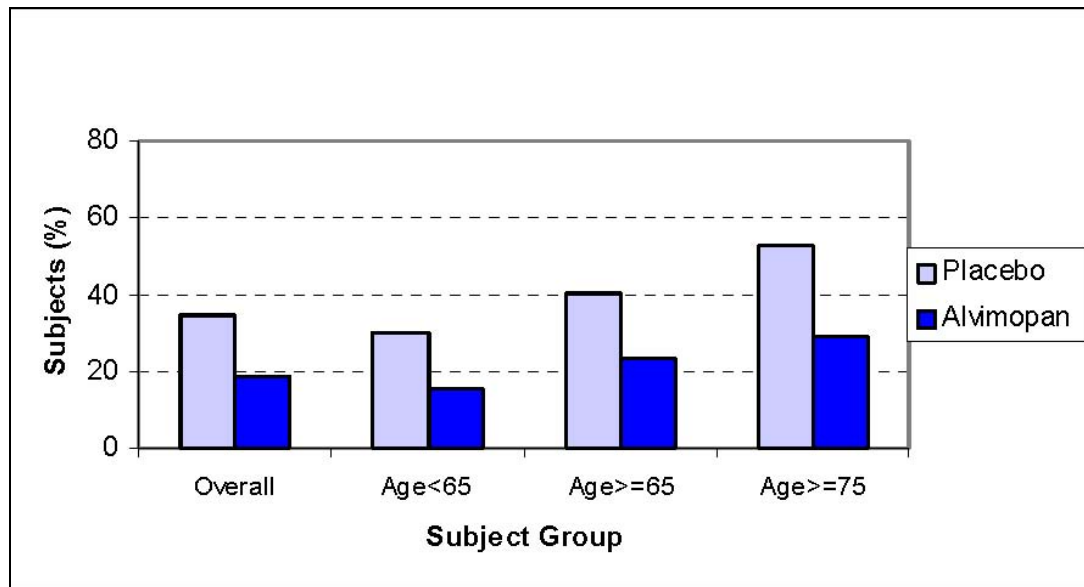
6.2.7.2.3   Length of Hospital Stay

The average LOS for patients who received alvimopan 12 mg or placebo in each of the five studies is presented in Table 14. The analysis differs from the time-to-event analysis because it was based on the observed date of DOW relative to the date of surgery, whereas in the survival analysis, patients who achieved this event after PSD 10 were censored at 264 hours after surgery. In three of the five studies, patients who received alvimopan 12 mg had shorter average LOS compared with those who received placebo, with an average difference of approximately 1 day.

The proportion of patients with DOW on or after PSD 7 was lower in the alvimopan 12 mg group than in the placebo group for each of the four NA studies (Figure 18).

Table 14   **Average Length of Stay (Days) by Study**

Treatment	Study 14CL314	Study 14CL313	Study 14CL308	Study 14CL302	Study GSK001
Placebo	6.2	7.4	6.6	6.4	9.2
Alvimopan 12 mg	5.2	6.1	5.7	6.1	8.9
Difference	1.0	1.3	0.9	0.3	0.2

Figure 18   **Proportion of Patients Remaining in the Hospital ≥ 7 Postsurgical Days**
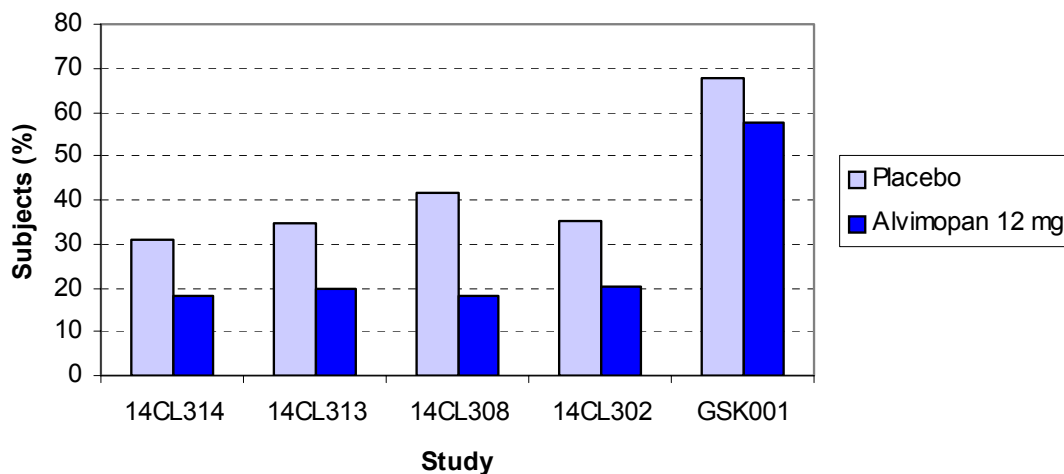
6.2.7.2.4 *Evaluating Hospital Discharge-Related Endpoints in GSK001*

In the NA studies, GI recovery (resolution of POI) was a primary determinant of LOS (i.e., discharge) with the time between achieving the mean GI-2 endpoint to mean DOW of approximately 1 day. This was not the case in GSK001, where the time from mean GI-2 to mean DOW was approximately 4 days. Using 14CL314 as a representation of the BR population, throughout most of the recovery period the difference between the GI-2 and DOW KM curves remains relatively consistent at approximately 24 hours as compared with approximately 72 hours in GSK001. Furthermore, as seen in Table 15, the average LOS in GSK001 was approximately 3 days longer compared to the pooled NA studies. These discrepancies are likely due to differences in both social and financial pressures related to hospital bed occupancy between the NA and Europe (Kehlet et al, 2006). Results from GSK001 with respect to discharge-related endpoints should be interpreted within this context and cannot be directly compared to the NA studies.

Table 15   **Patients With Complications of POI Resulting in Readmission**

Study	Placebo N	Alvimopan N	Placebo n (%)	Alvimopan 12 mg n (%)
14CL314	312	317	6 (1.9)	3 (0.9)
14CL313	142	160	3 (2.1)	2 (1.3)
14CL308	142	139	2 (1.4)	1 (0.7)
14CL302	99	98	3 (3.0)	1 (1.0)
GSK001	229	239	3 (1.3)	0

6.2.7.2.5   *Summary for Hospital Length of Stay*

The KM estimate mean differences demonstrate that treatment with alvimopan resulted in earlier times to both READY and DOW. Mean differences were associated with a reduction in hospital LOS of 1 day (as measured by calendar date of DOW) in three of the four NA Phase 3 studies. At or beyond the 75th percentile (representing a higher risk period or a period of extended LOS on the KM survival curves for DOW), treatment with alvimopan resulted in an earlier discharge of 1 to 2 days. This was also associated with a reduction in the proportion of alvimopan patients remaining in the hospital on or after PSD 7. Further support for the clinical benefit of alvimopan is demonstrated by a higher proportion of alvimopan responders achieving DOW before Day 7. The associated NNTs represented a meaningful individual patient benefit with alvimopan. Finally, in the alvimopan treatment group, a lower proportion of patients at least 65 years old remained in the hospital on or beyond PSD 7.

6.2.7.3   Postoperative Morbidity (Early Morbidity Related to POI)

A patient was considered as having POM if either of the following conditions was met: (1) postoperative NG tube insertion, or (2) complications of POI resulting in prolonged LOS or readmission within 7 days of actual discharge. Each of the 5 individual studies shows a lower proportion of patients with POM in the alvimopan 12-mg group vs. placebo (Figure 19).

Figure 19   **Proportion of Patients With Postoperative Morbidity**
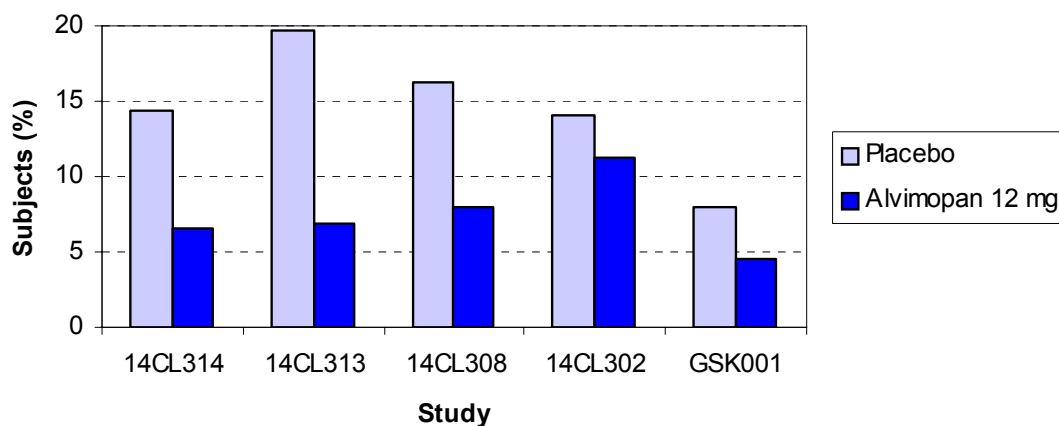
In four of the five Phase 3 studies, the proportion of patients with postoperative NGT insertion was lower in the alvimopan treatment group than in the placebo group (Figure 20). The fifth study showed a comparable incidence of postoperative NGT insertion. The reduction in the incidence of postoperative NGT insertion in the alvimopan treatment group vs. placebo ranged from < 2% to 10%. For the combined NA Phase 3 studies, the incidence of postoperative NGT insertion was reduced by 5% in the alvimopan treatment group, corresponding to an NNT of 20.

Figure 20   Proportion of Patients With Postoperative Nasogastric Tube Insertion
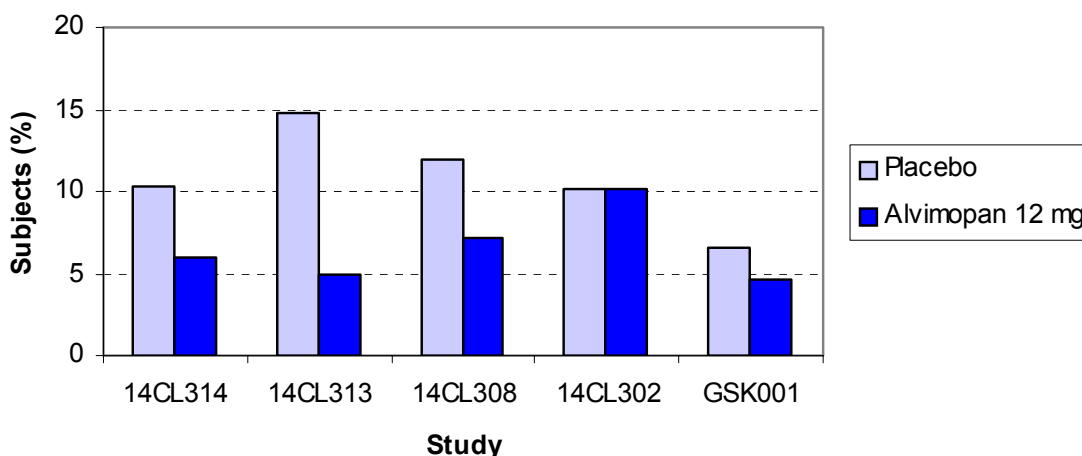
To explore whether there was a temporal association between symptoms of POI reported as AEs and the need for postoperative NG tube insertion, a post hoc analysis was performed. These results demonstrated that between Days 3 through 5 the incidence of both symptoms of POI and postoperative NGT insertion was lower in the alvimopan treatment group than in the placebo treatment group. This suggests that a reduction in the symptoms of POI with alvimopan treatment reduced the need for intervention with an NG tube.

Patients were considered as having complications of POI if they had the following SAEs that resulted in prolonged hospital stay or readmission: POI, ileus paralytic, or small intestinal obstruction. In all five studies, a lower proportion of patients in the alvimopan 12-mg group had overall complications of POI compared with the placebo group (Figure 21). The lower incidence of overall complications related to POI in GSK001 compared with the NA studies is likely due to the longer average LOS (3 days) in that study. As a result, AEs of POI, paralytic ileus, or early small intestinal obstruction were less likely to delay discharge or result in readmission in GSK001.

In each of the five studies, a lower proportion of patients in the alvimopan 12-mg group had complications of POI resulting in prolonged LOS compared with the placebo group (Figure 22).

Figure 21   Proportion of Patients With Complications of POI
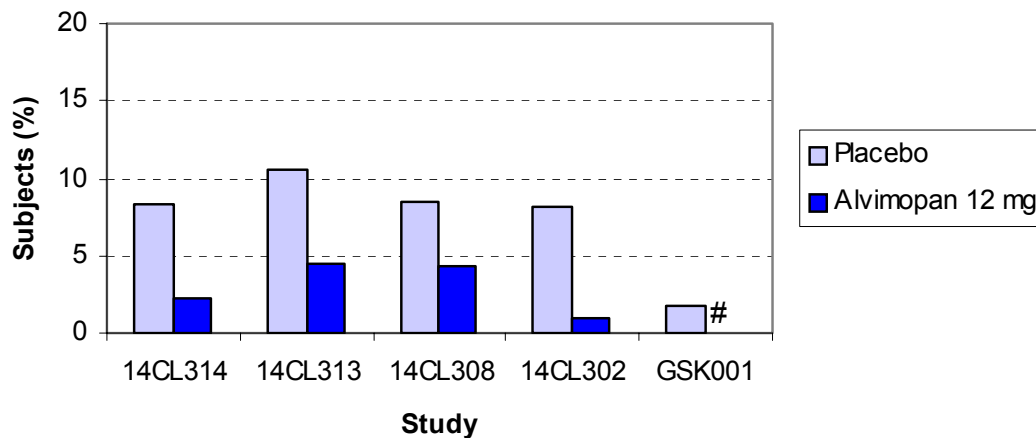
In Study GSK001, 0 patients in the alvimopan 12-mg group had overall complications of POI.

**Figure 22   Proportion of Patients With Complications of POI Resulting in
                     Prolonged Stay**
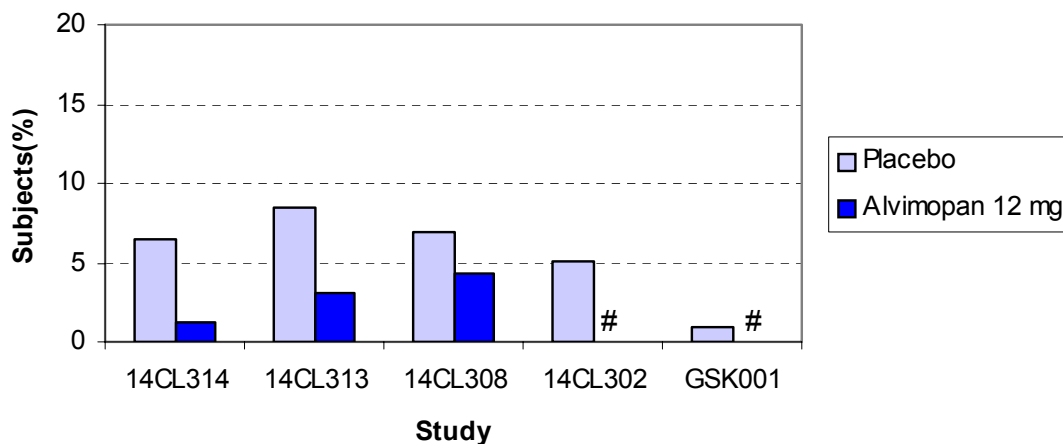
In Studies 14CL302 and GSK001, 0 patients in the alvimopan 12-mg group had complications of POI resulting in
   prolonged hospital stay.

Small numbers of patients overall had complications of POI resulting in hospital readmission
$\geq$ 7 days from hospital discharge; therefore, definitive conclusions could not be made. In
general, more patients in the placebo group had POI-related complications that led to
readmission than in the alvimopan 12-mg group in each of the five studies (Table 15).

The summary of data relating to readmissions for all causes within 10 days from hospital
discharge provides a broader comparison of readmission rate than does the summary of POI-
specific complications presented above in Table 15. All individual studies showed a lower
proportion of patients in the alvimopan 12-mg group having readmissions within 10 days of

hospital discharge compared with placebo, except for GSK001, which showed comparable proportions of patients (Figure 23).

Figure 23   **Proportion of Patients With Readmissions Within Ten Days of Hospital Departure**
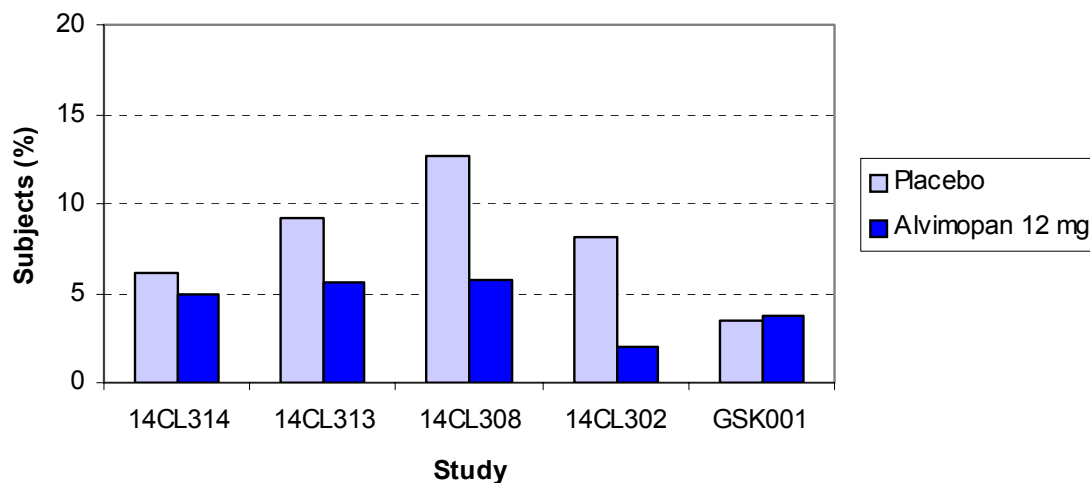
6.2.7.4   Opioid Analgesia

For the four pooled NA studies, there were no appreciable differences between treatment groups in preoperative, intra-operative, and postoperative daily average opioid consumption (Table 16) as well as visual analog scales that measure pain.

GSK001 was not included in the pooled analysis of opioid consumption. The protocol did not prohibit the use of concomitant non-opioid analgesics (NSAIDs or others) for opioid-sparing technique in this study compared with the NA Phase 3 studies. This was intentionally planned in GSK001 so that the participating hospitals could implement their usual pain management protocols.

Table 16   **Opioid Consumption (in Morphine Equivalent) During Pre- and Intra-Operative Periods—Four Pooled NA Studies**

| Time Period | Mean (SD) | |
	Placebo (N=695)	Alvimopan 12 mg (N=714)
Day 0 Preoperative	18.9 (15.49)	19.9 (15.88)
Day 0 Intra-operative	28.3 (28.93)	29.2 (30.10)
Postoperative daily average	28.8 (35.05)	27.2 (23.34)

6.2.8   Subgroup Analyses by Age, Sex, and Race

Based on data from five pooled studies, the effect of the covariates age, sex, and race on the GI recovery-related time-to-event endpoints was assessed individually using the Cox PH models that included the main effects of treatment and the covariate. The results of the covariate analyses are summarized in Table 17.

In general, patients $\geq$ 65 years old achieved events significantly later for GI-3 and solids than those < 65 years old (indicated by HR less than 1 and $p < 0.05$); males achieved events of GI-3 and Solids significantly later than females (indicated by HR less than 1 and $p < 0.05$), and Caucasian patients achieved events of GI-3 and Solids significantly sooner than non-Caucasian patients (indicated by HR greater than 1 and $p < 0.05$). The effect of age on GI-2 and the effect of sex on BM approached significance ($p > 0.05$ but $p < 0.10$).

Table 17   Covariate Assessment by Age, Sex, and Race for the Five Pooled Studies

| | Covariates | | | | | |
| | Age Group ($\geq$ 65 vs. <65 yr) | | Sex (M vs. F) | | Race Group (C vs. O) | |
Endpoint	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
GI-3	0.883 (0.813, 0.959)	0.003	0.914 (0.842, 0.993)	0.033	1.142 (1.007, 1.295)	0.038
GI-2	0.930 (0.854, 1.012)	0.091	0.974 (0.895, 1.060)	0.545	1.060 (0.933, 1.205)	0.373
BM	0.990 (0.912, 1.076)	0.820	1.083 (0.997, 1.176)	0.059	0.990 (0.873, 1.122)	0.872
Solids	0.899 (0.828, 0.976)	0.011	0.894 (0.823, 0.970)	0.007	1.144 (1.010, 1.297)	0.035
Flatus	0.956 (0.882, 1.037)	0.282	1.003 (0.925, 1.088)	0.936	1.097 (0.968, 1.242)	0.147

BM = bowel movement; C = Caucasian; O = other; HR = hazard ratio; M = male; F = female.

Treatment effect was evaluated within the subgroups of age, sex, and race, and results demonstrated that the alvimopan treatment effect within the demographic subgroups was consistent with and similar to that observed for the overall BR population.

Figure 24 presents the HRs and 95% CIs for GI-3 and GI-2, respectively, using the data from five pooled studies for each demographic subgroup.

Figure 25 presents the HRs and 95% CIs for READY and DOW using the data from four pooled studies for each demographic subgroup.

Figure 24   Hazard Ratios and 95% Confidence Intervals for GI-3 and GI-2 by Subgroup for the Five Pooled Studies
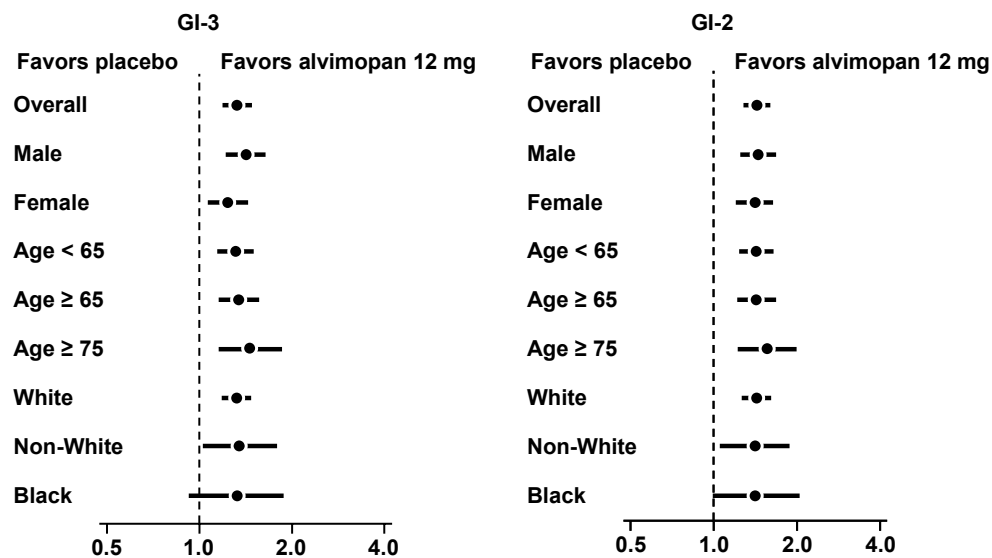
Figure 25   Hazard Ratios and 95% Confidence Intervals for READY and DOW by Subgroup for the Pooled NA Studies
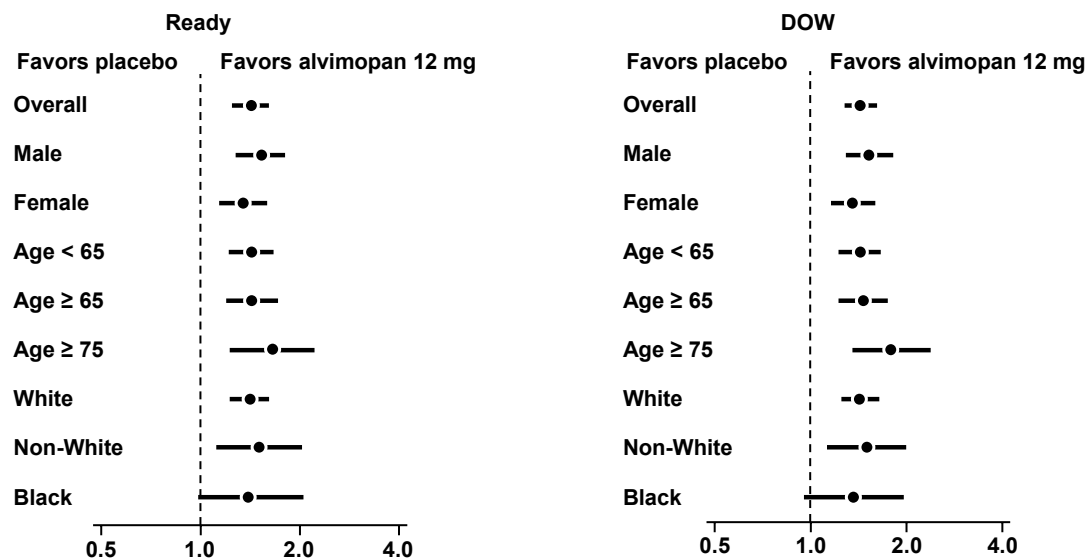
Within a subgroup, regardless of how each covariate may have affected the time at which patients achieved an event (as described above), patients in the alvimopan group were more likely to achieve the event sooner than patients in the placebo group (indicated by HRs > 1 in all subgroups). These results demonstrate that the alvimopan treatment effect was consistent among the subgroups and was not affected by these covariates.

6.2.9   Subgroup Analyses of Concomitant Medications and Crohn's Disease

Efficacy data (time to event) for the subset of patients who received concomitant treatments including preoperative antibiotics and mechanical bowel preparations or perioperative antibiotics with activity against GI flora were examined relative to the MITT BR population in order to evaluate potential changes in efficacy. Similarly, subgroup analyses were examined for the subset of patients who either took or did not take histamine H_2-receptor antagonists or proton-pump inhibitors, and for patients with or without Crohn's disease. A brief summary of these analysis follows:

- Results of time-to-event analyses indicated comparable efficacy profiles among BR patients who did or did not receive preoperative antibiotics and mechanical bowel preparation.

- Results of time-to-event analyses indicated comparable efficacy profiles among BR patients who did or did not receive perioperative antibiotics.

- Results of time-to-event analyses indicated comparable efficacy profiles among BR patients who did or did not receive histamine H_2-receptor antagonist or proton-pump inhibitors.

- Results of time-to-event analyses indicated higher HRs for small BR patients without Crohn's disease compared with those who had Crohn's disease. However the sample size was too small to draw definitive conclusions.

6.3   Efficacy Conclusions

Individual study data and the integrated analyses support the following conclusions:

- Alvimopan accelerated time to recovery of GI function in patients undergoing BR surgery as measured by the composite endpoints GI-2 and GI-3.

- In the NA studies, earlier GI recovery was associated with earlier time to READY, leading to shorter LOS with alvimopan treatment. A lower proportion of patients in the alvimopan 12-mg group had DOW $\geq$ 7days following surgery.

- Responder analyses of GI recovery and discharge-related endpoints consistently demonstrated a higher proportion of responders for alvimopan at each PSD evaluated in the NA studies, reinforcing the clinical benefit of alvimopan.

- A lower proportion of patients who received alvimopan required postoperative NG tube compared with placebo.

- Alvimopan accelerated GI recovery and hospital discharge but, importantly, did not reverse opioid analgesia.

- Alvimopan treatment effect was not affected by age, sex, or race.

- The efficacy of alvimopan was not affected by the concomitant use of antibiotics with activity against GI flora, with or without mechanical bowel preparations; histamine H_2-receptor antagonists; or proton-pump inhibitors.

7. CLINICAL SAFETY

Alvimopan has been evaluated in 55 Phase 1 through Phase 3 studies, exposing more than 5500 subjects/patients within North America, Europe, and other countries worldwide. Studies have been designed to assess the clinical pharmacology and safety of alvimopan in healthy volunteers and special patient populations (i.e., elderly patients, patients with renal or hepatic impairment, and patients with Crohn's disease); to assess the efficacy and safety of alvimopan for the management of POI in patients who received opioids after segmental BR with primary anastomosis or TAH; and to assess the effects of treatment in patients with OBD, and chronic idiopathic constipation (CIC). The safety data from the healthy, normal volunteer studies are not presented because alvimopan was well tolerated and because no safety issues were identified in these studies. The safety data collected in the Phase 2/3 POI studies as well as the OBD studies are presented in the following sections.

7.1   Safety in POI

Nine studies in patients scheduled to receive opioid-based IV PCA for postoperative pain management after either segmental BR with primary anastomosis or total abdominal hysterectomy have been completed in support of the clinical development of alvimopan for the management of POI. These studies were double-blind, placebo-controlled, parallel-group designs and include NA Studies 13C206, 13C213, 13C214, 14CL302, 14CL306, 14CL308, 14CL313, 14CL314, and non-NA study GSK001. Adverse events were captured during the patient's hospital stay and telephone follow-up, obtained within 2 weeks of the last dose of study medication. Serious AEs were reported through 30 days following last dose of study medication.

A total of 3975 patients are included in the worldwide POI safety database; 1365 patients received placebo and 2610 patients received alvimopan at doses of 1, 3, 6, or 12 mg. The dosing regimen for all studies was the following: one dose preoperatively followed by BID starting on POD 1 until discharge or up to a maximum of 7 days. POI patients in the worldwide safety database received a median of 9 to 10 doses of study drug over a median duration of 6 days. Exposure was similar in the subgroup of patients who underwent BR.

Alvimopan doses administered across these studies were 1, 3, 6, and 12 mg. For summarization purposes, these doses were pooled into groups of 1 to 3 mg, 6 mg, and 12 mg. The 1- to 3-mg group had a small sample size relative to the other treatment groups (n=62, vs. n=898 in the 6-mg group and n=1321 in the 12-mg group), making it difficult to draw comparisons. For this reason, tables herein are limited to the alvimopan 6 mg and 12 mg groups (Note: in all tables, the total alvimopan column includes the 1 to 3 mg group).

7.1.1   Patient Disposition

As shown in Table 18, more patients in the placebo group discontinued treatment due to AEs than patients in either the alvimopan 6 or 12 mg groups.

Table 18   Patient Disposition—Overall POI Population

| | | 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 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)

a The 62 patients in the alvimopan 1- to 3-mg group are included in the alvimopan total.

7.1.2 Demographics

As shown in Table 19, most patients in the POI studies were Caucasian, female, and
< 65 years of age (although over 30% were ≥ 65 years of age).

Table 19   Demographics—Overall POI Population

| | Placebo N=1365 n (%) | Alvimopan | | |
		6 mg N=898 n (%)	12 mg N=1650 n (%)	Total[a] N=2610 n (%)
Age, years				
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	491 (36.0)	373 (41.5)	511 (31.0)	898 (34.4)
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)

7.1.3   Types of Surgery

Bowel resection was the primary surgical type in more than 60% of the population, most of which were involving the large bowel, with a slightly higher number of left as compared to right resections. The mean duration of surgery (approximately 2 hours) was similar across the treatment groups (Table 20).

Table 20   Types of Surgery—Overall POI Population

	Placebo N=1365 n (%)	Alvimopan		
		6 mg N=898 n (%)	12 mg N=1650 n (%)	Total[a] N=2610 n (%)
Surgery				
BR	986 (72.2)	663 (73.8)	999 (60.5)	1681 (64.4)
rTAH	108 (7.9)	97 (10.8)	91 (5.5)	198 (7.6)
sTAH	222 (16.3)	102 (11.4)	511 (31.0)	646 (24.8)
Other surgeries	27 (2.0)	24 (2.7)	30 (1.8)	54 (2.1)
No surgery	22 (1.6)	12 (1.3)	19 (1.2)	31 (1.2)
Surgery duration, hours				
N	1341	886	1630	2577
Mean (SD)	2.2 (1.12)	2.3 (1.16)	2.0 (1.11)	2.1 (1.13)
Median	2	2.1	1.7	1.8
Minimum, maximum	0.2, 8.4	0.4, 8.8	0.3, 8.7	0.3, 8.8

BR = bowel resection; rTAH = radical total abdominal hysterectomy; sTAH = simple total abdominal hysterectomy.
a The 62 patients in the alvimopan 1- to 3-mg group are included in the alvimopan total.

7.1.4   Treatment-Emergent Adverse Events

7.1.4.1   Treatment-Emergent Adverse Events—Overall POI Population

The most commonly reported TEAE among POI patients was nausea (Table 21). The incidence of nausea and vomiting were comparable between the alvimopan 12-mg group and the placebo group, while patients in the alvimopan 6-mg group tended to have less nausea and vomiting. Other GI-related TEAEs, including abdominal distension, flatulence, abdominal pain, diarrhea, constipation, and dyspepsia, were reported at similar rates in the alvimopan treatment groups compared with the placebo group. The incidence of POI reported as a TEAE was lower in both alvimopan treatment groups compared with the placebo group.

Table 21   **Treatment-Emergent Adverse Events Reported in ≥ 5% of Patients in Any Treatment Group—Overall POI Population**

| | Placebo N=1365 n (%) | Alvimopan | | |
Preferred Term[a]		6 mg N=898 n (%)	12 mg N=1650 n (%)	Total[b] N=2610 n (%)
Nausea	699 (51.2)	367 (40.9)	858 (52.0)	1264 (48.4)
Vomiting	299 (21.9)	152 (16.9)	305 (18.5)	470 (18.0)
Abdominal distension	177 (13.0)	79 (8.8)	176 (10.7)	267 (10.2)
Hypertension	143 (10.5)	100 (11.1)	171 (10.4)	274 (10.5)
Pyrexia	189 (13.8)	84 (9.4)	165 (10.0)	255 (9.8)
Pruritus	135 (9.9)	70 (7.8)	162 (9.8)	236 (9.0)
Constipation	104 (7.6)	37 (4.1)	160 (9.7)	202 (7.7)
Flatulence	105 (7.7)	56 (6.2)	143 (8.7)	208 (8.0)
Headache	106 (7.8)	68 (7.6)	141 (8.5)	215 (8.2)
Insomnia	106 (7.8)	68 (7.6)	131 (7.9)	207 (7.9)
Hypotension	124 (9.1)	79 (8.8)	118 (7.2)	203 (7.8)
Hypokalemia	103 (7.5)	55 (6.1)	114 (6.9)	170 (6.5)
Dyspepsia	65 (4.8)	33 (3.7)	98 (5.9)	142 (5.4)
Tachycardia	103 (7.5)	53 (5.9)	96 (5.8)	155 (5.9)
Anemia	74 (5.4)	40 (4.5)	89 (5.4)	134 (5.1)
Diarrhea	98 (7.2)	66 (7.3)	88 (5.3)	156 (6.0)
Dizziness	61 (4.5)	29 (3.2)	87 (5.3)	119 (4.6)
Body temperature increased	82 (6.0)	44 (4.9)	73 (4.4)	117 (4.5)
Oliguria	78 (5.7)	54 (6.0)	67 (4.1)	123 (4.7)
Postoperative ileus	127 (9.3)	44 (4.9)	66 (4.0)	111 (4.3)

a A patient who had more than one AE in the same category was counted only once.
b The 62 patients in the alvimopan 1- to 3-mg group are included in the alvimopan total.

A summary of TEAEs that occurred in ≥ 1% of POI patients in the alvimopan 12 mg group with an incidence higher than placebo is presented in Table 22. In general, the incidence of these TEAEs was comparable across the three treatment groups.

Table 22   **Treatment-Emergent Adverse Events (Occurring in ≥ 1% of Alvimopan 12 mg Patients With an Incidence Higher Than Placebo) —Overall POI Population**

		Alvimopan		
Preferred Term[a]	**Placebo** **N=1365** **n (%)**	**6 mg** **N=898** **n (%)**	**12 mg** **N=1650** **n (%)**	**Total[b]** **N=2610** **n (%)**
Nausea	699 (51.2)	367 (40.9)	858 (52.0)	1264 (48.4)
Flatulence	105 (7.7)	56 (6.2)	143 (8.7)	208 (8.0)
Headache	106 (7.8)	68 (7.6)	141 (8.5)	215 (8.2)
Insomnia	106 (7.8)	68 (7.6)	131 (7.9)	207 (7.9)
Constipation	104 (7.6)	37 (4.1)	160 (9.7)	202 (7.7)
Dyspepsia	65 (4.8)	33 (3.7)	98 (5.9)	142 (5.4)
Dizziness	61 (4.5)	29 (3.2)	87 (5.3)	119 (4.6)
Anxiety	48 (3.5)	29 (3.2)	68 (4.1)	99 (3.8)
Urinary tract infection	52 (3.8)	23 (2.6)	68 (4.1)	94 (3.6)
Abdominal pain	44 (3.2)	17 (1.9)	59 (3.6)	80 (3.1)
Urinary retention	31 (2.3)	23 (2.6)	57 (3.5)	80 (3.1)
Back pain	36 (2.6)	19 (2.1)	56 (3.4)	77 (3.0)
Hiccups	26 (1.9)	18 (2.0)	38 (2.3)	56 (2.1)
Rash	21 (1.5)	11 (1.2)	30 (1.8)	42 (1.6)
Eructation	17 (1.2)	4 (0.4)	29 (1.8)	33 (1.3)
Procedural complication	10 (0.7)	6 (0.7)	25 (1.5)	31 (1.2)
Alanine aminotransferase increased	17 (1.2)	6 (0.7)	22 (1.3)	28 (1.1)
Asthenia	14 (1.0)	9 (1.0)	21 (1.3)	30 (1.1)
Retching	6 (0.4)	8 (0.9)	19 (1.2)	27 (1.0)
Wound dehiscence	14 (1.0)	8 (0.9)	18 (1.1)	26 (1.0)
Infusion site edema	8 (0.6)	12 (1.3)	17 (1.0)	30 (1.1)
Hot flush (#F)	6 (0.7)	3 (0.6)	15 (1.3)	20 (1.2)

a A patient who had more than one AE in the same category was counted only once.
b The 62 patients in the alvimopan 1- to 3-mg group are included in the alvimopan total.
#F indicates female-specific adverse event.

7.1.4.2   Treatment-Emergent Adverse Events—BR Population

As shown in Table 23, the incidence of POI and nausea were lower in both alvimopan groups compared with the placebo group among patients who underwent BR. Additionally, BR patients who received alvimopan 12 mg tended to have less vomiting and post operative ileus compared with patients who received placebo. The incidence of all other TEAEs among BR patients was similar across treatment groups.

Table 23   Treatment-Emergent Adverse Events Reported in ≥ 5% of Patients in Any Treatment Group—BR Population

		Alvimopan		
Preferred Term[a]	**Placebo** **N=986** **n (%)**	**6 mg** **N=663** **n (%)**	**12 mg** **N=999** **n (%)**	**Total[b]** **N=1681** **n (%)**
Nausea	491 (49.8)	246 (37.1)	433 (43.3)	691 (41.1)
Vomiting	209 (21.2)	111 (16.7)	141 (14.1)	256 (15.2)
Hypertension	117 (11.9)	84 (12.7)	126 (12.6)	213 (12.7)
Abdominal distension	137 (13.9)	59 (8.9)	120 (12.0)	183 (10.9)
Pyrexia	144 (14.6)	64 (9.7)	102 (10.2)	168 (10.0)
Hypotension	98 (9.9)	58 (8.7)	89 (8.9)	149 (8.9)
Pruritus	97 (9.8)	46 (6.9)	85 (8.5)	132 (7.9)
Hypokalemia	84 (8.5)	46 (6.9)	95 (9.5)	142 (8.4)
Insomnia	82 (8.3)	49 (7.4)	82 (8.2)	133 (7.9)
Postoperative ileus	113 (11.5)	33 (5.0)	60 (6.0)	94 (5.6)
Tachycardia	86 (8.7)	46 (6.9)	69 (6.9)	118 (7.0)
Diarrhea	84 (8.5)	55 (8.3)	57 (5.7)	113 (6.7)
Headache	67 (6.8)	44 (6.6)	68 (6.8)	113 (6.7)
Oliguria	59 (6.0)	45 (6.8)	50 (5.0)	96 (5.7)
Dyspepsia	45 (4.6)	27 (4.1)	70 (7.0)	103 (6.1)
Body temperature increased	64 (6.5)	30 (4.5)	43 (4.3)	73 (4.3)
Postoperative infection	59 (6.0)	23 (3.5)	45 (4.5)	68 (4.0)
Anemia	41 (4.2)	27 (4.1)	52 (5.2)	81 (4.8)

a A patient who had more than one AE in the same category was counted only once.
b The 19 BR patients in the alvimopan 1- to 3-mg group are included in the alvimopan total.

A summary of TEAEs that occurred in ≥ 1% of BR patients in the alvimopan 12 mg group with an incidence higher than placebo is presented in Table 24. In general, the incidence of these TEAEs was comparable across the three treatment groups.

Table 24   **Treatment-Emergent Adverse Events (Occurring in ≥ 1% of Alvimopan 12 mg Patients With an Incidence Higher Than Placebo)—BR Population**

Preferred Term[a]	Placebo N=986 n (%)	6 mg N=663 n (%)	12 mg N=999 n (%)	Total[b] N=1681 n (%)
Hypertension	117 (11.9)	84 (12.7)	126 (12.6)	213 (12.7)
Hypocalcaemia	84 (8.5)	46 (6.9)	95 (9.5)	142 (8.4)
Anemia	41 (4.2)	27 (4.1)	52 (5.2)	81 (4.8)
Dyspepsia	45 (4.6)	27 (4.1)	70 (7.0)	103 (6.1)
Hypomagnesaemia	43 (4.4)	24 (3.6)	49 (4.9)	73 (4.3)
Anxiety	34 (3.4)	22 (3.3)	40 (4.0)	64 (3.8)
Constipation	38 (3.9)	18 (2.7)	40 (4.0)	60 (3.6)
Abdominal pain	29 (2.9)	13 (2.0)	35 (3.5)	50 (3.0)
Back pain	17 (1.7)	10 (1.5)	33 (3.3)	43 (2.6)
Hiccups	25 (2.5)	17 (2.6)	33 (3.3)	50 (3.0)
Urinary retention	21 (2.1)	17 (2.6)	32 (3.2)	49 (2.9)
Eructation	17 (1.7)	4 (0.6)	26 (2.6)	30 (1.8)
Pharyngolaryngeal pain	23 (2.3)	12 (1.8)	25 (2.5)	38 (2.3)
Arthralgia	13 (1.3)	9 (1.4)	15 (1.5)	26 (1.5)
Muscle spasms	11 (1.1)	4 (0.6)	15 (1.5)	19 (1.1)
Wound infection	11 (1.1)	11 (1.7)	13 (1.3)	24 (1.4)
Alanine aminotransferase increased	10 (1.0)	6 (0.9)	12 (1.2)	18 (1.1)
Leukocytosis	11 (1.1)	2 (0.3)	12 (1.2)	14 (0.8)
Procedural complication	9 (0.9)	5 (0.8)	12 (1.2)	17 (1.0)
White blood cell count increased	10 (1.0)	10 (1.5)	11 (1.1)	21 (1.2)
Asthenia	9 (0.9)	6 (0.9)	10 (1.0)	16 (1.0)
Cellulitis	5 (0.5)	1 (0.2)	10 (1.0)	11 (0.7)
Infusion site edema	7 (0.7)	9 (1.4)	10 (1.0)	19 (1.1)

a A patient who had more than one AE in the same category was counted only once.
b The 19 BR patients in the alvimopan 1- to 3-mg group are included in the alvimopan total.

7.1.4.3   Treatment-Emergent Adverse Events of Interest—BR Population

Adverse events of interest included:

- GI-related AEs: nausea, vomiting, abdominal distension/bloating

- Opioid-related AEs: pruritus, post-procedural pain, urinary retention

- Surgery-related AEs: POI, small intestine obstruction, and anastomotic leak

Among patients who underwent BR, the incidences of nausea and POI were lower in the alvimopan 6 and 12 mg groups compared with the placebo group (Table 25). Except for vomiting, which was lower among BR patients who received alvimopan 12 mg compared with patients who received placebo in both databases, all other AEs of interest were comparable between the active and the placebo groups.

Table 25   Treatment-Emergent Adverse Events of Interest—BR Population

Preferred Term[a]	Placebo N=986 n (%)	Alvimopan 6 mg N=663 n (%)	Alvimopan 12 mg N=999 n (%)
Nausea	491 (49.8)	246 (37.1)	433 (43.3)
Vomiting	209 (21.2)	111 (16.7)	141 (14.1)
Abdominal distension	137 (13.9)	59 (8.9)	120 (12.0)
Pruritus	97 (9.8)	46 (6.9)	85 (8.5)
Postoperative ileus	113 (11.5)	33 (5.0)	60 (6.0)
Urinary retention	21 (2.1)	17 (2.6)	32 (3.2)
Post procedural pain	18 (1.8)	18 (2.7)	12 (1.2)
Small intestine obstruction	18 (1.8)	5 (0.8)	9 (0.9)
Anastomotic leak	11 (0.8)	8 (1.2)	8 (0.8)

a A patient who had more than one AE in the same category was counted only once.

The temporal relationship between GI-related TEAEs and POD among BR patients in the alvimopan 12 mg and placebo groups was explored in the following analyses. Figure 26, Figure 27, and Figure 28 depict the percentage of BR patients with nausea, vomiting, and abdominal distension, respectively, by POD. As expected following general anesthesia, most nausea occurred on the day of surgery (POD 0) and on POD 1. Patients in the alvimopan group had lower incidences of both nausea and vomiting on POD 2 through 6 or 7, respectively. Abdominal distension was lower in the alvimopan group than in the placebo group on POD 3 through 5. This may indicate that the lower incidence of nausea, vomiting, and abdominal distension in the alvimopan treatment groups was more likely reflective of earlier resolution of ileus than reduction in the postoperative nausea and vomiting that often occurs immediately following surgery.

Figure 26   Nausea by Postoperative Day—BR Population
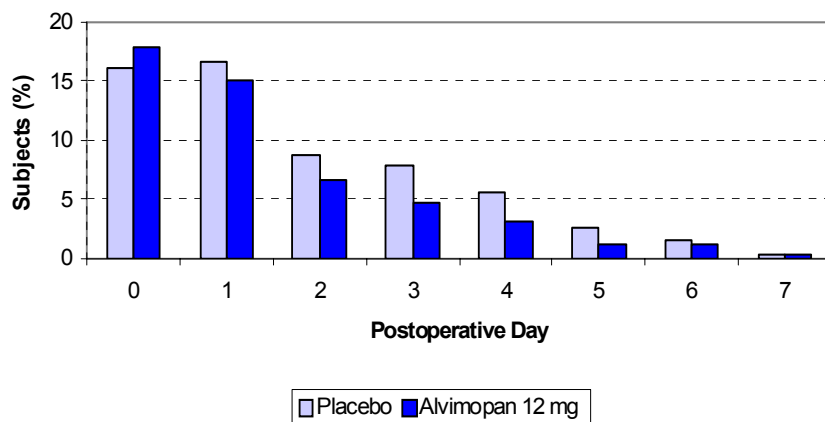
Figure 27   Vomiting by Postoperative Day—BR Population
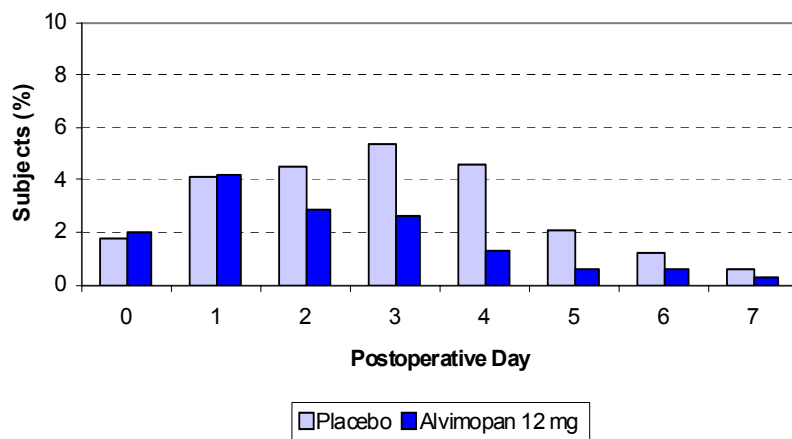
Figure 28   Abdominal Distension by Postoperative Day—BR Population
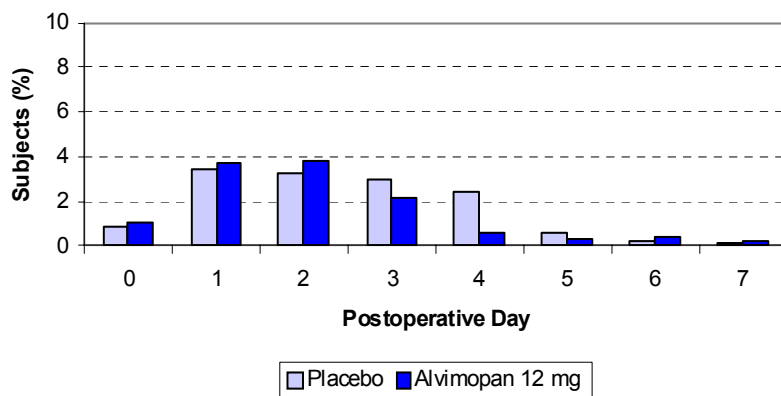
7.1.4.4   Serious Adverse Events—Overall POI Population

The percentage of patients who reported SAEs was lower in the alvimopan 6 and 12 mg groups than in the placebo group (Table 26). The incidence of POI reported as an SAE was 4- and 5-fold lower in the alvimopan 6 and 12 mg groups, respectively, than in the placebo group. All other SAEs were reported at similar rates across the three treatment groups. A total of 22 (9 placebo and 13 alvimopan) deaths were reported in the POI safety database. No SAE leading to death occurred at a frequency of ≥ 1%. In general, these SAEs and their frequency are consistent with that expected in patients undergoing BR or TAH surgery.

Table 26   Serious Adverse Events (≥ 1% in Any Treatment Group)—Overall POI Population

| | | Alvimopan | | |
| | Placebo
N=1365 | 6 mg
N=898 | 12 mg
N=1650 | Total[b]
N=2610 |
Preferred Term[a]	n (%)	n (%)	n (%)	n (%)
Patients with ≥ 1 SAE	250 (18.3)	110 (12.2)	192 (11.6)	309 (11.8)
Postoperative ileus	60 (4.4)	11 (1.2)	13 (0.8)	24 (0.9)
Small intestine obstruction	26 (1.9)	7 (0.8)	19 (1.2)	26 (1.0)
Postoperative infection	19 (1.4)	10 (1.1)	18 (1.1)	28 (1.1)
Postoperative abscess	15 (1.1)	12 (1.3)	11 (0.7)	25 (1.0)

a A patient who had more than one AE in the same category was counted only once.
b The 62 patients in the alvimopan 1- to 3-mg group are included in the alvimopan total.

7.1.4.5   Treatment-Emergent Adverse Events Leading to Discontinuation

Nausea, vomiting, and POI were the most common TEAEs leading to discontinuation in any treatment group. The percentage of patients who discontinued due to vomiting or POI was somewhat lower in the alvimopan treatment groups as compared to placebo (Table 27).

Table 27   Treatment-Emergent Adverse Events Causing Discontinuation (≥ 1% in Any Treatment Group)—Overall POI Population

| | | Alvimopan | | |
| | Placebo
N=1365 | 6 mg
N=898 | 12 mg
N=1650 | Total[b]
N=2610 |
Preferred Term[a]	n (%)	n (%)	n (%)	n (%)
Patients with ≥ 1 TEAEs causing discontinuation	162 (11.9)	74 (8.2)	125 (7.6)	206 (7.9)
Nausea	42 (3.1)	19 (2.1)	39 (2.4)	62 (2.4)
Vomiting	43 (3.2)	17 (1.9)	24 (1.5)	42 (1.6)
Postoperative ileus	45 (3.3)	11 (1.2)	20 (1.2)	31 (1.2)

a A patient who had more than one AE in the same category was counted only once.
b The 62 patients in the alvimopan 1- to 3-mg group are included in the alvimopan total.

7.1.5   Cardiovascular Evaluation

As discussed earlier, interim results from GSK014, a long-term safety study of alvimopan 0.5 mg BID for the treatment of OBD in patients with chronic non-cancer pain, demonstrated an imbalance in reports of serious CV events (MI) in the alvimopan treatment group compared with placebo. This imbalance was reported to FDA in May 2006. As a result, FDA requested additional information surrounding CV events in the POI population. FDA also requested a summary table of CV events of interest as well as additional source documentation (ECG tracings, cardiac biomarkers, etc), such that the balance of CV events across treatment groups in the POI population could be confirmed by adjudication.

In response to these requests and suggestions, the sponsor collected additional source documentation for all patients with CV events of interest and collaborated with the Duke Clinical Research Institute (DCRI) Clinical Events Committee (CEC) to provide a blinded, independent adjudication of the events. In total, 100 patients were identified as having a CV event of interest and source documentation was obtained for each of these patients. The results of the subsequent data analysis follow.

7.1.5.1   Demographic and Baseline Characteristics

In the overall POI population, the majority of patients who had CV events underwent BR (Table 28). Most patients were Caucasian, and the median age was 72 years. Approximately 80% of the population with reported CV events had concurrent CV risk factors at baseline.

In the subgroup of patients with CV events of interest, treatment groups were generally well balanced with respect to demographic and baseline characteristics, with the exception of the percentage of patients ≥ 65 years of age and the percentage of patients with established CV disease, both of which were higher in the alvimopan group when compared with placebo.

Table 28   Demographic and Baseline Characteristics

Demographic Baseline Characteristic	Worldwide POI Population		Overall POI Population With CV Event		POI Bowel Resection Population With CV Event	
	Alvimopan Group[a] N=2610	Placebo N=1365	Alvimopan Group[b] N=56	Placebo N=44	Alvimopan Group[c] N=45	Placebo N=39
Age, years						
Mean (SD)	57.0 (14.78)	58.0 (14.39)	70.1 (10.31)	68.3 (13.55)	71.1 (8.40)	70.0 (12.49)
Median (min - max)	57.0 (19.0 - 97.0)	58.0 (20.0 - 95.0)	72.0 (35.0 - 86.0)	72.0 (36.0 - 88.0)	72.0 (47.0 - 86.0)	74.0 (36.0 - 88.0)
≥ 65 years, n (%)	898 (34.4)	491 (36.0)	45 (80.4)	29 (65.9)	38 (84.4)	28 (71.8)
Race						
Black	238 (9.1)	132 (9.7)	4 (7.1)	5 (11.4)	3 (6.7)	4 (10.3)
Caucasian	2207 (84.6)	1156 (84.7)	51 (91.1)	38 (86.4)	41 (91.1)	34 (87.2)
Other	157 (6.0)	73 (5.3)	1 (1.8)	1 (2.3)	1 (2.2)	1 (2.6)
Sex						
Female	1680 (64.4)	850 (62.3)	24 (42.9)	20 (45.5)	19 (42.2)	16 (41.0)
Male	930 (35.6)	515 (37.7)	32 (57.1)	24 (54.5)	26 (57.8)	23 (59.0)
BMI, kg/m^2						
N	2575	1351	56	43	45	38
Mean (SD)	28.0 (6.18)	28.3 (6.20)	27.1 (6.18)	27.9 (6.20)	26.9 (6.02)	28.2 (6.25)
Median (min - max)	27.0 (13.8 - 70.8)	27.3 (15.4 - 67.0)	25.8 (19.1 - 49.7)	26.2 (19.1 - 46.7)	25.5 (19.1 - 49.7)	26.2 (20.3 - 46.7)
Surgery						
BR	1681 (64.4)	986 (72.2)	45 (80.4)	39 (88.6)	45 (100.0)	39 (100.0)
TAH	844 (32.3)	330 (24.2)	3 (5.4)	4 (9.1)	Not applicable	Not applicable
Other surgeries	54 (2.1)	27 (2.0)	3 (5.4)[d]	1 (2.3)[d]	Not applicable	Not applicable
No surgery	31 (1.2)	22 (1.6)	5 (8.9)[e]	0[e]	Not applicable	Not applicable
BR Surgery						
Large BR–Left	873 (33.4)	531 (38.9)	25 (44.6)	23 (52.3)	25 (55.6)	23 (59.0)
Large BR–Other	71 (2.7)	43 (3.2)	2 (3.6)	2 (4.5)	2 (4.4)	2 (5.1)
Large BR–Right	606 (23.2)	348 (25.5)	13 (23.2)	12 (27.3)	13 (28.9)	12 (30.8)
Small BR	131 (5.0)	64 (4.7)	5 (8.9)	2 (4.5)	5 (11.1)	2 (5.1)

Demographic Baseline Characteristic	Worldwide POI Population		Overall POI Population With CV Event		POI Bowel Resection Population With CV Event	
	Alvimopan Group[a] N=2610	Placebo N=1365	Alvimopan Group[b] N=56	Placebo N=44	Alvimopan Group[c] N=45	Placebo N=39
Established CV Disease	--	--	20 (35.7)	9 (20.5)	17 (37.8)	9 (23.1)
CV Risk Factors						
Any	--	--	46 (82.1)	36 (81.8)	37 (82.2)	33 (84.6)
Smoking	--	--	13 (23.2)	10 (22.7)	9 (20.0)	9 (23.1)
Hypertension	--	--	34 (60.7)	29 (65.9)	28 (62.2)	27 (69.2)
Hyperlipidemia	--	--	23 (41.1)	17 (38.6)	17 (37.8)	16 (41.0)
Obesity	--	--	9 (16.1)	6 (13.6)	8 (17.8)	6 (15.4)

Studies 13C206, 13C213, 13C214, 14CL302, 14CL306, 14CL308, 14CL313, 14CL314, and GSK001.

POI = postoperative ileus; CV = cardiovascular; SD = stable disease; BMI = body mass index; BR = bowel resection; TAH = total abdominal hysterectomy.

a Alvimopan group included the following alvimopan doses: 1-3 mg (N=62), 6 mg (N=898), and 12 mg (N=1650).

b Alvimopan group included the following alvimopan doses: 6 mg (N=19) and 12 mg (N=37).

c Alvimopan group included the following alvimopan doses: 6 mg (N=14) and 12 mg (N=31).

d Other surgeries include laparotomy; lysis of adhesions, surgery aborted.

e Reasons for no surgery: non-protocol–specified surgery; surgery cancelled.

This finding was consistent across the overall POI and BR populations who had CV events of interest (> 65 years of age, 14.5% and 12.6% higher and established CV disease, 15.2% and 14.7% higher in the alvimopan group in the POI and BR populations, respectively).

When the subgroup of patients with CV events was compared with the overall POI population, not unexpectedly, patients with CV events tended to be older (median age approximately 10 years older than the overall POI population). In addition, a greater proportion of the total population of patients who had a CV event was male and underwent BR.

7.1.5.2   CV Events of Interest—Overall POI Population

A summary of results from the worldwide POI safety database and results of the DCRI adjudication for CV events in the overall POI population is provided in Table 29.

Although some patients shifted into different categories of CV events based on adjudication using prespecified CV event definitions, there was no significant change between the POI safety database and DCRI adjudication results with respect to the incidence or relative risk of a CV event between those who received alvimopan and those who received placebo.

In total, a lower proportion of alvimopan-treated patients (1.92% [50/2610]) experienced a CV event of interest as compared with placebo-treated patients (2.86% [39/1365]) in the worldwide POI safety database (patients counted once only; includes non-CV death). Similar findings were observed based on the DCRI adjudication (alvimopan: 1.49% [39/2610]; placebo: 1.98% [27/1365]). Twenty-six patients with a CV event of interest based on the worldwide POI safety database were adjudicated as not experiencing a CV event by DCRI.

The incidence of individual events was low at < 1% and this, along with a sample size not prospectively powered to evaluate the rate of CV events in this population, resulted in wide CIs. In the POI safety database and DCRI adjudication results, the CIs included the null value of 1, indicating that there is no statistically significant difference in the risk of any of these CV events in the alvimopan group relative to the placebo group.

Table 29   Cardiovascular Events—Overall Population

	Worldwide POI Safety Database			DCRI Adjudication Results		
Event	Alvimopan N=2610 n (%)	Placebo N=1365 n (%)	Relative Risk Alv vs Pbo (95% CI)	Alvimopan N=2610 n (%)	Placebo N=1365 n (%)	Relative Risk Alv vs Pbo (95% CI)
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)
Any CV event	50 (1.92)	39 (2.86)	0.67 (0.44, 1.01)	27 (1.98)	39 (1.49)	0.76 (0.46, 1.23)
Death from CV 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)	--

Studies 13C206, 13C213, 13C214, 14CL302, 14CL306, 14CL308, 14CL313, 14CL314, and GSK001.

POI = postoperative ileus; DCRI = Duke Clinical Research Institute; Alv = alvimopan; Pbo = placebo; CV = cardiovascular; MI = myocardial infarction; CVA = cerebrovascular accident; CHF = congestive heart failure.

The KM estimate of the time to CV events for patients in the POI population is shown in Figure 29. Overall, results of this analysis indicate that the time to the first CV event was comparable between the alvimopan and placebo groups, with most events occurring before POD 10. Overall, however, the proportion of patients experiencing a CV event of interest in the alvimopan group was lower than that observed in the placebo group.

Figure 29   KM Estimate of Time to CV Event—Overall POI Population
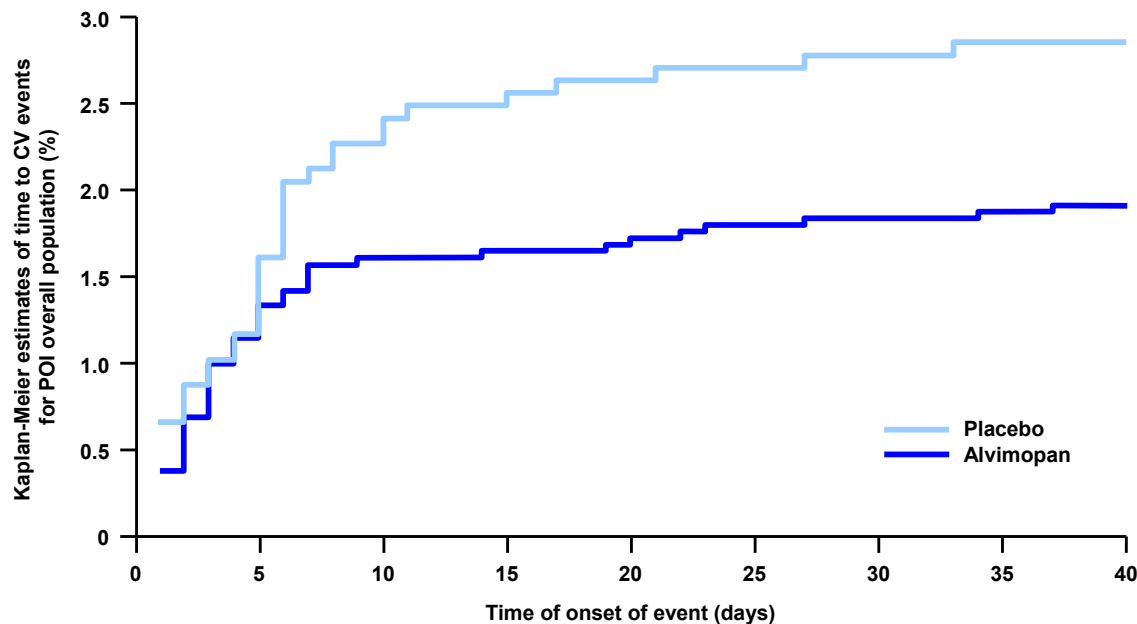
Studies 13C206, 13C213, 13C214, 14CL302, 14CL306, 14CL308, 14CL313, 14CL314, and GSK767905/001.
Note: Cardiovascular events in the above figure include cardiovascular death, fatal and nonfatal myocardial infarction,
     congestive heart failure, stroke, unstable angina, serious arrhythmia, and cardiac arrest.

7.1.5.3   CV Events of Interest—BR Population

A summary of the worldwide POI safety database and DCRI adjudication results for CV events in the BR population is provided in Table 30.

In total, a lower proportion of alvimopan-treated BR patients (2.38% [40/1681]) experienced a CV event of interest as compared with placebo-treated patients (3.65% [36/986]) in the worldwide POI safety database (patients counted once only; includes non-CV death). Similar findings were observed based on the DCRI adjudication (alvimopan: 1.96% [33/1681]; placebo: 2.43% [24/986]). Twenty-one patients with a CV event of interest based on the worldwide POI safety database BR population were adjudicated as not experiencing a CV event by DCRI.

As observed in overall population, there were no clinically meaningful differences between the alvimopan and placebo groups for any CV event in the worldwide POI safety database or in the DCRI adjudication results. Similar to the overall Worldwide POI Safety population, CIs were wide for similar reasons. In addition, all CIs include the null value of 1, indicating that there is no statistically significant difference in the risk of any of these CV events in the alvimopan group relative to the placebo group.

Table 30   Cardiovascular Events—BR Population

Event	Worldwide POI Safety Database			DCRI Adjudication Results		
	Alvimopan N=1681 n (%)	Placebo N=986 n (%)	Relative Risk Alv vs Pbo (95% CI)	Alvimopan N=1681 n (%)	Placebo N=986 n (%)	Relative Risk Alv vs Pbo (95% CI)
All-cause death	12 (0.71)	7 (0.71)	1.01 (0.4, 2.55)	12 (0.71)	7 (0.71)	1.01 (0.4, 2.55)
Death from CV events	4 (0.24)	2 (0.20)	1.17 (0.22, 6.39)	5 (0.30)	1 (0.10)	2.93 (0.34, 25.07)
Any CV event	40 (2.38)	36 (3.65)	0.65 (0.42,1.02)	33 (1.96)	24 (2.43)	0.81 (0.48,1.36)
MI: Overall	12 (0.71)	7 (0.71)	1.01 (0.4, 2.55)	12 (0.71)	7 (0.71)	1.01 (0.4, 2.55)
Fatal	1 (0.06)	0	--	1 (0.06)	0	--
Non-fatal	11 (0.65)	7 (0.71)	--	11 (0.65)	7 (0.71)	--
Unstable angina	0	4 (0.41)	0.07 (0, 1.21)	1 (0.06)	2 (0.20)	0.29 (0.03, 3.23)
CVA: Overall	3 (0.18)	4 (0.41)	0.44 (0.1, 1.96)	3 (0.18)	3 (0.30)	0.59 (0.12, 2.9)
Fatal	1 (0.06)	0	--	0	0	--
Non-fatal	2 (0.12)	4 (0.41)	--	3 (0.18)	3 (0.30)	--
CHF: Overall	15 (0.89)	11 (1.12)	0.8 (0.37, 1.73)	13 (0.77)	8 (0.81)	0.95 (0.4, 2.29)
Fatal	1 (0.06)	0	--	1 (0.06)	0	--
Non-fatal	14 (0.83)	11 (1.12)	--	12 (0.71)	8 (0.81)	--
Serious arrhythmia: overall	12 (0.71)	10 (1.01)	0.7 (0.31, 1.62)	10 (0.59)	4 (0.41)	1.47 (0.46, 4.66)
Fatal	0	0	--	0	0	--
Non-fatal	12 (0.71)	10 (1.01)	--	10 (0.59)	4 (0.41)	--
Cardiac arrest: Overall	3 (0.18)	5 (0.51)	0.35 (0.08, 1.47)	6 (0.36)	5 (0.51)	0.7 (0.22, 2.3)
Fatal	0	2 (0.20)	--	1 (0.06)	0	--
Non-fatal	3 (0.18)	3 (0.30)	--	5 (0.30)	5 (0.51)	--

Studies 13C213, 14CL302, 14CL308, 14CL313, 14CL314, and GSK001.

POI = postoperative ileus; DCRI = Duke Clinical Research Institute; Alv = alvimopan; Pbo = placebo; CV = cardiovascular; MI = myocardial infarction; CVA = cerebrovascular accident; CHF = congestive heart failure.

The KM estimate of the time to CV events for patients in the POI BR population is shown in Figure 30. Overall, results of this analysis were similar to results observed among patients in the overall POI population who had CV events of interest.

Figure 30   KM Estimate of Time to CV Event—BR Population
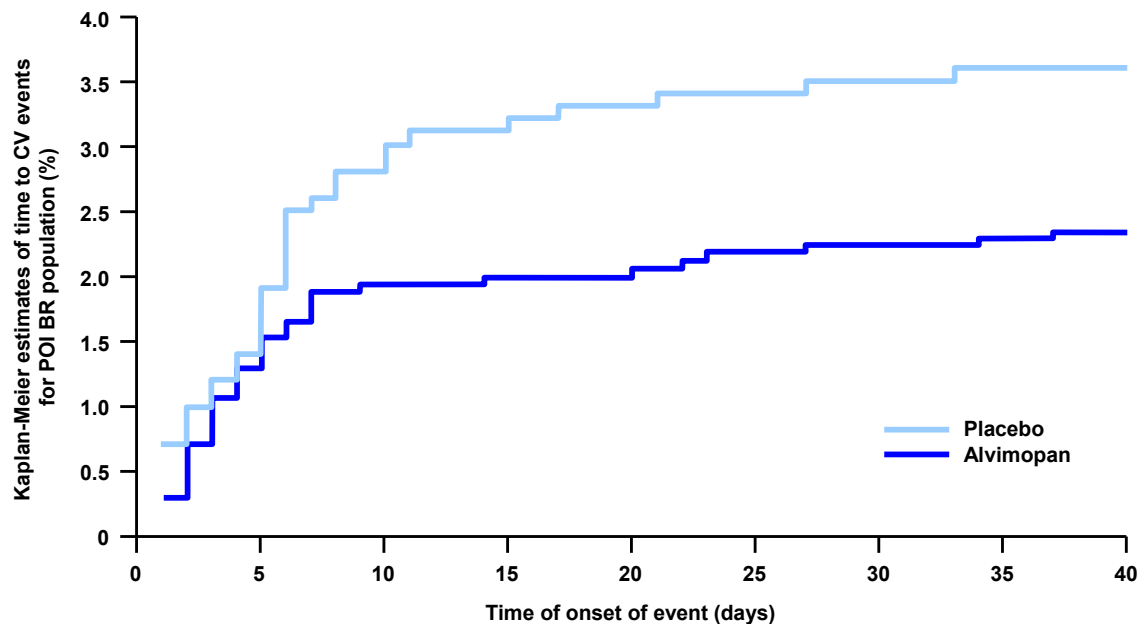
Studies 13C213, 14CL302, 14CL308, 14CL313, 14CL314, and GSK001.

Note: Cardiovascular events in the above figure include cardiovascular death, fatal and nonfatal myocardial infarction,
congestive heart failure, stroke, unstable angina, serious arrhythmia, and cardiac arrest.

The relationship between CV events of interest and alvimopan exposure was explored. The
detailed analysis is presented in Appendix 12.5.

7.1.5.4   Estimate of the Expected Incidence of MI Following BR

To estimate the expected incidence of MI in patients undergoing BR surgery, a literature
review was performed. Several publications were identified which assessed postoperative
30-day morbidity and mortality across a variety of major surgical populations using the
National Surgical Quality Improvement Program (NSQIP) database. The NSQIP is a
nationally validated, risk-adjusted, outcomes-based program developed to measure and
improve the quality of surgical care in both the Veteran's Administration (VA) Medical
Centers (VA NSQIP) and the private sector (American College of Surgeons [ACS] NSQIP).

Khuri et al. (2005) assessed 30-day morbidity and mortality in a total of 105,951 patients
undergoing major surgical procedures across eight surgical specialties from the years 1991-
1999. Procedures were defined using Common Procedural Terminology (CPT) codes. One of
the surgical subgroups within this population consisted of 19,895 patients undergoing
colectomy. The CPT codes used to define the colectomy group were broad in scope and
included not only the BR procedures permitted in the alvimopan POI clinical trials but more
extensive cases as well (e.g., total colectomy was included in this category; however, these
procedures were excluded from the POI clinical studies). A definition of MI was not reported
by the authors.

Based on their results, the incidence of MI using the VA NSQIP was comparable to that observed in the alvimopan POI safety database (Table 31).

Table 31   Patients With a MI Following BR Surgery—VA NSQIP Database

	Worldwide POI Safety Database		DCRI Adjudication Results		VA NSQIP Database
	Alvimopan	Placebo	Alvimopan	Placebo	
Number of patients	1681	986	1681	986	19,985
Percent (%) of patients with MI	0.71	0.71	0.71	0.71	0.96

MI = myocardial infarction; BR = bowel resection; POI = postoperative ileus; DCRI = Duke Clinical Research Institute; VA NSQIP = Veteran's Administration National Surgical Quality Improvement Program.

The data from this published study suggest that the incidence of MI or the percentage of patients with a CV AE (defined as having either an MI or cardiac arrest) observed in either the POI safety database or as a result of the DCRI adjudication is within the range of what might be expected in patients undergoing BR surgery (Asch et al, 2004; Davenport et al, 2007).

7.1.5.5   DCRI Conclusions

The DCRI CEC group adjudicated blinded patient-level data for prespecified CV events in the POI data set. Following the completion of event adjudication, the CEC were provided a summary of the unblinded data by the sponsor. Based on these data, the following conclusions were reached:

- There is no evidence of an excess in CV events between patients assigned to alvimopan and those assigned to placebo in the POI data set.
    o   This data set is limited by several features:
    o   The modest number of CV events in this populations.
- The reliance on AE reporting as the mechanism to identify potential CV events.
- Given the composite CV event rate (1% to 3%) in this population, a clinical trial adequate to exclude even a clinically important increase n CV events would require a very large sample size.

7.1.6   Bone Fracture and Neoplasm Evaluation

Only one bone fracture was reported in the POI clinical studies. This patient was an 84-year-old female who experienced multiple rib fractures associated with a fall. She was in the 12-mg alvimopan treatment group. A total of eight neoplasia events were reported in the POI clinical studies. Three (0.2%) events were reported in the placebo-treated group and five (0.2%) were reported in the alvimopan-treated group (6 mg and 12 mg combined). As these trials are of short duration and the events reported are chronic conditions, it is unlikely that study participation had any impact on the likelihood of reporting bone fracture or neoplasia during the trial period.

7.1.7   Overall Conclusions—Safety in POI

Approximately 2,600 patients have received alvimopan as a single dose preoperatively followed by BID administration initiated on POD 1 until hospital discharge or up to 7 days maximum. These patients were evaluated in two Phase 2 and five Phase 3 randomized, placebo-controlled clinical trials that incorporated a thorough safety evaluation.

The AE profile for alvimopan was consistent with what would be expected in patients undergoing abdominal surgery. Alvimopan was well tolerated in all studies. The incidence of AEs in the alvimopan treatment groups was comparable to that reported in the placebo groups.

The mortality rate in all Phase 2 and Phase 3 POI studies combined was less than 1% in both the alvimopan and placebo treatment groups, with no treatment-related, treatment-emergent deaths as determined by the investigator (with the exception of one placebo patient in a non-NA site whose cause of death and relationship was not determined by the investigator and who, therefore, was included per convention in the treatment-related category).

The incidence of MIs as determined both by AE reporting from clinical trials and by independent adjudication based on patient-level data (DCRI) is consistent with expected rates in this population and was comparable among the alvimopan and placebo treatment groups.

Anastomotic leak is one of the most serious complications after bowel resection surgery and significantly increases patient morbidity and mortality (Pickelman et al, 1999; Alves et al, 1999). In the Phase 3 studies, no evidence was found that the risk for anastomotic leak was increased with alvimopan treatment. The incidence of anastomotic leak was low and similar in patients receiving either alvimopan or placebo (0.8% and 1.1%, respectively).

Collectively, these results demonstrate a favorable safety profile for alvimopan for the proposed use in BR patients. Importantly, treatment with 12 mg of alvimopan was not associated with an increased risk of CV AEs or other SAEs.

7.2   Safety in OBD

Evidence of the safety of alvimopan in OBD patients is drawn from more than 1800 patients who received alvimopan in eight clinical studies conducted in the US and elsewhere.

In May 2006 during the course of the 12-month safety study, GSK014, GSK noted an imbalance of MIs in this study. Seven events occurred in the alvimopan arm and none in the placebo arm These events occurred in patients with pre-existing CV disease or underlying CV risk factors. GSK concluded that while the difference in rates of MIs and related SAEs in GSK014 compared to other OBD studies remained unexplained, the imbalance of events observed on alvimopan vs. placebo in GSK014 was not supported by the incidence of events in all OBD studies.

As the increased number of total MIs and related events in GSK014 could have been due to chance, GSK Global Safety Board determined that the study should continue with appropriate safeguards put in place to assure patient safety. Subsequently, GSK convened an Independent Data Monitoring Committee (IDMC) to ensure uniform evaluation of CV AEs and to make

recommendations appropriate to protect patient safety in studies with alvimopan for the treatment of OBD.

Following the completion of GSK014 and the unblinding of data in March 2007, the initial analysis of the frequency of AEs by MedDRA (Medical Dictionary for Regulatory Activities) system organ class showed a numerical imbalance in the reports of benign and malignant neoplasms in the alvimopan treatment arm as well as an increase in the incidence of bone fractures compared to placebo. The identification of the imbalance in neoplasms in GSK014 led to an interim analysis of the ongoing extension study in cancer pain (GSK684) 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 to allow further statistical evaluation of the data and a clinical evaluation of the reported events. Investigators and regulatory authorities were promptly notified.

The data and data analysis of the events in each of these categories, CV, neoplasms, and fractures, as well as the Sponsor's conclusions resulting from these analyses are presented.

7.2.1   *Cardiovascular Evaluation*

7.2.1.1   Cardiovascular Events

Analyses of CV events in the OBD population, according to categories requested by FDA, are provided in Table 32, Table 33 and Table 34.These data demonstrate a numerical imbalance in reports of MI in patients receiving 0.5 mg alvimopan vs. placebo in GSK014. Numerical imbalances are observed in other CV event categories in GSK014, occurring at lower frequency than MI events.

Table 33 shows that when the data from all previously conducted OBD studies are combined excluding GSK014, there is no excess of MIs in the alvimopan treatment group and, in fact the numerical imbalance in this category is reversed. When the data from all OBD studies including 014 are combined (Table 34), the numerical imbalances in MI and other events are less pronounced. Narratives for patients diagnosed with MI appear in Appendix 12.7.

Table 32   Summary of CV Events in GSK014

CV Event Category	Placebo N=267 n (%)	Alvimopan N=538 n (%)	Relative Risk Alvimopan/Placebo (95% CI)
All-cause 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)
MI: Overall	0	7 (1.30)	7.46 (0.43,130.1)
Fatal	0	1 (0.19)	--
Non-fatal	0	6 (1.12)	--
Unstable angina	0	3 (0.56)	3.48 (0.18,67.1)
Non-fatal CVA	0	1 (0.19)	1.49 (0.06,36.5)
CHF: Overall	0	1 (0.19)	1.49 (0.06,36.5)
Fatal	0	0	--
Non-fatal	0	1 (0.19)	--
Serious arrhythmia	0	2 (0.37)	2.49 (0.12,51.6)
Fatal	0	0	--
Non-fatal	0	2 (0.37)	--

Table 33   Summary of Cardiovascular Events in OBD Population (Excluding GSK014)

CV Event Category	Placebo Group N=523 n (%)	Alvimopan Group[a] N=1190 n (%)	Relative Risk Alvimopan/Placebo (95% CI)
All-cause death	0	2 (0.17)	2.20 (0.11,45.7)
Death from CV events	0	1 (0.08)	1.32 (0.05,32.3)
MI: Overall	2 (0.38)	1 (0.08)	0.22 (0.02,2.42)
Fatal	0	0	
Non-fatal	2 (0.38)	1 (0.08)	
Unstable angina	0	1 (0.08)	1.32 (0.05,32.3)
Non-fatal CVA	1 (0.19)	1 (0.08)	0.44 (0.03,7.01)
CHF: Overall	2 (0.38)	1 (0.08)	0.22 (0.02,2.42)
Fatal	0	0	
Non-fatal	2 (0.38)	1 (0.08)	
Serious arrhythmia	0	3 (0.25)	3.08 (0.16,59.5)
Fatal	0	0	
Non-fatal	0	3 (0.25)	

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

Table 34   Summary of Cardiovascular Events 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.

7.2.1.2   Possible Basis for Increased Reporting of CV Events in GSK014

7.2.1.2.1   GSK014 Demographics

A detailed examination of the data from GSK014 failed to identify any differences in patient demographics relative to the other alvimopan OBD studies that would explain the difference in the incidence of CV events observed in GSK014. Overall, the incidence of obesity (40% vs. 31%), tobacco use (39% vs. 21%), diabetes mellitus (16% vs. 7%), and history of hypertension (41% vs. 31%), MI (6% vs. 4%), and angina pectoris (9% vs. 4%) was higher in GSK014 than in the general adult population in the US, based on the most recent statistics published by the AHA (American Heart Association, 2007). Almost half of the patients in GSK014 reported pre-existing CV disease.. The most common pre-existing CV diagnosis reported was hypertension, which was reported by 41% of patients. Other CV conditions most frequently reported included diagnoses consistent with myocardial ischemia (angina pectoris, coronary artery disease, MI), and arrhythmia. As can be seen in the attached narratives, all of the patients suffering MIs had preexisting cardiovascular disease or significant risk factors.

7.2.1.2.2   GSK014 Regional Distribution

An anomalous regional distribution of these events was noted. A total of 230 study sites actively enrolled patients. The majority of patients with reported MIs (five of seven) were enrolled at only two of these 230 sites. As a result, 62.5% of these events of interest were reported from less than 1% of the participating clinical centers. A review of study conduct at

these two centers did not provide evidence of a deviation in patient evaluation or trial conduct that would explain the regional imbalance, except that one center (Glasgow) was noted to be located in an area of generally high incidence and prevalence of ischemic disease.

7.2.1.2.3   Timing of CV Events

The biggest difference between the design of GSK014 and other studies completed in OBD is the duration of the trial. Patients took investigational product for up to 1 year in GSK014, compared to 3 to 12 weeks in other efficacy/safety studies. In the case of MIs, a review of these events reported in GSK014 reveals that for five of seven of these events the time to onset of the patients' symptoms occurred within 90 days from the onset of drug treatment. There were no MIs beyond 111 days of study treatment. Given that the number of patients randomized in the two completed 12-week efficacy trials (total N=1003; n= 518 in GSK012 and n = 485 in GSK013) is larger than that in GSK014 (total N=805) and as the time to onset for most MIs in GSK014 was within the observation period of GSK012 and GSK013, the longer duration of GSK014 does not appear to be a factor contributing to the difference in the number of reported events. Figure 31 illustrates the time to CV events for the alvimopan 0.5 mg BID and placebo groups in the non-cancer OBD studies.

Figure 31   KM Estimates of Time to CV Events—Non-Cancer OBD Studies
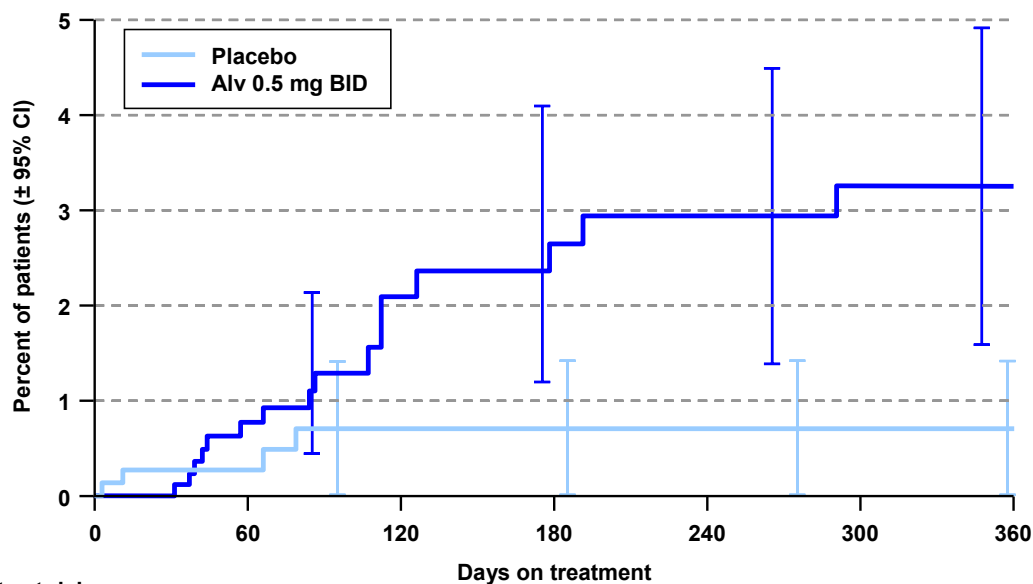
Patients at risk							
Placebo	790	467	176	160	150	138	74
Alv 0.5mg BID	1000	669	363	339	322	305	173

CV events include cardiovascular death, nonfatal myocardial infarction, congestive heart failure, stroke, unstable angina, and serious arrhythmia.
Data are from studies GSK011, GSK012, GSK013, GSK014, 13C217,and 13C304.

7.2.1.3   IDMC Evaluation of CV Events

An IDMC was established by GSK to ensure prospective, uniform evaluation of CV adverse events of special interest and to make recommendations appropriate to protect patient safety for GSK-sponsored studies of alvimopan. For its review, the IDMC considered of primary importance all confirmed SAEs that met the criteria of CV ischemia such as MI. Definitions and diagnostic criteria for other CV AEs of special interest were discussed in collaboration with the GSK study team to allow for the identification and independent adjudication of all major cardiac events. Adjudication was based primarily on source documents requested by the IDMC. GSK, in a blinded fashion, collected and collated the source documents and other information necessary for case extraction and adjudication from each of the OBD studies (GSK011, GSK012, GSK013 and GSK014), which account for substantially all of the patients in the non-cancer OBD program.. The IDMC reviewed these blinded cases of CV interest for clinical significance, attribution, and impact on the safety profile of alvimopan and determined whether they met the criteria for "Adjudicated Major Cardiac Events (AMCEs)." The IDMC then evaluated the totality of unblinded AMCEs in its evaluation of the benefit/risk balance of alvimopan therapy and on this basis provided recommendations to GSK.

As the IDMC strategy and scope varied somewhat from what was requested by FDA, there are minor differences in terms of the studies included and the number of cases reviewed and analyzed in specific categories. However, in both methodologies, the review of CV events was quite broad and not limited to myocardial ischemia and related events. In addition, small differences could arise from the adjudication process, as the events of interest were labeled by the Adjudication Board as a result of their case review, which was based upon their review of source documents as requested and not necessarily by how the event was described in the CRF.

The recommendations forwarded to GSK by the IDMC reflect their review of both the datasets provided to FDA and the adjudication database. Despite the differences in methodology, their recommendations have remained consistent upon their collective review or their individual review of either dataset.

For their review, the IDMC specified that adjudicated CV events were to be categorized as follows:

- All CV events

- Ischemic CV events: acute MI, new onset/unstable angina, congestive cardiac failure, cerebrovascular accident (CVA)/transient ischemic attack (TIA), cardiac arrest, sudden death

- Other CV events: bradycardia, atrial fibrillation, supraventricular tachycardia, hypotension, venous thrombosis, pulmonary embolism, syncope

Summary statistics derived from the adjudication database are presented in Table 35.

Table 35   CV Event Summary—IDMC Adjudication Database

	Total N=2624 n (%)	Placebo N=817 n (%)	Alvimopan N=1807 n (%)	Relative Risk Alv/Pla (95% CI)
Adjudicated cases	84	21	63	--
Any CV event[a]	35 (1.3%)	9 (1.1%)	26 (1.4%)	1.30 (0.61,2.77)
Ischemic CV events	19 (0.7%)	6 (0.7%)	13 (0.7%)	0.98 (0.37,2.57)
Other CV events	17 (0.6%)	3 (0.4%)	14 (0.8%)	2.11 (0.61,7.32)

a Study GSK014 / Patient 807 had both ischemic and Other CV events.

CV = cardiovascular; IDMC = Independent Data Monitoring Committee; Alv = alvimopan; PLA = placebo.

Final summary recommendations from the IDMC regarding CV safety data generated by the OBD clinical development program are as follows:

- The risk of ischemic heart disease has been largely discharged

- The incidence of other CV events with alvimopan vs. placebo was not statistically significant

- Further studies should confirm these conclusions if it is decided to pursue the indication for OBD.

- Enhanced monitoring for CV risk and any CV events, with IDMC oversight, should continue.

7.2.1.4   Exposure-Response Analyses

In the small number of patients with CV AEs and available plasma samples from studies GSK011, GSK012, GSK014, and GSK008, the plasma concentrations of alvimopan and metabolite were as expected based on dose (see Appendix 12.5.3). Overall, CV AEs do not appear to be explained by higher concentrations of alvimopan or metabolite; there is unlikely to be an exposure-response relationship for this AE.

7.2.1.5   Epidemiological Analyses

GSK014 recorded seven cases of MI in the alvimopan arm and none in the placebo arm of the trial. The objective of this analysis is to compare the number of observed events to the expected numbers of events in the two treatment arms, given the 2:1 allocation ratio of patients assigned to alvimopan vs. placebo and the age, sex, and opioid usage characteristics of the two treatment groups.

The analysis was conducted in three steps: (1) calculating the number of subjects in each age-sex-dose stratum in the trial population, (2) calculating the age-sex-dose specific incidence rates in the reference population, and (3) calculating the respective expected number of MIs and comparing them to the observed number of MIs in each treatment group separately and for all patients regardless of treatment.

7.2.1.5.1   *Calculating the Number of Subjects in Each Age-Sex-Dose Stratum in the Trial Population*

To standardize the expected incidence rates by the trial population, the trial population was characterized by its age, sex, and opioid usage distribution. In a previous study, chronic opioid usage was found to be associated with an elevated risk of MI compared to the general population with rates increasing with higher total daily opioid doses.

Subjects in GSK014 were stratified by age and sex, resulting in a total of 10 strata. A median morphine equivalent total daily dose (METDD) was calculated for each of the 10 strata. Median METDD ranged from 46 mg among 37 males ($\geq$ 65 years old) in the alvimopan group to 1110.3 among three males (18 to 29 years old) in the placebo group. These median doses were categorized into three levels (Table 36).

Table 36   Dose Categories for METDD

Opioid Exposure Category	Cutpoints of METDD
Medium	30 to <90 mg
High	90 to < 200 mg
Very High	$\geq$ 200 mg

Each subject from each of the 10 age-sex strata was assigned to one of the three METDD categories, yielding a final total of 30 age, sex and METDD strata.

7.2.1.5.2   *Calculating the Age-Sex-Dose Specific Incidence Rates in the Reference Population*

Chronic opioid users in the Ingenix Research Data Mart (RDM), identified in our previous study, were used as the reference population. The RDM contains 176,715 person-years of observation in chronic opioid users from 2003 through 2005. Patients were stratified by age and sex and METDD, and incidence rates were calculated for each of the 30 age, sex, and METDD strata.

7.2.1.5.3   *Calculating the Expected Number of MIs*

Expected numbers of MI cases for the GSK014 population were derived by multiplying the annual age-sex-METDD-specific incidence rates of MI from the RDM population by the corresponding number of subjects in each of the 30 strata of the GSK014 population for each treatment group. These expected numbers were summed over all age, sex, and METDD strata to obtain the expected number of events both overall and within each treatment group. While no MIs in the placebo group and seven MIs in the alvimopan group were observed in GSK014, the resulting numbers of expected MI cases were 2.24 in the placebo group and 5.30 in the alvimopan group. The fact that the expected number in the alvimopan group was slightly more than twice the expected number in the placebo group is due to the 2:1 treatment allocation ratio (alvimopan:placebo) as well as a slightly elevated baseline MI risk (based on

the distribution of age, sex, and METDD). The total number of 7.54 expected MIs was very close the total number of seven observed MIs.

The probability of observing the GSK014 number of events given the expected number of events was calculated separately for each treatment group using the Poisson distribution. For the placebo group, the probability of observing zero MIs when expecting 2.24 MIs in that group was 0.11. For the alvimopan group, the probability of observing seven or more MIs when expecting 5.30 was 0.28 (Table 37).

Table 37   MI Probability Calculations

	Placebo	Alvimopan	Total
Expected number of MIs	2.24	5.30	7.54
Observed number of MIs	0	7	7
Poisson probability of number of observations (or more for Alv & total)	0.11	0.28	0.63

7.2.1.5.4   Discussion and Summary

This analysis aimed to evaluate the observations from GSK014 with external data from a health insurance claims database. Care has been taken to make the external reference population as comparable as possible to the GSK014 population with respect to MI risk by stratifying the analysis by age, sex, and total daily opioid dose categories. However, the possibility that an imbalance in risk factors exists between the GSK014 population and the external reference population cannot be excluded.

In summary, the overall observed number of MI cases in GSK014 was close to the expected number. In the alvimopan group the number of observed MIs was somewhat higher than expected, while in the placebo group it was somewhat lower than expected. The deviation from the expected was larger (in probability terms) in the placebo group than in the alvimopan group.

7.2.1.6   Overall Conclusions—Cardiovascular

GSK and Adolor believe that the numeric imbalance of CV SAEs, and in particular MIs, observed in GSK014 may be a chance finding that is not supported by the breadth of the safety data generated to date in clinical trials of alvimopan in patients with OBD. No prior evidence suggesting an association of increased risk of CV events with exposure to alvimopan has been identified from mechanistic studies, preclinical evaluation, and a large number of completed clinical trials in healthy volunteers or patients with OBD, POI, and CIC. This includes clinical studies with similar inclusion and exclusion criteria and which, based upon a review of available demographic information, included populations similar in composition to that of GSK014. In particular, GSK012 and GSK013, which provided experience in similar populations over 3 months of exposure to investigational treatment, did not demonstrate the observed numerical imbalance in CV ischemic events observed in GSK014.

The IDMC also adjudicated the entire OBD clinical database according to their specifications, providing an independent clinical assessment of the CV data. See Section 7.2.1.3 for details. While a numeric imbalance was noted for ischemic events in GSK014, these results were not statistically significant and the between-treatment numerical difference in the incidence of ischemic events was considered to be most consistent with chance, stemming from a comparison of a small total number of events in a study not designed to make formal assessments of CV safety. Furthermore, the relative risk (alvimopan/placebo) of all ischemic events across all studies, as defined by the IDMC, approached unity: RR = 0.98 (95% CI = 0.37, 2.57). As noted in the summary IDMC recommendations the perspective of the independent committee, in reviewing all of the available OBD data, considered that the risk of ischemic heart disease had been largely discharged by these analyses.

GSK014 therefore represents an isolated observation. When the data are evaluated in totality the conclusion is that this imbalance is more consistent with a chance finding than with a causal relationship to alvimopan.

7.2.2   Bone Fracture Evaluation in OBD

7.2.2.1   GSK014

The GSK014 population consisted of patients treated with opioid analgesics for chronic non-cancer pain. Patients were predominantly white, two-thirds were female, and the average age was 53 years. Patients were frequently overweight (30%) and obesity (40%) was common in the population, as was the use of tobacco (39%). With the exception of age 65 years or older, the alvimopan and placebo groups were reasonably balanced for demographic factors (Table 38).

The mean opioid METDD, excluding intrathecal administration, at baseline was 183.5 mg in the alvimopan group, ranging from 4.5 to 1668.9 mg. The average METDD was 209.6 mg in the placebo group, ranging from 0 to 2345.6 mg.

Table 38   Demographic Characteristics of All Patients—GSK014

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

The incidence of bone fractures was 3.7% (20/538) in the alvimopan group compared with 1.1% (3/267) in the placebo group. The HR estimate was 3.16 (95% CI = 0.94, 10.62). Patients who reported bone fractures during alvimopan treatment were typically white women; the mean age was approximately 57 years with 30% ≥ 65 years of age.

Of the 20 fractures reported in the alvimopan group, 15 occurred in women (Table 39). Seven patients in the alvimopan fracture group had BMI values ≥ 30; no placebo cases were ≥ 30.

The mean METDD, however, was two-fold higher in the alvimopan fracture group. Excluding intrathecal administration, the average METDD at baseline was 203 mg in the alvimopan fracture group, ranging from 21.5 to 727.5 mg. For placebo fracture cases, the average METDD was 100 mg, ranging from 30 to 210.5 mg.

Table 39   Demographic Characteristics of Bone Fracture Patients—GSK014

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

The average time on treatment prior to bone fracture was 182 days, ranging from 8 to 324 days, for alvimopan-treated patients. The corresponding time for placebo-treated patients was 276 days, ranging from 227 to 359 days. The time of bone fracture occurrence in the alvimopan and placebo groups are graphically displayed in Figure 32. The majority of bone fractures were reported after 120 days of treatment.

Figure 32   KM Estimates of Time to Bone Fracture—GSK014

Patients at risk							
Placebo	267	196	175	160	149	136	73
Alvimopan	538	398	383	338	318	298	168
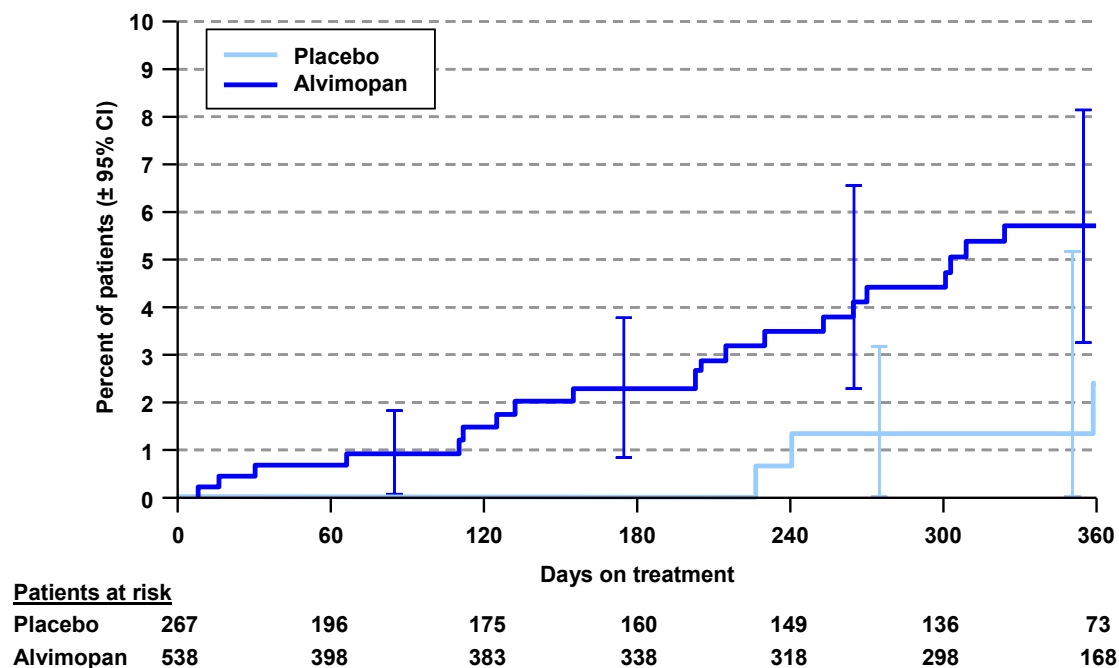
Fractures involving more than one bone were uncommon, as were the more typical osteoporotic-type fractures to the hip or vertebrae. The bones most often reported as broken were the ribs and those in the extremities. For patients treated with alvimopan, the bones more commonly affected were the ribs, humerus, ankle, and foot. As the fracture incidence is higher in women ≥ 60 years of age (Jones et al, 1994), bone fractures are listed by sex within treatment group in Table 40.

Table 40   Location of Bone Fractures—GSK014

	Placebo		Alvimopan		Total	
Fracture Location	**Female n = 1**	**Male n = 2**	**Female n = 15**	**Male n = 5**	**Female n =16**	**Male n = 7**
Vertebra	0	0	1	1	1	1
Rib[1]	1	0	3	1	4	1
Clavicle[2]	0	0	0	1	0	1
Humerus	0	0	1	2	1	2
Hip	0	1	0	0	0	1
Femur	0	0	1	0	1	0
Patella/fibula/tibia	0	1	2	0	2	1
Ankle	0	0	3	0	3	0
Foot	0	0	4	0	4	0

1 Patient 22763 was a 66-year-old, white, postmenopausal female who initially reported a rib fracture after 16 days of alvimopan treatment. Follow-up with the investigator revealed that two radiographs failed to show an acute fracture.

2 Patient 23250 was a 42-year-old, white male who initially reported a fractured clavicle after 8 days of alvimopan treatment. Follow-up with the investigator revealed the patient was diagnosed with a shoulder impingement syndrome.

Additional information on each fracture case was requested from investigators through the use of a fracture-specific data collection form. This form sought information regarding fracture cause and outcome, verification of fracture, medical and family history for fractures and bone disease, and known risk factors for fractures.

Fifteen of the 23 patients reported that the fracture was confirmed by a diagnostic test; however, copies of the diagnostic report were available for only eight of the 20 fractures in the alvimopan group and one of the three fractures in the placebo group.

Information regarding the cause of the fracture was available on 12 patients. Nine patients in the alvimopan group and two in the placebo group reported the fracture resulted from a fall (minor trauma). One patient in the placebo group suffered a broken fibula in a motorcycle accident. The available data indicated healing was normal with standard management in 17 alvimopan cases and one placebo case. Previous fractures were reported for five patients in the alvimopan group and two in the placebo group.

Ten of the alvimopan fracture cases had a history for bone or joint disease; these included degenerative disc disease (n = 1), osteoarthritis (n = 1), osteonecrosis (n = 1), osteoporosis (n = 5), osteopenia (n = 1), and scoliosis (n = 1). One patient in the placebo group had a

history for osteoporosis. Five patients in the alvimopan group and one in the placebo group were under treatment with bisphosphonates.

Of the 15 women who experienced a fracture in the alvimopan group, 12 were postmenopausal. The lone female with a fracture in the placebo group was also postmenopausal.

Physical impairments or medical conditions considered predisposing factors for falls were reported for nine patients in the alvimopan group and two in the placebo group. A history of falls in the past year was present in three patients in the alvimopan group and one patient in the placebo group.

7.2.2.2   Summary of Data From All OBD Studies

Combining all 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 HR estimate was 1.15 (95% CI = 0.55, 2.39).

Of patients reporting fractures, the alvimopan group had a higher percentage of women, more individuals 65 years or older, and a higher average BMI (Table 41).

Table 41   Demographic Characteristics of Bone Fracture Patients—All OBD Studies

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

The time of fracture occurrence in the alvimopan and placebo groups are graphically displayed in Figure 33. The incidence of fractures for the alvimopan group was similar to the placebo group through 120 days of treatment; however, the percentage of fractures in the alvimopan group was higher relative to the placebo group following 120 days of exposure. This difference is represented by fractures occurring in patients randomized to alvimopan in GSK014.

Figure 33 **KM Estimates of Time to Bone Fracture—All OBD Studies**
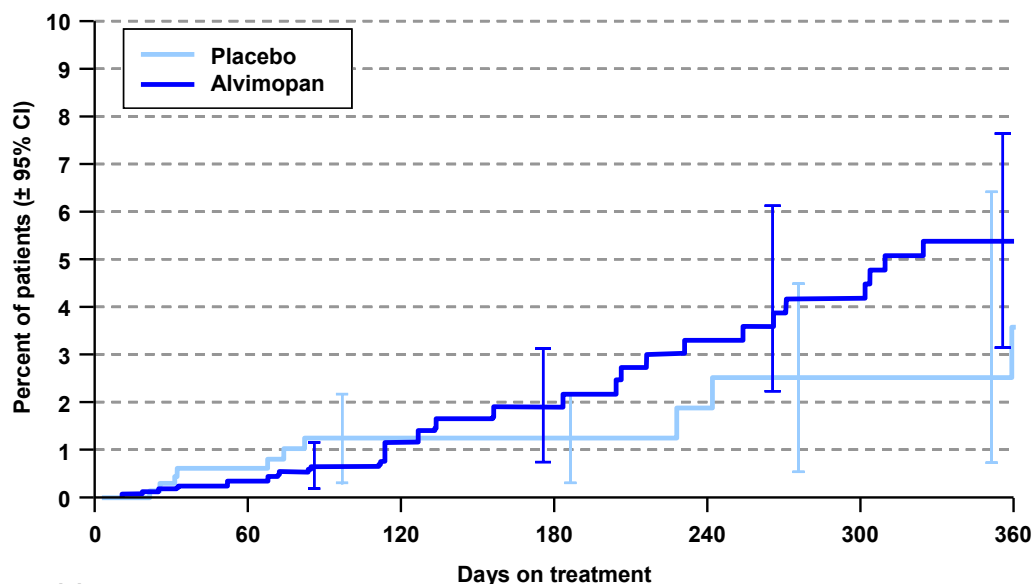
Patients at risk							
Placebo	802	479	186	166	153	139	75
Alvimopan	1758	989	396	368	339	318	187

The database was also examined for concomitant medications that are associated with increased risk for fracture or that serve as a marker for bone disease. The effects of systemic corticosteroid therapy on bone are well known, but there was no difference between the alvimopan and placebo fracture groups in corticosteroid use. However, the use of other medications implicated as risk factors for bone fracture was higher in the alvimopan fracture group compared with the placebo group. These medications included proton pump inhibitors, laxatives, antiepileptics, and psychoanaleptics.

The percentage of patients prescribed drugs for treatment of osteoporosis was threefold higher in the alvimopan fracture group. Hormone replacement therapy was also higher in the alvimopan group (Table 42).

Table 42   Concomitant Medications Used in Bone Fracture Cases

	Placebo N = 10 n (%)	Alvimopan N = 25 n (%)
Corticosteroids	3 (30%)	8 (32%)
Drugs for bone diseases	1 (10%)	8 (32%)
Acid-related disorders	1 (10%)	19 (76%)
Antiepileptics	3 (30%)	14 (56%)
Thyroid disorders	1 (10%)	8 (32%)
Psychoanaleptics	5 (50%)	22 (88%)
Psycholeptics	6 (60%)	17 (68%)
Laxatives	4 (40%)	17 (68%)
Hormone replacement	0 (0%)	4 (16%)

7.2.2.3   Additional Analyses of the GSK014 Population

Interrogation of the available data suggested an imbalance may have existed between groups for factors associated with fracture. Therefore, proportional hazards modeling was performed to determine if any of these factors predicted fracture in GSK014 and to adjust, as necessary, relative risk estimates for imbalances in these factors.

Stepwise variable selection was used to identify predictors from among the following variables: treatment, age, sex, race, smoking status, baseline METDD, BMI, and the use of the following drug classes: corticosteroids, drugs for bone diseases, drugs for acid-related disorders, antiepileptics, drugs for thyroid disorders, hormone therapies, and proton pump inhibitors. Stepwise variable selection identified use of drugs for bone diseases as the only significant predictive factor for fracture Table 43.

In the final model with drugs for bone diseases as a predictive factor, the adjusted HR for alvimopan vs. placebo was 3.09 (95% CI = 0.92, 10.4).

Initial analyses of GSK014 assumed that fracture diagnoses were accurate. However, as noted earlier, subsequent investigation revealed that acute fractures did not occur in two of the alvimopan cases. Exclusion of these two cases results in a lower HR as expected.

In contrast, a sensitivity analysis using only fracture cases with a confirmatory radiographic report shows an increase in the HR, but the reduction in the number of events resulted in increased variability and a 3-fold increase in the width of the 95% CI.

These analyses illustrate the difficulty in gauging fracture risk in the absence of prospectively defined and confirmed endpoints.

Table 43   Hazard Ratio for Bone Fracture and Sensitivity Analyses—GSK014

	Alv/Pla Crude HR (95% CI)	HR for Predictor Variables (95% CI)	Alv/Pla Adjusted HR (95% CI)
Use of drugs for bone diseases	3.16 (0.94, 10.62)	5.3 (2.24, 12.49)	3.09 (0.92, 10.40)
Excluding patients 22763 and 23250	3/267 (1.1%)	18/538 (3.4%)	3.0 (0.88, 10.02)
Confirmed fracture diagnosis	1/267 (0.4%)	8/538 (1.5%)	4.0 (0.50, 31.58)

7.2.2.4   Exposure-Response Analyses

The relationship between exposure to alvimopan and/or metabolite and the AE of fracture were evaluated and are shown in Appendix 12.5.3. The plasma concentrations of parent and metabolite in those experiencing a fracture were as expected based on dose. Fractures do not appear to be explained by higher concentrations of alvimopan or metabolite. Although limited, the data suggest that there is unlikely to be an exposure-response relationship for this AE.

7.2.2.5   Overall Interpretation of Risk of Bone Fracture

Patients studied in the OBD non-cancer program have typically been white (90%), female (65%), and in their early fifties. For the cancer program, patients were typically white (82%), female (60%), and in their late 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. Although a higher fracture incidence was reported in patients randomized to alvimopan treatment in GSK014, careful examination of the available data has identified a number of factors that confound the interpretation of the GSK014 findings and make difficult any conclusion of a causal relationship.

7.2.2.5.1   Case Ascertainment of Bone Fracture

Analysis of bone fractures reported in OBD studies is made difficult by the fact that fracture information was not collected prospectively in a standardized manner, as no safety signal had been previously identified prior to completion of GSK014. Most fractures were reported as AEs rather than SAEs, so information regarding the location, cause, outcome, and pertinent medical history was limited initially. Although additional information for fracture cases was collected retrospectively, using a standardized, fracture-specific data collection form, complete information was not available for all fracture cases. For example, radiographic reports confirming a bone fracture were available for GSK review in only 12 of the 35 fracture cases. As a result, the analyses are based upon an incomplete and imperfect dataset, one that cannot confirm a bone fracture in 66% of the reported fractures. The importance of case ascertainment is highlighted by the findings of the GSK014 sensitivity analyses, which illustrated the difficulty in assessing fracture risk in the absence of prospectively defined and confirmed endpoints.

7.2.2.5.2   Increased Risk in Alvimopan Patients Who Reported Bone Fracture

The risk of fracture is related to the decline in bone mass and neuromuscular function after menopause in women and with advancing age in men. Although fractures of the spine, hip, and wrist are regarded as the typical osteoporotic fractures, prospective studies have shown that almost all types of fracture are increased in patients with low bone density. Most hip fractures take place after a fall; 80% occur in women and 90% in individuals older than 50 years. Approximately 25% of vertebral fractures result from falls, with most related to routine everyday activities. The prevalence of vertebral fractures in men is almost as high as that in women and is thought to be due to occupation-associated trauma in men.

Most wrist fractures happen in women, 50% of whom are older than 65 years. The incidence in men is low and does not increase much with age. Incidence rates for fractures of the proximal humerus, pelvis, proximal tibia, and distal femur also increase with age in elderly women and, to a lesser extent, in aging men. Roughly 75% of all proximal humerus fractures are due to moderate trauma, typically a fall from standing height or less. Foot and ankle fractures are among the most common nonspinal fractures in older women. Foot fractures appear to be associated with a decline in bone mass, whereas the risk for ankle fractures has been linked to obesity and history of prior falls.

In addition to age and low bone density, a number of additional risk factors for fracture have been identified; these include female sex; Asian or Caucasian race; premature menopause; prior fracture; factors such as poor vision, reduced mobility, or CNS-active drugs predisposing to falls; smoking; and glucocorticoid therapy.

While the incidence of fractures for the OBD program is similar for the alvimopan and placebo groups, an excess fracture incidence occurred in women treated with alvimopan, the majority of whom participated in GSK014. Careful examination of each of the GSK014 cases found that these 15 women were at increased risk for fracture. All women were white, 12 were ≥ 50 years of age, and 12 were postmenopausal. Five patients were diagnosed with

osteoporosis and treated with bisphosphonate therapy, three had a history of previous fractures, and seven were considered to have impairments predisposing to fall.

Fractures typically involved the appendicular skeleton, consistent with the systemic effect of osteoporosis on the skeleton and data showing an increased risk for almost all types of fracture in individuals with low bone density. Seven of the 15 fractures involved the foot or ankle. The three patients reporting ankle fractures had BMI greater than 30 and the breaks were associated with a fall.

Most fractures result from falls, and use of CNS-active medicines can increase the risk for falls. As noted earlier, the mean METDD was two-fold higher in the alvimopan fracture group than in the placebo group. The effect of opioid analgesics to impair alertness and neuromuscular function is well known. The Osteoporotic Fractures Research Group found an increased risk for any nonspine fracture in older women taking opioid analgesics (Ensrud, 2003). However, data demonstrating an increased fracture risk with increasing doses of opioid analgesics are limited and conflicting (Vestergaard, 2006).

7.2.2.5.3 *Study Design Factors*

An imbalanced randomization scheme was selected in an effort to recruit and retain patients, as patients would have two chances in three for randomization to alvimopan treatment. However, it is conceivable that the imbalanced randomization scheme may have decreased the probability of detecting infrequent, but important AEs in the placebo group given the smaller sample size in this group. Stated another way, allocation of more patients to the active regimen reduces the probability of detecting infrequent AEs in the placebo group.

7.2.2.6 Overall Conclusions—Bone Fracture

No imbalance in reported bone fractures was apparent from clinical studies prior to the completion of GSK014, nor is there biologic evidence for an effect of alvimopan or other μ-opioid receptor antagonists on bone metabolism.

Analysis of the available data is confounded by the lack of prospectively defined, fracture-specific data and an imbalance in the treatment assignment of patients.

Moreover, the available data suggest the increased number of fractures occurring in patients treated with alvimopan in GSK014 may well be related to an increased number of risk factors in these patients for bone fragility, which predisposed to fracturing with minor trauma.

Although not conclusive, the possibility of increased bone fragility, independent of alvimopan, leading to a greater susceptibility to fracture must be considered.

A cause-and-effect relationship cannot be established given these factors. Additional assessment of the observation is required via a prospective study using clear definitions for the identification and evaluation of bone fractures.

7.2.3   Neoplasm Evaluation

7.2.3.1   Non-Cancer Studies

7.2.3.1.1   Incidence of Neoplasms

No excess of neoplasia events in alvimopan-exposed patients was noted before the availability of final data from GSK014. An initial analysis of AE frequencies in GSK014 showed an imbalance in the frequency of events coded as "neoplasms." These events included both malignant and benign neoplasms. Benign neoplasms represented a heterogeneous group including leiomyoma, lipoma, skin papilloma, hair follicle tumor, neuroma as well as single basal cell and squamous cell skin carcinomas. Given this heterogeneity, it was felt appropriate to review all AEs reported in GSK014, and compare the incidence between treatment groups of malignant and benign neoplasms separately.

Table 44 shows the distribution of benign lesions in GSK014. While the relative risk estimates are elevated, CIs are wide and the p value is consistant with a chance finding. Given the variety of histological types seen, it is difficult to posit a single etiological agent in their pathogenesis. Subsequent analyses therefore focused on malignant lesions.

Table 44   Benign Neoplasms—GSK014

	Placebo n/N (%)	Alvimopan n/N (%)	Rel Risk (Alv/Pla)	Hazard Ratio (Alv/Pla)	p value**
	1/267	8/538	4.0	3.6	
GSK014	(0.4%)	(1.5%)	(0.50, 31.58)	(0.45, 28.61)	0.199

** Log-rank test.

Table 45 summarizes the incidence of all malignant neoplasia events reported in GSK011, GSK012, GSK013, and GSK014, along with estimates of the relative risk and HR calculations. Results from GSK014 alone are also depicted.

Following the initial finding of the numerical imbalance of malignant neoplasm, GSK communicated with site investigators concerning these malignant events. During the course of that interaction, GSK became aware of an additional case of neoplasm for a placebo patient (#7846) in GSK014. This report was unsolicited and GSK did not systematically screen all investigators for additional cases of neoplasia. Analyses including this case are also summarized in Table 45.

Table 45   Neoplasia Event Summary—All Malignant Neoplasms

	Placebo n/N (%)	Alvimopan n/N (%)	Rel Risk (Alv/Pla)	Hazard Ratio (Alv/Pla)	p value**
Initial Analysis					
Non-cancer pain studies*	2/732 (0.3%)	10[b]/1598 (0.6%)	2.3 (0.50, 10.43)	2.4 (0.52, 10.83)	0.250
GSK014	1/267 (0.4%)	5/538 (0.9%)	2.5 (0.29, 21.13)	2.3 (0.27, 20.04)	0.424
Including Additional Patient[a]					
Non-cancer pain studies*	3/732 (0.4%)	10[b]/1598 (0.6%)	1.5 (0.42, 5.53)	1.6 (0.43, 5.72)	0.487
Study GSK014	2/267 (0.7%)	5/538 (0.9%)	1.2 (0.24, 6.35)	1.2 (0.23, 5.99)	0.858

* Non-cancer pain studies: GSK011, GSK012, GSK013, GSK014.

** Log-rank test.

a Patient #7846 was randomized to placebo in GSK014. Patient identified following post-analysis communication with study investigators. This report was unsolicited and GSK did not systematically screen all investigators for additional cases of neoplasia.

b Includes a case reported 6 months after study completion, patient 2077 (GSK011) with adenocarcinoma of the lung.

The additional placebo case caused a reduction in the magnitude of the numeric imbalance in the number of malignant neoplasms overall, as well as in GSK014 alone. This reduces the initial imbalance in GSK014 to a ratio of 2.5:1, which is wholly in keeping with the 2:1 randomization. This single additional case eliminates the appearance of an imbalance in GSK014 and the non-cancer studies overall highlighting the instability of risk estimates based on a small number of events.

7.2.3.1.2   Case Discussions—GSK014

Overall, the incidence of malignant neoplasms was low in GSK014 (consistent with all other OBD studies in non-cancer pain), and the relative risk estimates were not significantly greater than 1. The specific malignancies that occurred in patients in GSK014 are presented in Table 46. Narratives for patients diagnosed with a malignant neoplasm in GSK014 appear in Appendix 12.7.

Table 46   Patients With Malignant Neoplasms—GSK014

Patient ID	Pathology	Study Day Malignancy Diagnosed	Comments
Alvimopan-Treated Patients			
16803 63 yo ♂	Squamous cell cancer: lung	Within 2 weeks	On long-term F/U of lung space occupying lesion – Δ noted within 2 wks onset therapy
3233 81yo ♂	Lung cancer	Day 133	2-yr h/o pre-existing cavitary lung disease. Refused biopsy.
18857 77yo ♂	Malignant melanoma	Day 174	Non-healing lesion on ear, excised as an outpatient. 4x4 mm, purple color, no pathology report available
3553 61 yo ♂	Squamous cell cancer: lung	Day 270	Picked up on pre-op CXR (umbilical hernia surgery)
3555 74 yo♀	Squamous cell cancer: larynx	Day 316	Clinically palpable node R neck – 2.5 cm
Placebo-Treated Patients			
8523 68 yo ♂	Prostate cancer: metastatic	Day 47	Picked up on chest CXR, suggestive of metastatic prostate disease
7846[a] 57 yo ♂	Lung cancer	Day 414	Picked up on CXR

a Patient identified following post-analysis communication with study investigators. This report was unsolicited and GSK did not systematically screen all investigators for additional cases of neoplasia.

The cancers reported in alvimopan-treated patients are notable for several characteristics. At least two of the patients exhibited detectable signs or symptoms of cancer in the months prior to randomization. One patient was undergoing yearly follow-up for evaluation of a lesion in the lung, while another had cavitary lung disease and a history of hemoptysis and had refused further evaluation. Finally, a third patient self-reported a melanoma, but it was impossible to obtain pathology results or confirmation from the investigator and the method of excision was inconsistent with standard of care for melanoma.

7.2.3.1.3   *Case Discussions—Non-Cancer Pain Studies Excluding GSK014*

A numerical imbalance of malignant neoplasms of 5:1, alvimopan:placebo, was also seen in non-cancer OBD studies outside of GSK014. In these studies, randomization was again approximately 2:1 Among patients on alvimopan, these included two cases of breast cancer (Days 48 and 62), a pancreatic adenocarcinoma (Day 5), a chronic lymphocytic leukemia (CLL) (Day 88), and an adenocarcinoma of the lung (reported 6 months after study completion). The placebo-treated patient had metastatic colon cancer that was diagnosed 106 days after the start of therapy. Of note, the pancreatic carcinoma was reported 5 days

after the start of treatment, in the course of an evaluation of abdominal pain. The CLL was reported as a non-serious AE in the setting of a patient with preexisting high-grade lymphocytosis being monitored for possible CLL. Narratives for patients diagnosed with a malignant neoplasm appear in Appendix 12.7. The heterogeneity of histology among lesions in alvimopan-treated patients speaks against a causal relationship with therapy. The finding of pancreatic carcinoma after only 5 days of therapy can only be understood as a preexisting lesion. Given the 2:1 ratio of alvimopan:placebo patients, these findings diminish any initially apparent imbalance .

7.2.3.1.4   Sensitivity Analyses

The above discussions and analyses of the malignant neoplasms in GSK014 are for the most part based on the worst-case assumptions regarding the baseline presence of cancer, or the accuracy of the cancer diagnosis. It is assumed that cancers were not present prior to their detection, when in fact current understanding of cancer biology would suggest that most of these malignancies were likely present prior to study start.

Had there been slightly more rigorous screening prior to enrollment it is likely that at least two of the cases would not have been enrolled due to the possibility of underlying malignancy. A simple chest x-ray would have detected the previously known cavitary lesion seen in patient 3233, and the space-occupying lesion in patient 16803 that was seen to have changed from previous appearance less than 2 weeks after randomization. Table 47 demonstrates that exclusion of these two cases results in a marked reduction in the appearance of the increased risk of malignant neoplasms in the alvimopan group in GSK014.

Table 47   Sensitivity Analysis Summary Excluding Likely Pre-existing Malignant Neoplasms

	Placebo n/N (%)	Alvimopan n/N (%)	Relative Risk (Alv/Pla)	Hazard Ratio (Alv/Pla)	p value Log-Rank Test
Non-cancer studies*	3/732 (0.4%)	8/1598 (0.5%)	1.2 (0.33, 4.59)	1.2 (0.33, 4.73)	0.737
GSK014	2/267 (0.7%)	3/538 (0.6%)	0.7 (0.13, 4.43)	0.7 (0.12, 4.11)	0.679

* Non-cancer studies: GSK011, GSK012, GSK013, GSK014.

Likewise, for the sake of maximizing sensitivity to a signal, standards of documentation of neoplasia were loosely applied, and resulted in two of the five index cases having no histopathological verification of the diagnosis. These are the cases for the 81-year-old Taiwanese man (patient 3233) with the known cavitary lesion who was diagnosed at an outside hospital, and for the 78-year-old woman (patient 18857), who reported a malignant melanoma on her ear.

While adequate circumstantial evidence exists to suggest that patient 3233 did in fact have cancer, the case for patient 18857 is much more dubious. Though a small non-healing lesion of the ear was noted on physical exam, the investigator was unable to get confirmation that the patient ever visited a dermatologist or that an appropriate wide excision was ever performed. Subsequent clinic visits to the site of investigator make no further mention of the ear lesion or suggest abnormalities on physical exam consistent with a wide excision. A verbal report from the study coordinator suggests that the lesion was "frozen off"; however, this is not consistent with the standard of care for the treatment of melanoma.

Given the doubt surrounding this case, and the uncertainty of the diagnosis it is reasonable to examine risk estimates in the absence of this case. Table 48 demonstrates the sensitivity of risk estimates for malignant neoplasms to the exclusion of this single case.

Table 48   Sensitivity Analysis Excluding Undocumented Melanoma Case

	Placebo n/N (%)	Alvimopan n/N (%)	Relative Risk (Alv/Pla)	Hazard Ratio (Alv/Pla)	p value Log-Rank Test
Non-cancer studies	3/732 (0.4%)	9/1598 (0.6%)	1.4 (0.37, 5.06)	1.4 (0.38, 5.24)	0.599
GSK014	2/267 (0.7%)	4/538 (0.7%)	1.0 (0.18, 5.38)	0.9 (0.17, 5.07)	0.931

Again the result is that in GSK014 the imbalance is eliminated, and we have a case distribution entirely consistent with chance. These analyses demonstrate the tenuousness and fragility of the initially identified imbalance and supports the null hypothesis, that alvimopan is not associated with an increased risk of malignant cancers.

7.2.3.2   Cancer-Related Pain Studies

GSK008 and its long-term extension, GSK684, were conducted separately from the non-cancer pain OBD trials to eliminate the potentially confounding factors inherent in the underlying cancer disease state. Enrollment criteria required that subjects have pain due to cancer, and a minimum three month life expectancy. For the most part, patients had existing malignancies however disease type or status were not considered in the randomization of patients. Study duration in GSK008 was 3 to 6 weeks. If a patient elected to participant in the extension study, they continued on the same treatment as they were randomized to in GSK008. There was no designated end date or time for treatment duration in GSK684.

7.2.3.2.1   All-Cause Death

While the number of deaths reported in the non-cancer pain studies was low, several deaths were reported during the Phase 2b study in cancer-related pain, GSK008 (n = 10, 4%), and its extension study, GSK684 (n = 13, 20%). Of these 23 patients, 3 (4%) were placebo-treated patients and 20 (13%) were alvimopan-treated patients. Overall, a total of 230 persons

received investigational product during the short-term efficacy study and 65 patients continued in the extension study.

As the cumulative person-time for alvimopan-treated patients who progressed into the extension study was much greater than that for the placebo-treated patients who progressed into the extension study, incidence rates and the incidence density ratio (IDR) were used initially to assess the risk of death. Incidence rates and the IDR use person-time rather than number of patients and therefore can account for differences in exposure. The IDR for all deaths in the cancer pain studies is listed in Table 49.

Table 49   Incidence Density Ratio (IDR) —GSK008 and GSK684

	Placebo (N=70)	Alvimopan (N=160)	IDR (Alv/Pla)
Patient years	11.2	43.3	
All-cause death	3 (26.8/100 pt-yrs)	20 (46.2/100 pt-yrs)	1.72 (0.51, 9.06)

These deaths were ultimately attributed by the investigators to progression of the underlying cancer. Lung cancer was the most common underlying malignancy overall and was the cause of death in 10/13 cases in GSK684. Table 50 lists all deaths in both studies along with corresponding index cancer information.

Table 50   List of Deaths—GSK008 and GSK684

GSK008			Study GSK684		
Patient ID	Treatment	Index cancer	Patient ID	Treatment	Index cancer
1346	Alvimopan	Breast	116	Alvimopan	Non-small cell lung cancer
1347	Alvimopan	Genitourinary	119	Alvimopan	Non-small cell lung cancer
1349	Alvimopan	Breast	125	Alvimopan	Non-small cell lung cancer
1676	Alvimopan	Breast	145	Alvimopan	Breast
1747	Alvimopan	Breast	200	Alvimopan	Genitourinary
1756	Alvimopan	Genitourinary	801	Alvimopan	Non-small cell lung cancer
1758	Alvimopan	Gynecologic	803	Alvimopan	Non-small cell lung cancer
1888	Alvimopan	Breast	806	Alvimopan	Non-small cell lung cancer
2065	Alvimopan	Non-small cell lung cancer	2006	Alvimopan	Non-small cell lung cancer
2077	Placebo	Gynecologic	2203	Placebo	Non-small cell lung cancer
			2225	Placebo	Small cell lung cancer
			2226	Alvimopan	Non-small cell lung cancer
			2047	Alvimopan	Prostate

Patients enrolled in GSK008 were required to have a life expectancy of at least 3 months. However, 10 patients died during the study even though the maximum total time of participation was limited to 5 to 8 weeks. Nine of these patients received alvimopan. Some variability is to be expected in this regard, as life expectancy is difficult to predict. Regardless, it is possible the entry criteria may have been inconsistently applied at some sites. Of interest, five of the 10 deaths were reported by two sites that enrolled a total of 10 patients (50%) while the other five deaths were reported across 78 sites that enrolled the remaining 223 patients. The randomization ratio for GSK008 was 2.3:1 (alvimopan:placebo) contributing to the appearance of imbalance. The randomization ratio for GSK684 was even higher (3.4:1), further contributing to the apparent imbalance.

The greater number of alvimopan-treated patients choosing to enroll in the extension study suggests a patient-perceived benefit of alvimopan therapy. Patients receiving placebo who also chose to enroll may have also perceived benefit, and thus were likely less ill. Indeed, analysis showed that placebo patients appeared to have less advanced disease at baseline.

Disease type or status (i.e. cancer stage) were not considered in the randomization of patients. (See Section 7.2.3.2.7.)

Time to death in the alvimopan and placebo groups for patients participating in the cancer pain studies is depicted in Figure 34. The duration of exposure for patients who participated in both studies was based on the total number of days between the date of initial exposure in GSK008 and the final date of exposure in GSK684, irrespective of any interruption of investigational product that may have occurred.

Figure 34   KM Estimates of Time to All-Cause Death—GSK008 and GSK684

Patients at risk						
Placebo	70	14	10	6	4	3	2
Alvimopan	160	44	33	29	22	21	20
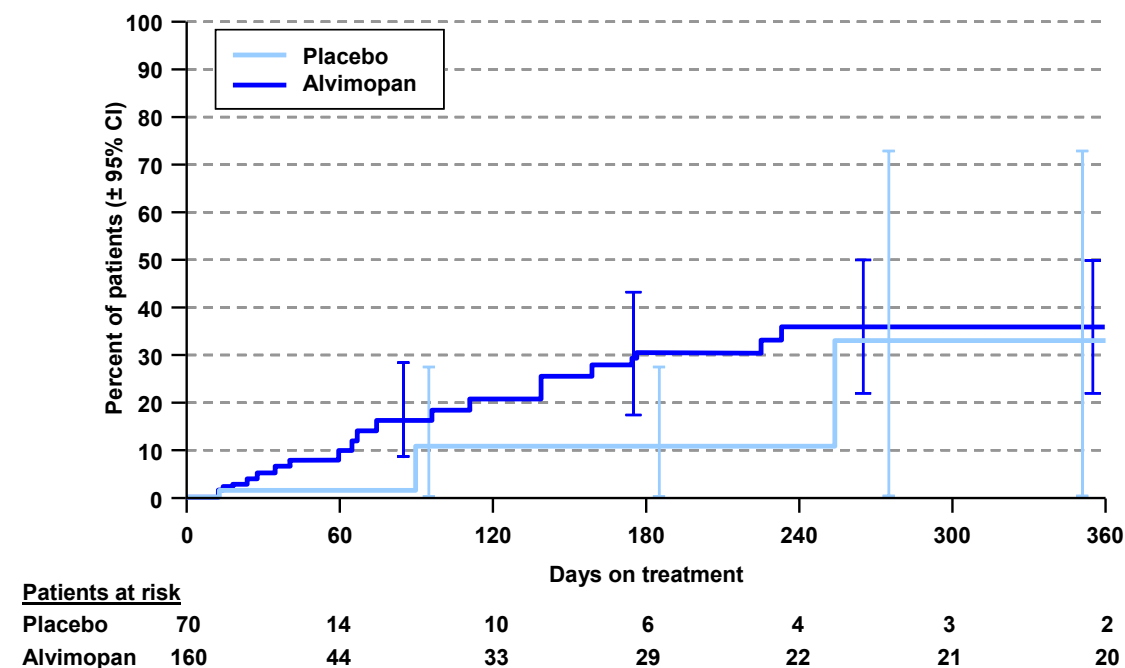
As the duration of actual exposure in GSK008 was only 3 to 6 weeks, the number of patients at risk declines markedly after that time. Less than 1/3 of these patients (n = 65) received treatment in GSK684. Confidence intervals are wide and overlapping suggesting no difference between treatment groups (p = 0.223, log-rank test). As the study was conducted over a long period of time in patients with malignant cancer, it is expected that these curves would eventually converge. All analyses of these data are limited by the small number of patients at risk, particularly after the initial 3 to 6 weeks, and especially in the placebo group.

Analyses were performed to further characterize the cancer pain patients from GSK008 and specifically the subset who subsequently enrolled in GSK684. The purpose was to explore whether selection bias could have influenced the disproportionate number of reported neoplasia events and/or deaths in patients who received alvimopan in GSK684.

It should be noted that only 15 patients received placebo during GSK684. Therefore, small changes in the number of patients for any parameter produce proportionally large changes in calculated percentages.

7.2.3.2.2 Demographics

The demographics for patients from GSK008 and GSK684 are summarized in Table 51.

Table 51   Demographic Characteristics—GSK008 and GSK684

	GSK008		GSK684	
	Placebo n=70	Alvimopan n=160	Placebo n=15	Alvimopan n=50
Age, years	59	59	56	57.3
> 65 years, %	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

Overall, the demographic characteristics appear similar between the GSK008 population and the subset enrolled in the extension study, GSK684. There also appears to be equal distribution overall between placebo and alvimopan groups within each study. The slightly higher mean BMI in the placebo group in GSK684 is disproportionately influenced by one patient who weighed 174 kg. The mean BMI of the placebo group is 26.6 if this patient is excluded. Analysis showed that regional distribution of the GSK008 population and the GSK684 subset did not appear to be a significant factor that distinguished the two groups from each other.

7.2.3.2.3 Primary Cancer Diagnosis in Patients in GSK008 and GSK684

All patients who enrolled into the cancer-pain studies were required to either have a systemic cancer or have chronic pain as a result of previous treatment for a systemic cancer. These diagnoses are summarized in Table 52.

Table 52   Primary Cancer Site Reported in > 1 GSK684 Patient or > 3 Patients in GSK008

	GSK008		GSK684	
	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

As might be expected, there were a wide range of underlying cancer types reported in these populations overall. The most common cancer types in both studies were breast, lung, and genitourinary (i.e., prostate), which is consistent with the worldwide prevalence of these cancers. It should be noted that most patients with colectomies were excluded from enrollment into GSK008 for the purposes of limiting confounds to efficacy assessments. This is why so few patients with colorectal cancer were studied.

Two imbalances are noted upon examination of the enrolment in the placebo vs. active treatment arms within studies. In GSK008, more patients with head and neck cancers received alvimopan (n = 14) than placebo (n = 1). As only three of these patients (all received alvimopan) enrolled in GSK684, it is doubtful that this had any impact on the AEs reported in that study. More importantly, there were many more patients with non-small cell lung cancer in GSK684 who received alvimopan (n = 16, 31%) than placebo (n = 1, 7%). As lung cancer was the most common diagnosis implicated in reported malignancy-related deaths, this imbalance may have had an impact on the number of deaths reported in patients receiving placebo vs. active treatment.

7.2.3.2.4   *Metastatic Disease*

Metastatic disease was common in the cancer-pain patients studied in GSK008 and GSK684. The most common sites of metastases were bone and lymph nodes in both studies. See Table 53 for details regarding the number of sites of metastases reported in these patients.

Table 53   Number of Sites of Metastases at Baseline—GSK008

	GSK008		GSK684	
Number of Metastases	Placebo n=70 n (%)	Alvimopan n=160 n (%)	Placebo n=15 n (%)	Alvimopan n=50 n (%)
0	20 (29%)	52 (32%)	6 (40%)	18 (36%)
1	27 (39%)	51 (31%)	5 (33%)	15 (28%)
2	10 (14%)	28 (18%)	0	8 (16%)
3+	13 (19%)	31 (19%)	4 (27%)	10 (20%)

The subset of patients who enrolled in GSK684 appears similar to the entire GSK008 population from the standpoint of severity of metastatic disease. The alvimopan and placebo groups appear to be reasonably well matched in both studies.

7.2.3.2.5   Functional Status

The Karnofsky Performance Status score is a clinician-administered scale used to measure the degree of functional impairment in cancer patients. Possible scores range from 0 (deceased) to 100 (normal function). Karnofsky scores measured during the GSK008 randomization visit are summarized in Table 54.

Table 54   Baseline Karnofsky Performance Score

	GSK008		GSK684	
Karnofsky Score	Placebo n=70 n (%)	Alvimopan n=160 n (%)	Placebo n=15 n (%)	Alvimopan n=50 n (%)
100	13 (19%)	25 (16%)	5 (33%)	11 (22%)
90	11 (16%)	33(21%)	5 (33%)	10 (20%)
80	21 (30%)	41 (26%)	3 (20%)	8 (16%)
70	13 (19%)	30 (19%)	2 (13%)	13 (26%)
60	10 (14%)	19 (12%)	0	6 (12%)
50	2 (3%)	10 (6%)	0	2 (4%)
40	0	1 (1%)	0	0

As displayed in Table 54, patients in GSK008 appear similar with respect to baseline Karnofsky score upon entering GSK008. The proportion of patients with baseline Karnofsky scores ≤ 70 was similar between treatment groups in GSK008. However, in GSK684, 21 of 50 (42%) patients receiving alvimopan had Karnofsky scores ≤ 70, while 2 of 15 (13%) patients receiving placebo had scores in this range, indicating that persons receiving alvimopan were more debilitated and in need of assistance.

7.2.3.2.6 *Baseline Characteristics of Deaths in GSK008*

While the number of patients who died in the long-term extension study (GSK684) were, in the majority, individuals with an index diagnosis of non-small cell lung cancer, this was not the case for patients who died in the course of the short-term treatment study (GSK008). There were nine deaths among patients treated with alvimopan, and one death among placebo-treated patients in this study. Clinical characteristics of these patients including index diagnosis, Karnofsky scores, number of sites of metastasis and country distribution are shown in Table 55, Table 56, Table 57, and Table 58.

Table 55   Primary Cancer Diagnosis Among Patients Who Died in GSK008

Cancer Diagnosis	Placebo (n=1)	Alvimopan (n=9)
Breast	0	5 (56%)
Gynecologic	1 (100%)	1 (11%)
Genitourinary	0	2 (22%)
Lung (non-small cell)	0	1 (11%)

Table 56   Number of Metastatic Sites Among Patients Who Died in GSK008

Number of Metastatic Sites	Placebo (n=1)	Alvimopan (n=9)
0	1 (100%)	1 (11%)
1	0	1 (11%)
2	0	1 (11%)
3	0	4 (44%)
6	0	2 (22%)

Table 57   Baseline Karnofsky Status Among Patients Who Died in GSK008

Baseline Karnofsky Score	Placebo (n=1)	Alvimopan (n=9)
100	0	0
90	0	0
80	1 (100%)	3 (33%)
70	0	2 (22%)
60	0	1 (11%)
50	0	3 (33%)

Table 58   Country Distribution Among Patients Who Died in GSK008

Country	Placebo (n=1)	Alvimopan (n=9)
Argentina	1 (100%)	0
France	0	1 (11%)
Italy	0	3 (33%)
Russia	0	3 (33%)
South Africa	0	1 (11%)
Thailand	0	1 (11%)

These analyses indicate that breast cancer was the most common index diagnosis in this group, as it was for the population in general. Persons who died in this study and received alvimopan tended to have lower Karnofsky scores and more sites of metastasis. Deaths appeared to occur more commonly outside of the United States, and most frequently in Italy and Russia. It was subsequently suggested that these are countries where the standard of care dictates the withholding of opioids until the later stages of disease.

7.2.3.2.7   *Multivariate Modeling*

Analyses of baseline characteristics in the cancer extension study, GSK684, indicated a number of imbalances, including baseline Karnofsky status and index cancer diagnosis, that were likely caused by the self-selection of patients progressing from GSK008 into GSK684. To determine if any of these factors predicted the outcome of death in the combined GSK008-GSK684 cancer-related pain studies and to subsequently adjust relative risk estimates for imbalances in these factors, proportional hazard modeling was undertaken.

Stepwise variable selection was used to identify those significant predictors from among the following explanatory variables: treatment assignment, age, sex, Karnofsky status, number of sites of metastasis and an indicator variable for the presence of non-small cell lung cancer (index cancer). The stepwise variable selection process identified Karnofsky status, number of metastatic sites, and non-small cell lung cancer indicator as significant predictors; age and sex were not significant.

For Karnofsky status, each 10-point decrement in Karnofsky score produced a 50% increase in risk of death, while each additional site of metastasis increased the risk of death by 90% (Table 59). The baseline presence of non-small cell lung cancer was the strongest predictor with a HR of 2.8 (95% CI = 1.16, 6.78).

In the final model with Karnofsky status, number of metastatic sites, and non-small cell lung cancer indicator as explanatory predictors, the adjusted HR for alvimopan vs. placebo (Table 59, column 3) was not statistically significantly at 1.4, with a corresponding 95% CI of 0.40, 5.04. Table 59 also shows the crude HR estimate for death before adjustment for these highly predictive factors.

Table 59   Multivariate Analyses of Cancer-Related Pain Study Data

	Crude (unadjusted) HR for Alv/Pla (95% CI)	HR for Prognostic Variables (95% CI)	Adjusted HR for Alv/Pla (95% CI)
All-cause death	2.1 (0.62, 7.10)	Non-small cell lung vs. other cancer 2.8 (1.16, 6.78) Per 10-point ↓ Karnofsky 1.5 (1.13, 2.04) Per additional metastatic site 1.9 (1.26, 2.80)	1.4 (0.40, 5.04)

7.2.3.3   Exposure-Response Analyses

The relationship between exposure to alvimopan and/or metabolite and neoplasm was investigated in the OBD population. The plasma concentrations of parent and metabolite in those experiencing a neoplasm were as expected given the dose (Appendix 12.5.3). Neoplasms (whether benign or malignant) do not appear to be explained by higher concentrations of alvimopan or metabolite. The limited data suggest that there is unlikely to be an exposure-response relationship for this AE.

7.2.3.4   Overall Conclusions-Neoplasia

Benign Neoplasia

The analyses presented indicate a numerical imbalance in the incidence of benign neoplasia occurring in GSK014. This finding is isolated to GSK014 and not consistant with observations from the other noncancer OBD studies. The reported events represent a heterogeneous mix of benign histologic findings based on AE reports grouped in the "neoplasms" MedDRA systems organ class. Evaluation of the events and their etiology was submitted for review to an external panel of oncologists, epidemiologists and statisticians, who suggested that these observations were not clinically meaningful and that the focus of analysis should be on malignant neoplasia.

Malignant Neoplasia

There was a numerical imbalance in reported malignant neoplasia in the non-cancer OBD studies. This imbalance of 10:3 (alvimopan: placebo) represented a relative imbalance of 1.5 to 1 given the unequal randomization in the studies. Given the low incidence of events and wide confidence intervals, a statistical analysis in not instructive in explaining the observed difference. An examination of the patient narratives together with additional information available from investigators suggests that most if not all of these were present at baseline. It is important to note the preclinical carcinogenicity studies of alvimopan in two species were negative. Furthermore, alvimopan did not produce any significant genotoxicity or mutagenicity in animals. The extensive review of clinical data along with preclinical

findings does not support a causal relationship between alvimopan and the induction or progression of malignant neoplasia.

Death in OBD Cancer Studies

There was a numerical imbalance in deaths on alvimopan compared to placebo in GSK008 and GSK684. Multivariate modeling demonstrated that disease type, extent of disease (i.e. number of metastases) and functional status (Karnofsky score) likely accounted for the numerical differences observed in reported deaths. In addition, a greater percentage of patients randomized to alvimopan compared to placebo elected to continue therapy in GSK684 leading to a 3.4:1 randomization imbalance in this study. Furthermore, the alvimopan treated patients tended to remain in the study for a longer duration as compared to placebo, thus increasing the probability of reported deaths in the alvimopan treatment group. Again, while a causal relationship can not be ruled out, the totality of these data do not suggest the observed imbalance is drug related.

7.2.4   *Literature Review of Opioid Receptors and CV, Neoplasm, and Bone Fracture Events*

An extensive review of the literature was conducted to identify a possible mechanism that could explain the CV, neoplasm, and fracture events observed in GSK014 (Derelanko et al, 2007; Windh et al, 2007). A brief summary of those findings is summarized below:

7.2.4.1   Cardiovascular Effects

Opioid peptides and exogenous opioids such as morphine are believed to exert important CV effects:

- Majority of work conducted in preclinical models
- Results frequently contradictory regarding the role of agonists/antagonists with regard to CV function and ischemic risk
- No consensus regarding the role that opioids play in the regulation of the CV system
- Unclear whether primary effect of opioids on CV system to be effects on:
  - Preconditioning
  - Heart rate
  - Alterations to hemodynamics (vascular resistance)
  - Risk of ischemic arrhythmogenesis

7.2.4.2   Immune Suppression and Carcinogenicity

Opioid receptor agonists and antagonists exhibit a range of activities in immunosuppression, growth promotion, and growth inhibition.

The proliferative or antiproliferative actions of opioid receptor agonists or antagonists are dependent on:

- Concentration or dose tested,

- Cell line or system studied, and

- Therapy regimen.

Data generated for opioid antagonists naloxone or naltrexone have shown the following:

- Failure to demonstrate consistent effects on growth promotion or inhibition when administered in the absence of an opioid receptor agonist

- Failure to demonstrate a consistent pattern of antagonism of opioid-induced effects in the presence of an opioid receptor agonist

Chronic administration of the opioid antagonists naltrexone (Rosenkrantz H. J Clin Psychiatr. 1984; 45:11) or alvimopan to mice or rats failed to result in carcinogenicity.

7.2.4.3   Fractures and Bone Metabolism

Minimal direct evidence for effect of μ-opioid receptor antagonist on bone:

- The combination of opioid antagonist naloxone with calcium gluconate increases bone density in bone lesion model.

- Opioid peptides and receptors are expressed in bone and joint tissues.

- In vitro, opioids suppress osteoblast differentiation markers and inhibit osteoclast bone resorption.

- In vivo, opioids promote inflammation in adjuvant-induced arthritis model, decrease tumor-induced bone destruction, and suppress bone marrow macrophage colony formation.

- μ-opioid receptor knockout mice exhibit increased proliferation of granulocyte-macrophage, erythroid, and multipotential progenitor cells in bone marrow and spleen.

In aggregate, these effects do not make a compelling case for μ-opioid receptor antagonists increasing fractures.

8. RISK MANAGEMENT PROPOSAL

A risk management plan has been proposed that will communicate the possible CV risk of longer-term alvimopan exposure as well as minimize off-label use.

In order to meet these objectives, Adolor is committed to a number of activities to promote use consistent with product labeling and minimization of the potential risks. Risk minimization proposals include a comprehensive set of activities to communicate data regarding use of the drug consistent with product labeling and patient populations, including educational, communication, and promotional activities, as described hereunder:

- **Proposed professional labeling** includes language that will communicate:

  o The imbalance of reports of MI between alvimopan 0.5 mg BID and placebo treatment groups in a 12-month safety study of patients taking opioids for treatment of chronic non-cancer pain, GSK014.

  o Entereg is contraindicated in patients who have taken therapeutic doses of opioids for more than 7 consecutive days immediately prior to taking Entereg.

  o Entereg is for hospital use only.

- **Education of healthcare providers:** Educational efforts will be directed to healthcare providers involved in the care of BR surgery patients, including surgeons, anesthesiologists, hospitalists, nurse anesthetists, hospital nurses, and hospital pharmacists. These educational pieces will communicate the approved patient population, key safety sections of the labeling, including the section related to GSK014, and the approved dosing regimen—particularly a maximum of 15 total doses administered in the hospital only.

- **The Patient Counseling Information** in the package insert provides the information needed by the patient. Because Entereg Capsules are administered in the hospital by a health professional, the information can be verbally given to the patient. In this manner, the health professional can ensure the patient understands the benefits and risks of Entereg. It may be better understood by the patient prior to surgery than an insert given to the patient for the patient to read.

- **Targeted Sales Force:** Selling efforts will be directed only to surgeons and other hospital-based personnel involved in, or who influence the management of, large or small BR patients, such as anesthesiologists, hospitalists, nurse anesthetists, hospital nurses, and hospital pharmacists.

- **Targeted Promotion:** Advertisements will be limited to journals associated with surgeons and other hospital personnel who manage patients undergoing BR as mentioned above. Commercial booths will be limited to professional meetings attended by these healthcare professionals. There will be no direct-to-consumer advertising for this hospital use only product.

- **Samples:** No samples will be provided for this product.

- **The hospital cost** for Entereg 12 mg will be covered under the DRG payment for BR surgery, i.e., a lump-sum payment from the payer directly to the hospital. Therefore, Adolor and GSK will not seek outpatient managed care coverage for Entereg 12-mg capsules, which has the potential to discourage use out of the hospital setting.

- **"Hospital Use Only"** will be printed on the outer packaging carton and between the rows of blistered capsules on the front of the blister card. Blister cards showing the "Hospital Use Only" are also attached.

- **Wholesale Distribution Agreement** will specify that 12 mg Entereg capsules should be distributed only to hospitals.

- **An electronic notice** will be established in retail pharmacy drug information systems to alert community pharmacists not to dispense 12 mg Entereg.

9. BENEFIT/RISK ASSESSMENT

9.1   Benefits of Entereg in the Management of POI

Although evaluated in patients undergoing either BR or TAH, clinically meaningful benefits within the hospital setting were demonstrated for the BR population only.

In the two large NA studies in which ≥ 95% of the MITT population was composed of BR patients (14CL313 and 14CL314), treatment with alvimopan vs. placebo resulted in a clinically meaningful acceleration of GI recovery as demonstrated by:

- A reduction in mean time to GI recovery of 16 hours to 1 day earlier than placebo.

- A significantly higher proportion of alvimopan responders for GI recovery for each PSD (Days 3 through 8).

  - A 10% to 18% absolute increase in the proportion of alvimopan responders within the first 5 PSDs relative to placebo, with NNTs ranging from 6 to 10.

  - GI recovery that occurred 1 to 3 days earlier for patients at higher risk for prolonged POI (at or beyond the 75th percentile); this is a subset of the BR population that cannot be definitively identified before surgery.

Reduction in time to GI recovery resulted in:

- A reduction in the mean time to READY for discharge by 11 to 16 hours.

- A reduction in the mean time to DOW by 18 to 19 hours.

- A reduction in the average LOS (DOW by calendar date) by 1 day.

- A 11% to 22% absolute increase in the proportion of alvimopan responders achieving DOW before POD 7, with NNTs ranging from 5 to 9.

- A reduction in the time to DOW by 1 to 2 days in patients at higher risk for prolonged LOS (at or beyond the 75th percentile, generally corresponding to PSD 5 to 6).

- A 13% to 24% absolute reduction with alvimopan in the proportion of patients remaining in the hospital on or after POD 7, with NNTs ranging from 4 to 8.

- A reduction in the proportion of older patients who remained in the hospital on or after POD 7 (17% reduction for those ≥ 65 years old and 24% reduction for those ≥ 75 years old).

- A 5% absolute reduction in the need for postoperative NG tube insertion in the combined NA Phase 3 studies, with NNT of 20, and a reduction in the incidence of prolonged POI, with no associated increase in hospital readmission for POI or any cause within 7 or 10 days, respectively, of discharge.

The results achieved with alvimopan in the two large NA studies and further supported by the additional Phase 3 studies clearly demonstrate both statistical superiority and clinically

meaningful patient benefit. Earlier resolution of POI, shortening of hospital LOS and reductions in POI-related morbidity are consistent with the primary objectives of postoperative management and consistent with recent initiatives to improve overall surgical quality of care in BR patients.

9.2   Risks of Treatment With Entereg in Patients With POI

Risk assessment, according to the FDA Guidance Document *Premarketing Risk Assessment (March 2005)*, "consists of identifying and characterizing the nature, frequency and severity of the risks associated with the use of a product" (Food and Drug Administration, 2005). This process is iterative and occurs throughout all stages of product development.   The safety of alvimopan has been evaluated in more than 2,600 patients undergoing either major abdominal or pelvic surgery at doses ranging from 1 to 12 mg BID for up to 7 PODs, and more than 1,800 patients at doses ranging from 0.125 to 4.5 mg primarily QD or BID for more than 1 year in the treatment of OBD; a total of more than 4,400 patients in both clinical development programs. This represents a broad and comprehensive safety database for preapproval evaluation of alvimopan for the management of POI, an acute indication with use restricted to the hospital.

The worldwide POI safety database supports a favorable risk profile for use of alvimopan in BR patients. Short duration of treatment and use restricted to the controlled hospital setting supplements the conclusions drawn from the safety results. Implementation of the proposed Risk Management Plan will further enhance the risk profile and help to ensure safe use of alvimopan in patients undergoing BR surgery.

The size and scope of the combined preclinical and clinical safety database along with the additional post hoc analyses and scientific review of the safety signals observed in GSK014 provides a thorough assessment of alvimopan risk. Based on the entirety of these data, the potential risk associated with alvimopan treatment in patients undergoing BR is not elevated over placebo. When this favorable safety profile is considered with the statistically significant and clinically meaningful benefits associated with alvimopan treatment compared with placebo, the overall benefit/risk balance in patients undergoing BR and short-term therapy in the hospital is highly favorable.

9.3   Continued Unmet Medical Need—Limitations of Alternative Therapies

There are no approved drug or non-drug therapies/approaches for the management of POI. Traditional approaches have met with limited success in accelerating GI recovery following abdominal or pelvic surgery. Current approaches to the management of POI, which include NG suction, use of prokinetic agents, early mobilization, early enteral feeding, and opioid-sparing techniques, have not demonstrated consistent benefits in randomized, controlled trials in shortening the duration of POI (Woods, 2000; Holte and Kehlet, 2002; Luckey et al, 2003; Kehlet, 2000). Importantly, each of these approaches/strategies has limitations that must be considered. In addition, some of these techniques address only the symptoms of POI, with no impact on potential causative factors.

Nasogastric tubes cause significant patient discomfort, and their routine use following abdominal surgery is no longer recommended (Cheatham et al, 1995). Recent studies indicate that NG tube decompression does not shorten the duration of ileus and may, in fact, contribute to postoperative complications such as nasal and pharyngeal injury, fever, atelectasis, increased gastric reflux and regurgitation, and pneumonia (Luckey et al, 2003; Sagar et al, 1992; Manning et al, 2001; Platell and Hall, 1997). Results of a meta-analysis of the available trials of NG tubes indicate that they should not be used routinely for the management of POI and that their use may further delay GI recovery (Cheatham et al, 1995).

No drug therapy has been shown to consistently shorten the duration of POI. Available literature does not support consistent benefit of prokinetic agents in reducing the duration of POI (Resnick et al, 1997; Bungard and Kale-Pradhan, 1999). Studies of metoclopramide have failed to demonstrate a benefit. Some studies have demonstrated a clinical benefit of cisapride, but there are as many studies where no benefit was demonstrated. Importantly, the significant risks associated with cisapride, risks that led to market withdrawal in the US, far outweigh the limited and inconsistent potential benefits in POI. Available data on erythromycin fail to demonstrate an effect on time to flatus, first meal, or first BM. Laxatives, which may appear to be a logical choice for POI, have not been evaluated in randomized clinical trials and are not used in the clinical setting due to their lack of efficacy in this condition (Holte and Kehlet, 2000; Luckey et al, 2003).

Although early mobilization can positively affect other aspects of postoperative recovery, it has not been shown to shorten the duration of POI (Waldhausen and Schirmer, 1990). Early oral feeding has also shown inconsistent results in the management of POI (Woods, 2000; Frankel and Horowitz, 1989). Opioid-sparing approaches may potentially reduce the duration of POI although that has to be balanced by the need for effective post-surgical pain relief. Opioid-based regimens are still considered the "gold standard" for postoperative pain management and non-opioids, such as NSAIDs, may not provide the level of analgesia provided by opioids (Tang et al, 2002; Powell et al, 1990; Power et al, 1990; Cepeda et al, 1995). Epidural analgesia also has limitations, including inconvenience, increased cost to providers and insurers, and added attention from the hospital staff to ensure proper placement and retention of the catheter (Andersen et al, 2000). Importantly, the efficacy of these approaches in the management of POI, i.e., shortening the duration of POI, has not been definitively established in robust, prospective, randomized, and well-controlled clinical trials. Therefore, there are no currently available drugs or other non-drug approaches that have been consistently proven in adequate and well-controlled randomized trials to effectively manage POI by accelerating recovery of GI function following surgery in patients at risk.

The average hospital LOS following laparotomy for BR has been estimated at approximately 5 to 12 days by numerous authors (Basse et al, 2000; Delaney et al 2001; Pritts et al, 1999). This may increase to an average of 13 days in the elderly population (Spivak et al, 1996). Recent Health Care Financing Administration reimbursement data between October 1999 and September 2000 for 161,000 Medicare patients undergoing intestinal resections documented an average LOS of 11 days with a cost of $1.75 billion dollars. As a result of this strain on healthcare system resources and the increased risk to patients as hospital stay increases,

multimodal clinical care pathways and "fast track" postoperative management plans have been developed. These programs usually involve a combination of strategies aimed at safely reducing postoperative risks, strain on resources, and ultimately hospital stay. Methods used in these pathways include preoperative patient education, early ambulation, early diet advancement, opioid=-paring techniques (epidural analgesia with local anesthetics, NSAIDs), early NG tube removal, early switch to oral analgesia, and standardized discharge criteria based primarily on GI recovery.

Some of the more aggressive pathways (i.e., discharge after tolerating liquids only) have been associated with increased rates of readmission (Behrns et al, 2000). Nevertheless, implementation of these multimodal care programs may reduce hospital stay as well as the associated costs to the healthcare system (Basse et al, 2000; Delaney et al 2001; Pritts et al, 1999; Delaney et al 2001; Basse et al, 2002).

9.4   Benefit/Risk Conclusions

The impact of POI on patients remains substantial and clinically serious. This is particularly the case for patients undergoing BR surgery, as they are at highest risk. Alvimopan has demonstrated clinically meaningful benefits in the management of POI for this surgical population, consistent with important early postoperative recovery milestones. Acceleration of GI recovery and an associated reduction in hospital LOS of up to 1 day was demonstrated in four large clinical trials. In addition, important reductions in NG tube insertion, prolonged hospital stay, and readmission for POI were also achieved in patients treated with alvimopan.

These benefits were achieved without increased risk of AEs or reversal of opioid analgesia. Thorough evaluation of the large POI safety database supports a favorable risk profile, with no evidence of clinically meaningful findings safety signals.

Additionally, the proposed risk management plan will further optimize the benefit/risk balance.

A higher reported incidence of AEs in the alvimopan treatment group within the MedDRA coding categories of CV, neoplasia, and fracture observed in the long-term OBD study (GSK014) were unexpected based on the preclinical and clinical safety data across all indications. A comprehensive clinical and scientific review of the OBD clinical database along with additional patient-level data suggests that GSK014 represents an isolated observation and supports a conclusion that these imbalances more likely represent a chance finding or an unidentified disproportionate patient risk prior to randomization as opposed to a causal relationship with alvimopan. Additionally, GSK014 was not prospectively designed or powered to provide an evaluation of the rates of CV, neoplastic or bone fracture events in the OBD population.

Overall, the available efficacy and safety data from the clinical studies support a positive benefit/risk profile for alvimopan in patients undergoing BR with primary anastomosis. Alvimopan fulfills an unmet medical need and represents a significant advance in the practice of medicine and standard of care for this surgical population.

10.   SPONSOR CONCLUSIONS

The results achieved with alvimopan in the NA studies clearly demonstrate both statistical superiority and clinically meaningful patient benefit. The benefits achieved with alvimopan in POI are without added risk or AEs (including CV events, fractures, or neoplasia) or reversal of opioid analgesia. Treatment with alvimopan represents a significant advance in the practice of medicine and standard of care for patients undergoing BR surgery.

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12.   APPENDICES

12.1 Abbreviations and Definitions of Terms

12.1 Abbreviations and Definitions of Terms

12.1.1 Abbreviations

Abbreviation	Definition
ACS	American College of Surgeons
AE	Adverse event
AERS	Adverse Event Reporting System
AHA	American Heart Association
AMCE	Adjudicated Major Cardiac Event
AUC	Area under the curve
BID	Twice daily
BM	Bowel movement
BMI	Body mass index
BR	Bowel resection
CI	Confidence interval
CIC	Chronic idiopathic constipation
C_{max}	Maximal concentration
CNS	Central nervous system
CPI	Common Procedural Terminology
CrCl	Creatinine clearance
CSR	Clinical study report
Cox PH model	Cox Proportional Hazards model
CRFs	Case report forms
CV	Cardiovascular
CVA	Cerebrovascular accident
CXR	Chest Xray
DCRI	Duke Clinical Research Institute
DOW	Discharge order written
DRG	Diagnosis-related group
ECG	Electrocardiogram
GI	Gastrointestinal
GI-2	Last to occur of time to first solids, BM, or flatus
GI-3	Last to occur of time to first solids or BM
GSK	GlaxoSmithKline
HCFA	Health Care Financing Administration
HR	Hazard ratio
IBD	Inflammatory bowel disease
IDMC	Independent Data Monitoring Committee
IDR	Incidence density ratio

IM	Intramuscular
ISE	Integrated Summary of Efficacy
IV	Intravenous
IV PCA	Intravenous patient-controlled opioid analgesia
K_i	Inhibitory binding constant
KM	Kaplan-Meier
LOS	Length of stay
MedDRA	Medical Dictionary for Regulatory Activities
METTD	Morphine equivalent total daily dose
MI	Myocardial infarction
MITT	Modified intent-to-treat
NA	North America
NDA	New Drug Application
NG	Nasogastric
NNT	Number needed to treat
NOAEL	No observed adverse effect level
NSAIDs	Non-steroidal anti-inflammatory drugs
NSQIP	National Surgical Quality Improvement Program
OBD	Opioid-induced bowel dysfunction
PAM-OR	Peripherally-acting µ-opioid receptor
PCA	Patient-controlled analgesia
PGP	P-glycoprotein
PK	Pharmacokinetics
POD	Postoperative Day
POI	Postoperative ileus
POM	Postoperative morbidity
PSD	Postsurgical Day
QOL	Quality of Life
READY	Ready for Discharge
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
TAH	Total abdominal hysterectomy
TEAE	Treatment-emergent adverse event
TIA	Transient ischemic attack
TID	Three times daily
T_{max}	Time to maximal concentration
US	United States
VA	Veteran's Administration
VAS	Visual analogue scale

12.1.2   Definitions of Terms

BM: Time to first bowel movement.

Complications of POI: A patient was considered to have complications of postoperative ileus (POI) if they had any of the following serious adverse events (SAEs) that resulted in prolonged hospital stay or readmission ≥ 7 days from the initial hospital discharge: POI, ileus paralytic, or small intestinal obstruction. Note that determination of "Prolonged Stay" was made solely by the investigator.

DOW: Time to hospital discharge order written.

GI-2: Time to recovery of gastrointestinal (GI) function measured by a two-component composite endpoint, representing full (upper and lower) GI recovery, and defined as time to first BM and toleration of solid food, whichever occurred last.

GI-3: Time to recovery of GI function measured by a three-component composite endpoint, representing full (upper and lower) GI recovery, and defined as the later of the following events: time to toleration of first solid food and time to either first flatus or BM (whichever occurred first).

READY: Time to ready for hospital discharge based solely on GI recovery as defined by the surgeon.

Responder: Defined as any patient who achieved the event by the cut-off point and subsequently did not develop complications of POI.

Postoperative morbidity (POM): If a patient had either of the following conditions they were considered as having POM: (1) postoperative nasogastric (NG) tube insertion, or (2) complications of POI.

Postoperative NG tube insertion: Patients were considered as having had a postoperative NG tube insertion when an NG tube was inserted postoperatively as an intervention for an acute event (e.g., nausea, vomiting, abdominal bloating/distension).

Post Operative Day (POD): Each 24 hour interval based on the calendar day.

Postoperative morbidity (POM): If a patient had either of the following conditions they were considered as having POM: 1) postoperative nasogastric (NG) tube insertion, or 2) complications of POI.

Post Surgical Day (PSD): Each 24 hour interval from the end of surgery time.

Prolonged POI: POI, ileus paralytic, or small intestinal obstruction (per MedDRA preferred term), which prolonged the patient's hospital stay as determined solely by the investigator.

12.2 Statistical Methods

12.2 Statistical Methods

12.2.1 *Efficacy Endpoints*

Endpoints used in the alvimopan clinical program can be grouped into 4 categories:

- GI recovery-related time to event endpoints
- Hospital discharge-related time to event endpoints
- Responders (derived from the time to event endpoints above)
- Other endpoints (excluding Quality of Life [QOL])

Table 12.2-1 provides the details of all endpoints collected or derived in each of the Phase 3 studies in the order that they were conducted.

**Table 12.2-1   Summary of Efficacy Endpoints Specified in the Final Statistical
Analysis Plan in Each POI Phase 3 Study**

	Study No.				
Endpoints	**14CL302**	**14CL313**	**14CL308**	**GSK001**	**14CL314**
GI Recovery Related Time to Events					
GI-3 (derived endpoint)	P	P	P	P	S
GI-2 (derived endpoint)	Post hoc	S	S	S	P
First BM	S	S	S	S	S
Toleration of solid food	S	S	S	S	O
First flatus	S	S	S	S	O
Return of appetite	NC	NC	NC	S	NC
Discontinuation of IV hydration fluids	NC	NC	NC	S	NC
Tolerance of enteral fluid	NC	NC	NC	S	NC
Discharge-related Time to Events					
Ready for hospital discharge based solely on the recovery of gastrointestinal function	S	S	S	S	S
Discharge order written (DOW)	S	S	S	S	S
Ready for hospital discharge based on medical fitness of the subject as a whole	NC	NC	NC	S	NC
Actual Departure	NC	NC	NC	NC	S
Length of hospital stay based on postoperative days of DOW	NA	NA	NA	NA	S
Responders (Derived Endpoints)					
BR subjects who achieved GI-3 by 108 hr after surgery.	S	S	S	NA	NA
BR subjects who achieved GI-3 by 5 cutoff time points: 96, 108, 120, 144, and 168 hr post surgery	NA	NA	NA	S	NA
BR subjects who achieved DOW by 2 cutoff time points: 120 and 168 hr post surgery	NA	NA	NA	S	NA
BR subjects who achieved an event by 6 cutoff time points: 72, 96, 120, 144, 168 and 192 hr post surgery and did not have complications of POI during the study. Responders were assessed for each of the following 6 events: GI-3, GI-2, BM, READY, DOW, and Departure	NA	NA	NA	NA	S
Other Endpoints					
Need for postoperative NG tube insertion	O	O	O	S	S
Opioid consumption (postoperative daily, total for each period (preoperative, intra-operative, postoperative)	O	O	O	S	Safety
Maximum and daily pain intensity (VAS)	O	O	O	S	NC

| | Study No. | | | | |
Endpoints	14CL302	14CL313	14CL308	GSK001	14CL314
Maximum and daily nausea intensity (VAS)	O	O	O	S	NC
Maximum and daily abdominal bloating/distension intensity (VAS)	O	O	O	S	NC
Number of postoperative emetic episodes.	O	O	O	S	NC
Postoperative chest x-ray	O	O	O	NC	O
Maximum postoperative daily temperature	O	NC	NC	NC	NC
Postoperative abdominal x-ray	NC	NC	NC	NC	O
Complications of POI (derived endpoint)	NA	NA	NA	NA	O
Postoperative morbidity (derived endpoint)	NA	NA	NA	NA	O
Readmission for all causes within 10 days of actual departure	NA	NA	NA	NA	O

GI-3 = the last to occur of the following events: time to first solids and either BM or flatus (whichever occurred first); GI-2 = the last to occur of the following events: time to first solids and BM; P = primary efficacy endpoint; S = secondary efficacy endpoint; post-hoc = post hoc analysis included in the CSR; BM = bowel movement; O = other efficacy endpoint of interest; NC = data not collected; IV = intravenous; DOW = discharge order written; NA = analysis not applicable because either the endpoint or the analysis was proposed after the study CSR was completed;.BR = bowel resection; POI = postoperative ileus; READY = ready for discharge; NG = nasogastric, VAS = visual analogue scale.

12.2.2   *Analysis Methods for Time to Event Endpoints*

Analysis Methods for Time to Event Endpoints

In the evaluation of efficacy, the primary analysis set used for both original study findings and for BR patients only was one based on a Modified Intent-to-Treat (MITT) approach. Patients in this population included all randomized and treated patients who received protocol-specified surgeries (BR surgery only in this setting) and who had at least one on-treatment evaluation for flatus, BM, or solid food.

The effect of alvimopan compared to placebo on time to event endpoints was evaluated using Cox Proportional Hazards (Cox PH) model. In studies 14CL302 and 14CL308, where two surgery populations (BR and TAH) were included in the MITT population, the Cox PH models originally had a stratification variable (surgery type) in the primary analysis. Since only BR patients are considered in the proposed indication, Cox PH models include the main effect for treatment only.

In the reporting of results for the above studies, the Hochberg method (Hochberg, 1988) where appropriate was used in analyses of time-to-event variables to adjust for multiple comparisons between the two alvimopan groups and placebo. With this approach, if the p-values for both comparisons are ≤ 0.05, then both comparisons are statistically significant. If one of the p-values is > 0.05 (so the comparison is not statistically significant), then the other p-value must be ≤ 0.025 for this second comparison to be statistically significant. In all other cases, both comparisons would not be statistically significant. Although the 6-mg dose is not being considering in the proposed indication with respect to BR patients, all Cox PH models include the 6-mg dose, and the Hochberg correction has been retained for consistency of

approach when deciding whether the 12-mg comparison against placebo is statistically significant.

Use of Kaplan-Meier (KM) Means to Characterize Treatment Effect

After the completion of 14CL302, it became evident that although hazard ratios (HRs) and survival curves were statistically most appropriate for characterization of the treatment effect over time, physicians often have difficulty interpreting the actual clinical benefit of a drug treatment from the HR alone. The statistical analysis plan (SAP) for the NA Phase 3 studies was subsequently amended to include the difference between alvimopan and placebo in KM mean estimates to time to events. The difference in KM mean in hours was also the pre-specified method for descriptive statistics for Study GSK001.

Although the difference between alvimopan and placebo could be measured either by the horizontal distance or vertical distance between the KM curves over time, mathematically the difference in KM means represents the area in between the two KM survival curves. Moreover, the decision to use the difference in KM means was primarily based on the characteristics of the KM survival curves for the time-to-event endpoints in the POI population, which are described below:

- There was a low likelihood of recovering both upper and lower GI function (i.e., achieve GI-2 or GI-3 event) within the first 24 to 48 hours after surgery such that the separation between the treated and placebo groups slowly became evident during this period.

- As POI eventually resolves in all patients, the KM curves have long flat tails by the end of the observation period, i.e., most subjects had achieved the GI recovery endpoints (flatus, BM, solid food) by that time, and the subsequent conditional likelihood (i.e., hazard) of additional events becomes nearly zero. Hence, the number of censored observations was small compared to that typically seen in an oncology survival curve analysis.

- Although the difference between alvimopan and placebo, measured either by the horizontal distance or vertical distance on the KM curves, changes over time, none of the KM curves cross during the observation period.

- The shape of the KM survival curves for time to READY and time to DOW is stepwise or cyclical in appearance, which is consistent with clinical practice, i.e., surgical rounds and associated orders for discharge primarily occur within a 12-hour period during the hospital day. Therefore, the difference in KM medians is inaccurate as the only descriptive statistic with respect to these curves because the median may coincidentally occur at a point where the curves are either narrowly or widely separated.

While the difference in KM mean time may be a better way to illustrate the difference in the length of time to recovery in this population, difference in median time has been historically used to evaluate treatment differences. For this reason, 14CL314 used both the KM mean and the differences in KM estimates at the 25th, 50th (median), and 75th percentiles to express the magnitude of treatment effect in hours.

The treatment effect on the endpoint of DOW was analyzed in two ways: first, Cox PH models were used to provide estimates of HRs and 95% CIs when comparing the alvimopan arm to the placebo arm in each study. In this analysis, all DOW reported after the efficacy end of observation period (10 days for the four NA studies and 14 days for the non-NA study) were censored. Second, the distributions of DOW based on the postoperative days of DOW were compared between the treatment groups and the descriptive statistics, including mean, median and standard deviations, were provided for each treatment group. In this analysis, all observations were included as observed.

Summary of Analyses Performed

The primary population for the alvimopan POI program is defined as the subset of subjects having BR surgery. Therefore, analyses were performed based on the MITT BR subjects using prospectively collected data for Studies 14CL302, 14CL308, 14CL313, and GSK001 to allow for comparisons with Study 14CL314. Analyses included:

- Cox PH models comparing alvimopan to placebo for each time-to-event endpoint

- Differences between alvimopan and placebo in KM estimates at the 25th, 50th (median), and 75th percentiles for each time-to-event endpoint

- KM survival curves for MITT BR subjects for each time to event

- Responder analysis: The analysis was performed for each of GI-3, GI-2, READY, and DOW endpoints, and each has 6 cut-off time points. Departure data were not collected in any of the first 4 studies; hence, the responder analysis based on Departure was not applicable for those studies.

- Length of hospital stay based on the postoperative days of DOW

- Proportion of subjects with postoperative NG tube insertion by POD, and complications of POI resulting in prolonged stay by POD

- Proportion of subjects with postoperative morbidity

- Proportion of subjects with readmission for all causes within 10 days after the actual departure.

Subgroups, which include sex, age, and race as well as key concomitant medications and absence vs. presence of Crohn's disease, were examined in analyses based on pooled data across studies.

12.3 Supplemental Information—Efficacy

12.3 Supplemental Information—Efficacy

The following table provides a summary of the time-to-event data for the 12 mg dose group in all Phase 3 studies.

Table 12.3-1   Summary of Alvimopan 12 mg Effect on Time-to-Event Endpoints in MITT BR Subjects

Study No.	N (% censored)		Cox PH Model Analysis		KM Estimates			
	Placebo	12 mg	Hazard Ratio (95%CI)	Wald p value	Placebo		Difference (Placebo-12 mg)	
					Median	Mean	Median	Mean (95% CI)
GI-3								
14CL302	99 (9.1)	98 (9.2)	1.295 (0.964, 1.741)	0.086	108.3	113.9	10.8	10.3 (-1.7, 22.3)
14CL308	142 (9.2)	139 (10.1)	1.317 (1.029, 1.686)	0.029	109.8	122.1	11.8	12.4 (0.1, 24.7)
14CL313	142 (16.9)	160 (10.0)	1.494 (1.167, 1.914)	0.001*	98.9	119.2	4.8	20.2 (7.4, 32.9)
14CL314	312 (7.1)	317 (6.0)	1.452 (1.233, 1.710)	<0.001*	82.6	97.8	9.1	15.8 (8.9, 22.6)
GSK001	229 (8.3)	238 (8.0)	1.132 (0.936, 1.370)	0.200	81.7	92.1	3.2	4.8 (-2.6, 12.2)
GI-2								
14CL302	99 (14.1)	98 (11.2)	1.400 (1.035, 1.894)	0.029*	113.3	119.9	11.9	13.2 (1.2, 25.2)
14CL308	142 (16.2)	139 (15.1)	1.365 (1.057, 1.764)	0.017*	116.8	130.3	15.0	14.0 (0.7, 27.2)
14CL313	142 (25.4)	160 (15.0)	1.625 (1.256, 2.102)	<0.001*	115.2	132.0	17.2	26.1 (12.5, 39.7)
14CL314	312 (14.1)	317 (12.0)	1.533 (1.293, 1.816)	<0.001*	96.6	111.8	16.6	19.8 (11.9, 27.6)
GSK001	229 (12.7)	238 (8.8)	1.299 (1.070, 1.575)	0.008*	95.9	108.8	3.1	10.6 (2.7, 18.5)
BM								
14CL302	99 (12.1)	98 (5.1)	1.615 (1.201, 2.172)	0.002*	95.2	104.7	7.8	18.3 (7.8, 28.8)
14CL308	142 (12.0)	139 (8.6)	1.538 (1.195, 1.979)	<0.001*	93.9	107.9	4.1	17.3 (5.8, 28.8)
14CL313	142 (15.5)	160 (9.4)	1.436 (1.126, 1.832)	0.004*	90.1	100.3	10.8	16.2 (5.9, 26.6)
14CL314	312 (10.3)	317 (8.5)	1.512 (1.280, 1.786)	<0.001*	88.8	96.2	15.5	15.6 (9.4, 21.7)
GSK001	229 (10.5)	238 (6.7)	1.360 (1.122, 1.649)	0.002*	80.2	89.2	5.3	11.8 (3.8, 19.7)
Flatus								
14CL302	99 (8.1)	98 (6.1)	1.188 (0.887, 1.591)	0.247	75.5	86.7	-3.3	5.4 (-5.5, 16.4)
14CL308	142 (5.6)	139 (5.0)	1.213 (0.952, 1.545)	0.118	77.3	83.0	4.5	6.8 (-3.7, 17.2)
14CL313	142 (9.2)	160 (8.1)	1.285 (1.013, 1.631)	0.039	74.3	84.0	2.2	10.4 (1.0, 19.9)
14CL314	312 (5.1)	317 (6.3)	1.370 (1.164, 1.611)	<0.001*	74.0	79.2	6.4	9.6 (3.9, 15.2)
GSK001	229 (5.7)	238 (6.3)	1.369 (1.132, 1.655)	0.001*	65.2	68.6	5.1	8.7 (3.3, 14.1)
Solid								
14CL302	99 (8.1)	98 (9.2)	1.180 (0.879, 1.584)	0.270	101.2	104.7	6.1	6.4 (-6.2, 19.1)
14CL308	142 (9.2)	139 (9.4)	1.288 (1.007, 1.648)	0.044	104.9	118.6	7.9	11.0 (-1.7, 23.7)
14CL313	142 (16.2)	160 (10.0)	1.438 (1.123, 1.840)	0.004*	95.7	112.2	6.4	19.8 (6.2, 33.5)
14CL314	312 (6.1)	317 (4.7)	1.186 (1.008, 1.395)	0.039*	55.6	81.7	0.6	9.1 (1.7, 16.5)
GSK001	229 (7.9)	238 (7.6)	1.044 (0.864, 1.263)	0.654	72.5	83.0	0	1.5 (-6.7, 9.6)

| Study No. | N (% censored) | | Cox PH Model Analysis | | KM Estimates | | | |
| | Placebo | 12 mg | Hazard Ratio (95%CI) | Wald p value | Placebo | | Difference (Placebo-12 mg) | |
					Median	Mean	Median	Mean (95% CI)
READY								
14CL302	84 (6.0)	84 (6.0)	1.519 (1.105, 2.089)	0.010*	113.0	120.7	13.5	16.4 (4.3, 28.4)
14CL308	142 (8.5)	139 (7.9)	1.395 (1.092, 1.783)	0.008*	119.0	129.7	11.5	14.7 (3.3, 26.2)
14CL313	142 (14.8)	160 (8.1)	1.537 (1.204, 1.962)	<0.001*	111.1	126.1	16.1	20.9 (8.6, 33.1)
14CL314	312 (9.6)	317 (6.9)	1.380 (1.169, 1.628)	<0.001*	91.3	102.7	10.6	13.1 (6.1, 20.1)
GSK001	229 (12.7)	238 (11.8)	1.111 (0.915, 1.349)	0.287	139.5	143.7	12.1	6.8 (-3.2, 16.8)
DOW								
14CL302	99 (5.1)	98 (5.1)	1.289 (0.967, 1.718)	0.084	136.4	143.2	16.3	12.9 (0.3, 25.5)
14CL308	142 (4.9)	139 (3.6)	1.555 (1.222, 1.979)	<0.001*	139.8	149.1	22.3	21.3 (10.2, 32.4)
14CL313	142 (12.7)	160 (5.6)	1.423 (1.120, 1.807)	0.004*	121.8	147.0	6.0	19.3 (6.3, 32.2)
14CL314	312 (8.7)	317 (4.4)	1.400 (1.189, 1.647)	<0.001*	119.9	138.1	7.8	17.6 (9.4, 25.8)
GSK001	229 (14.4)	238 (14.7)	1.071 (0.880, 1.303)	0.493	203.6	203.3	14.2	6.3 (-3.2, 15.8)

Cox PH = Cox Proportional Hazards model; KM = Kaplan-Meier; CI = Confidence intervals; GI-3 = the last to occur of the following events: time to first solids and either BM or flatus (whichever occurred first); GI-2 = the last to occur of the following events: time to first solids and BM; READY = ready for discharge; DOW = discharge order written.

Note: Asterisk indicates statistically significant at the 0.05 level after adjustment for two alvimopan dose comparisons with placebo using the Hochberg method.

12.4 Supplemental Information—Preclinical

12.4 Supplemental Information—Preclinical

12.4.1   In-Vitro Receptor Binding Assays

Table 12.4-1   In Vitro Receptor Binding and Enzyme Assays Where No Activity Was Observed With Alvimopan

Acetylcholinesterase[1]	$GABA_B$[1]	Nicotinic, α-bungarotoxin
Adenosine, nonselective	Galanin	insensitive
Adrenergic α_1, nonselective	Glutamate, AMPA	Nitric oxide synthase, neuronal
Adrenergic α_2, nonselective	Glutamate, Kainate	Norepinephrine transporter
Adrenergic β, nonselective	Glutamate, NMDA	Oxytocin
Angiotensin II AT_1	Glutamate, NMDA, glycine,	Platelet activating factor
Angiotensin II AT_2	strychnine-insensitive	Potassium channel, ATP-
Bradykinin B_2	Glutamic acid decarboxylase	sensitive
Calcium channel, L-type	Glycine, strychnine-sensitive	Potassium channel, Ca^{2+} act, VI
(dihydropyridine binding site)	Histamine H_1	Potassium channel, Ca^{2+} act, VS
Calcium channel, N-type	Histamine H_2	Serotonin, nonselective
Cannabinoid CB_1, human	Histamine H_3	Serotonin 5-HT_{1A}, human
Cannabinoid CB_2, human	Leukotriene B_4	Serotonin 5-HT_{1B}, human
CGRP, central	Leukotriene D_4	Serotonin 5-HT_3, human
Cholecystokinin CCK_A	MAO-A	Serotonin 5-HT_4
Cholecystokinin CCK_B	MAO-B	Serotonin 5-HT_{4e}, human
Choline acetyltransferase	Muscarinic, nonselective,	Serotonin transporter
Corticotropin-releasing factor	peripheral	Sigma, nonselective
Dopamine, nonselective	Muscarinic M_1	Sodium, site 1
Dopamine transporter	Muscarinic M_2	Sodium, site 2
Endothelin ET_A, human	Muscarinic, nonselective, central	Testosterone
Endothelin ET_B, human	Neurokinin NK_1	Thromboxane TXA_2, human
Estrogen	Neurokinin NK_2, human	Thyrotropin releasing hormone
$GABA_A$, agonist site	Neurokinin NK_3	Vasoactive intestinal peptide,
$GABA_A$, benzodiazepine, central		nonselective
site		Vasopressin$_1$

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; CGRP = calcitonin gene-related peptide; GABA = γ-aminobutyric acid; HT = hydroxytryptamine; MAO = monoamine oxidase; NMDA = N-methyl-D-aspartic acid.

Table 12.4-2   In Vitro Receptor Binding and Enzyme Assays Where No Activity Was Observed With Alvimopan's Metabolite

Adenosine A_1, human	$GABA_B$	Nicotinic, muscle type
Adenosine A_{2A}, human	Galanin	Norepinephrine transporter,
Adenosine A_{2B}, human	Glutamate, AMPA	human
Adenosine A_3, human	Glutamate, Kainate	Oxytocin, human
Adrenergic α_1, nonselective	Glutamate, NMDA	Platelet activating factor
Adrenergic α_2, nonselective	Glutamate, NMDA, glycine,	Potassium, K^+_{ATP} channel
Adrenergic β_1, human	strychnine-insensitive	Potassium, K^+_V channel
Adrenergic β_2, human	Glycine, strychnine-sensitive	Potassium, SK^+_{Ca} channel
Angiotensin II AT_1, human	Histamine H_1, central	Serotonin 5-HT_{1A}, human
Angiotensin II AT_2, human	Histamine H_1, peripheral	Serotonin 5-HT_{1B}
Benzodiazepine, central	Histamine H_2	Serotonin 5-HT_3, human
Bradykinin B_2, human	Histamine H_3	Serotonin 5-HT_4
Calcium channel, L-type	Leukotriene B_4, human	Serotonin 5-HT_{4e}, human
(dihydropyridine binding site)	Leukotriene D_4, human	Serotonin, nonselective
Calcium channel, N-type	MAO-A	Serotonin transporter, human
Cannabinoid CB_1, human	MAO-B	Sigma, nonselective
Cannabinoid CB_2, human	Muscarinic, nonselective	Sodium, site 1
Cholecystokinin CCK_A, human	Muscarinic M_1, human	Sodium, site 2
Cholecystokinin CCK_B	Muscarinic M_2, human	Thromboxane TXA_2, human
Corticotropin-releasing factor$_1$	Neurokinin NK_1, human	Thyrotropin releasing hormone
Dopamine D_1, human	Neurokinin NK_2, human	Vasoactive intestinal peptide
Dopamine D_2, human	Neurokinin NK_3, human	VIP_1, human
Dopamine transporter, human	Nicotinic, neuronal, α-	Vasoactive intestinal peptide
Endothelin ET_A, human	bungarotoxin sensitive	VIP_2, human
Endothelin ET_B, human	Nicotinic, neuronal, α-	Vasopressin $V1_A$, human
Estrogen	bungarotoxin insensitive	Vasopressin $V1_B$, human
$GABA_A$		

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; GABA = γ-aminobutyric acid; HT = hydroxytryptamine; MAO = monoamine oxidase; NMDA = N-methyl-D-aspartic acid.

12.4.2   Mouse Carcinogenicity Study

This study was conducted to determine the effects of alvimopan on the incidence and morphology of tumors in a 104-week oral gavage dose study in the CD 1 mouse. Groups of mice were given 0 (water), 0 (vehicle), 100, 1000 or 4000 mg/kg/day alvimopan by oral (gavage) administration once daily for up to 104 weeks.

There were no adverse findings and no neoplastic findings of an unusual incidence or nature suggestive of a carcinogenic effect of alvimopan.

Fibroblastic tumors were observed in females dosed at 4000 mg/kg/day; however, the incidence of these (8.3%) fell within the historical control range (0 to 9.8%) for this tumor in this mouse strain/sex in this laboratory and these tumors are commonly encountered in this laboratory species. This apparent increased incidence is therefore considered not to be related to treatment with alvimopan and is considered to be a chance event.

Compared with historical control incidence data (0 to 2.9%) there was a marginally higher incidence (6.7%) of osteogenic tumors in females given 4000 mg/kg/day. However, the incidence in control animals in the present study (3.3%) was also slightly higher than the historical range and in the absence of a consistent benign/malignant status or site of origin, and as there were no degenerative, inflammatory, or non-neoplastic proliferative lesions involving tissues in which these osteogenic tumors were observed, this finding is considered not to be related to treatment with alvimopan.

Systemic exposure to alvimopan, as measured by composite AUC_{0-t}, increased (approximately 1.7 to 4.3 fold) between Weeks 4 and 26, at all doses and in both sexes, with consistently higher exposures in females than in males. Overall, for a 40-fold increase in dose from 100 to 4000 mg/kg/day, AUC_{0-t} increased to approximately 8-fold in males and to approximately 6-fold in females.

Systemic exposure to the major (amide hydrolysis) metabolite of alvimopan, as measured by composite AUC_{0-t} and C_{max} , was generally similar at Weeks 4 and 26, and did not increase with escalating dose or demonstrate any notable sex differences. Systemic exposure to the metabolite was generally higher than that to alvimopan in both sexes on all occasions.

The following Table summarizes the exposures to alvimopan and its metabolite at Week 26.

Table 12.4-3   Systemic Exposure for Alvimopan and Its Metabolite in the Mouse Carcinogenicity Study

Dosage (mg/kg/day)	Sex	Alvimopan[a]		Metabolite[a]	
		C_{max} (ng/mL)	$AUC_{(0-24)}$ (ng•h/mL)	C_{max} (ng/mL)	$AUC_{(0-24)}$ (ng•h/mL)
100	M	4.62	25.8	23.8	183
	F	8.15	54.4	36.5	306
1000	M	30.8	136	17.5	224
	F	35.1	238	32.0	407
4000	M	29.1	203	45.0	242
	F	23.2	317	13.2	164

In conclusion, there were no adverse findings and there were no neoplastic findings of an unusual incidence or nature suggestive of a carcinogenic effect of alvimopan in mice. The no observed adverse effect level (NOAEL) was 4000 mg/kg/day.

12.4.3   Rat Carcinogenicity Study

This study was designed to determine the effect of alvimopan on the incidence and morphology of tumors in a 104-week oral gavage carcinogenicity study in F344 rats. Groups of rats were given 0 (water), 0 (vehicle), 30 (females only) 100, 200 or 500 mg/kg/day alvimopan by oral (gavage) administration once daily for 104 weeks.

There were no adverse findings and no neoplastic findings of an unusual incidence or nature suggestive of a carcinogenic effect of alvimopan.

In addition, treatment with alvimopan had no effect on survival and there were no in-life findings associated with treatment. Compared with male decedent vehicle controls, a statistically significant increased incidence of enlargement (27.3% vs. 0 in controls) was seen in the deep cervical lymph nodes in male decedent rats given 500 mg/kg/day. However, in terminal kill males given 500 mg/kg/day the incidence of deep cervical lymph node enlargement (3.7%) was similar to that in vehicle control males (3.3%). Compared with male vehicle controls, a statistically significant increased incidence of enlargement (51.7% vs. 28.3%) was noted in the lumbar lymph nodes of male rats (decedent and terminal combined) given 500 mg/kg/day.

For both of these observations there was no consistent microscopic correlate and no evidence of any treatment-related change for any of the microscopic findings in these lymph nodes.

Systemic exposure to alvimopan, as measured by composite AUC_{0-t} and C_{max}, was generally similar on Day 1 and in Week 52, but in some cases varied quite considerably at the different toxicokinetic occasions. Systemic exposure did not increase with escalating dose or demonstrate any consistent notable sex differences. Systemic exposure to alvimopan's metabolite (as measured by composite AUC_{0-t} and C_{max}) did not increase with escalating dose in male rats, and increased in a less than proportional manner with escalating dose in female rats. Overall in female rats in Week 52, for a 16-fold increase in dose from 30 to 500

mg/kg/day, AUC_{0-t} only increased to approximately 2.4-fold. Irrespective of dose or sex, the systemic exposures to the metabolite in Week 52 ranged between approximately 3- and 11-fold those achieved on Day 1.

Systemic exposure (AUC_{0-t}) to the metabolite was consistently higher (to approximately 1.4-fold to 86.4-fold) than that for alvimopan.

The following table summarizes the exposures to alvimopan and its metabolite at Week 52.

Table 12.4-4   Systemic Exposure for Alvimopan and Its Metabolite in the Rat Carcinogenicity Study

Dosage (mg/kg/day)	Sex	Alvimopan		Metabolite	
		C_{max} (ng/mL)	$AUC_{(0-24)}$ (ng•h/mL)	C_{max} (ng/mL)	$AUC_{(0-24)}$ (ng•h/mL)
30	M	--	--	--	--
	F	116	146	97.8	1370
100	M	5.46	57.7	38.3	517
	F	10.3	76.7	80.8	1360
200	M	19.7	86.5	37.0	671
	F	20.8	131	185	2940
500	M	9.61	119	47.5	835
	F	23.9	213	205	3260

In conclusion, there were no findings associated with treatment with alvimopan and no neoplastic or non-neoplastic findings suggestive of a carcinogenic effect. The NOAEL was 500 mg/kg/day.

12.5 Supplemental Information—PK and PK/PD

12.5 Supplemental Information—PK and PK/PD

12.5.1   Drug Interactions and Special Patient Populations

12.5.1.1   Concomitant Drug Effect on the PK of Alvimopan and Metabolite

Based on in vitro data, concomitant administration of alvimopan with inducers or inhibitors of CYP enzymes is unlikely to result in any clinically significant drug interactions. Alvimopan is not a substrate for cytochrome P450 enzymes. No clinical studies have been performed with inducers or inhibitors of cytochrome P450 enzymes.

In vitro studies suggest that alvimopan and its metabolite are substrates for p-glycoprotein (PGP). Population pharmacokinetics (PK) analysis in POI showed that alvimopan PK were not influenced by concomitant medications that are mild to moderate p-glycoprotein inhibitors. Thus, concomitant administration of alvimopan with PGP inhibitors would be unlikely to result in any clinically significant drug interactions.

The PK of alvimopan was not affected by concomitant administration of acid blockers or antibiotics. Plasma concentrations of the metabolite were lower in patients receiving acid blockers or preoperative oral antibiotics in POI patients (49% and 81%, respectively). Because the metabolite is not required for efficacy, no dosage adjustments are necessary in these patients.

12.5.1.2   Alvimopan or Metabolite Effect on the PK of Other Drugs

Alvimopan and its metabolite are not inhibitors of CYP 1A2, 2C9, 2C19, 3A4, 2D6, and 2E1 in vitro at concentrations far in excess (> 800-fold) of those observed clinically. Alvimopan and its metabolite are not inducers of CYP450 enzymes. In vitro studies suggest that alvimopan and its metabolite are not inhibitors of PGP. Thus, concomitant administration of alvimopan with substrates for CYP enzymes or PGP is unlikely to result in any clinically significant drug interactions.

Alvimopan and its metabolite do not appear to alter the PK of morphine (a known PGP substrate) nor affect the formation or elimination of the morphine metabolite, morphine-6-glucuronide.

12.5.1.3   Special Patient Populations:

Population PK analysis showed that there was no evidence that the PK of alvimopan or its metabolite varied as a function of body size, body mass index, or sex. Thus, no dosage adjustments are considered necessary.

Age

Population PK analysis in POI showed that increased age is associated with slightly higher concentrations of alvimopan (approximately 30% to 40% in a > 70 year old than in a < 30 year old) but not the metabolite. This effect was not clinically important based on the

moderate variability in alvimopan PK. Thus, dosage adjustment based on increased age is not required.

Race

Population PK analysis in POI showed that the PK of alvimopan was not affected by Black or Hispanic race. However, plasma metabolite concentrations were lower in Black and in Hispanic subjects than in Caucasian subjects following alvimopan administration. No dosage adjustments are considered necessary.

Hepatic Impairment

Exposure to alvimopan following a single 12-mg dose tended to be higher (up to 6-fold) in subjects with mild or moderate hepatic impairment (as defined by Child-Pugh Class A and B, n = 6 each) compared with healthy controls (n = 4). There were no consistent effects on the C_{max} or half-life of alvimopan in subjects with hepatic impairment. The C_{max} of the metabolite tended to be more variable in subjects with mild or moderate hepatic impairment than in matched normal subjects. In a study of three subject volunteers with severe hepatic impairment (Child-Pugh Class C), a single dose of alvimopan 12 mg was well tolerated. The PK of alvimopan indicated similar exposure in two subjects and an approximately 10-fold increase in C_{max} and exposure in one subject with severe hepatic impairment when compared with healthy control volunteers.

Although there is a potential for higher plasma levels of drug in patients with mild-to-moderate hepatic impairment, dosage adjustment in these patients is not required. However, the possibility of increases in AEs (e.g., diarrhea, gastrointestinal pain, and abdominal cramping) in patients with hepatic impairment due to higher alvimopan concentrations cannot be ruled out.

Alvimopan is not recommended for use in patients with severe hepatic impairment.

Renal Impairment

There is no relationship between renal function (i.e., creatinine clearance [CrCl]) and plasma alvimopan PK (C_{max}, AUC, or half-life) in subjects with mild (CrCl 51 to 80 mL/min), moderate (CrCl 31 to 50 mL/min) or severe (CrCl < 30 mL/min) renal impairment (n = 6 each). Renal clearance of alvimopan is related to renal function; however, because renal clearance is only a small fraction of the total clearance, renal impairment has no effect on the apparent oral clearance of alvimopan. The PK of the metabolite were highly variable in all groups. Exposure to the metabolite tended to be 2- to 5-fold higher in subjects with moderate or severe renal impairment compared to subjects with mild renal impairment or control subjects.

Population PK analysis in POI patients showed that there was no relationship between renal function and alvimopan or its metabolite concentrations..

Subjects with end-stage renal disease were not studied. Because the renal clearance of alvimopan was only 35% of the total clearance and the renal clearance of the metabolite was even lower, it is unlikely that there would be clinically significant differences in the PK of alvimopan in end-stage renal disease. However, the possibility of increases in AEs (e.g.,

diarrhea, gastrointestinal pain, and abdominal cramping) in patients with end-stage renal disease due to higher alvimopan concentrations cannot be ruled out.

Crohn's Disease

There is no relationship between disease activity in subjects with Crohn's disease (measured as Crohn's Disease Activity Index or BM frequency) and alvimopan PK (AUC or C_{max}). Subjects with active or quiescent Crohn's disease have increased variability in alvimopan PK, and exposure tended to be 2-fold higher in subjects with quiescent disease than in those with active disease or normal subjects. Concentrations of the metabolite are lower in subjects with Crohn's disease.

Population PK in POI patients (including volunteers and POI subjects with inflammatory bowel disease [IBD]) showed that there were no differences between IBD patients and non-IBD patients, but concentrations of the metabolite were lower in patients with IBD than in those not having IBD. No dosage adjustments are considered necessary in IBD patients.

12.5.2   *Exposure and Exposure-Response in POI Patients*

12.5.2.1   Exposure in POI Patients

In addition to the population PK approach that evaluated plasma concentrations from Studies 14CL308 and GSK001, the observed C_{min} of alvimopan and metabolite were estimated based on data from GSK001 because all patients had a Day 3 trough sample available. As illustrated in Figure 12.5-1, the median C_{min} of alvimopan (3.1 ng/mL) was much higher than the median C_{min} of metabolite (0.1 ng/mL).

Figure 12.5-1 C_{min} of Alvimopan (A) and Metabolite (B) in POI Patients on Day 3 (GSK001)

B
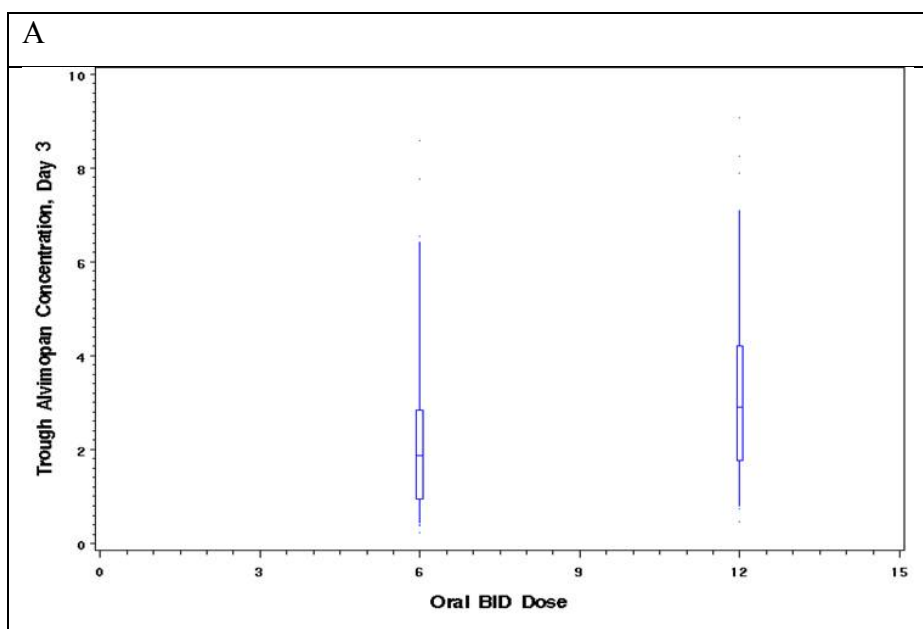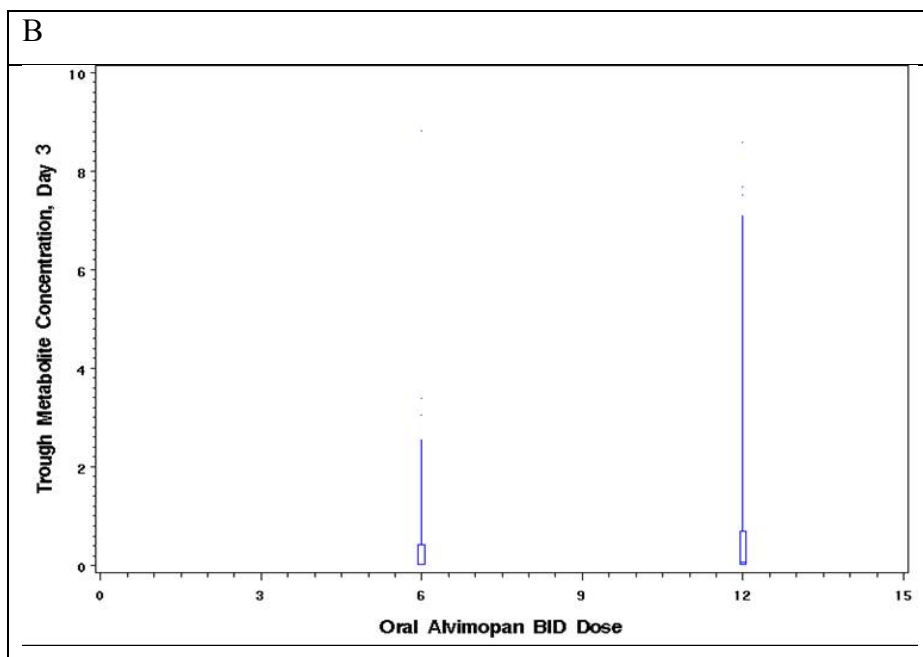
12.5.2.2 Exposure-Response in POI Patients

The relationship between exposure to alvimopan or metabolite and efficacy in POI was evaluated using data from Studies 14CL308. The endpoint used was time to first BM, which is the most objective endpoint. Plots were also created for each PK parameter (C_{max}, AUC, C_{min}, and time above the K_i) for each component (alvimopan or metabolite) as well as the combined components (corrected for protein binding). There was no apparent relationship between exposure (to alvimopan and metabolite) and time to first BM regardless of which exposure endpoint was used. A representative plot is given in Figure 12.5-2.

**Figure 12.5-2   The Relationship Between Alvimopan AUC (A) or Metabolite AUC (B)
for the 24 hr Prior to the First BM and Response (Time to First BM)
(14CL308)**
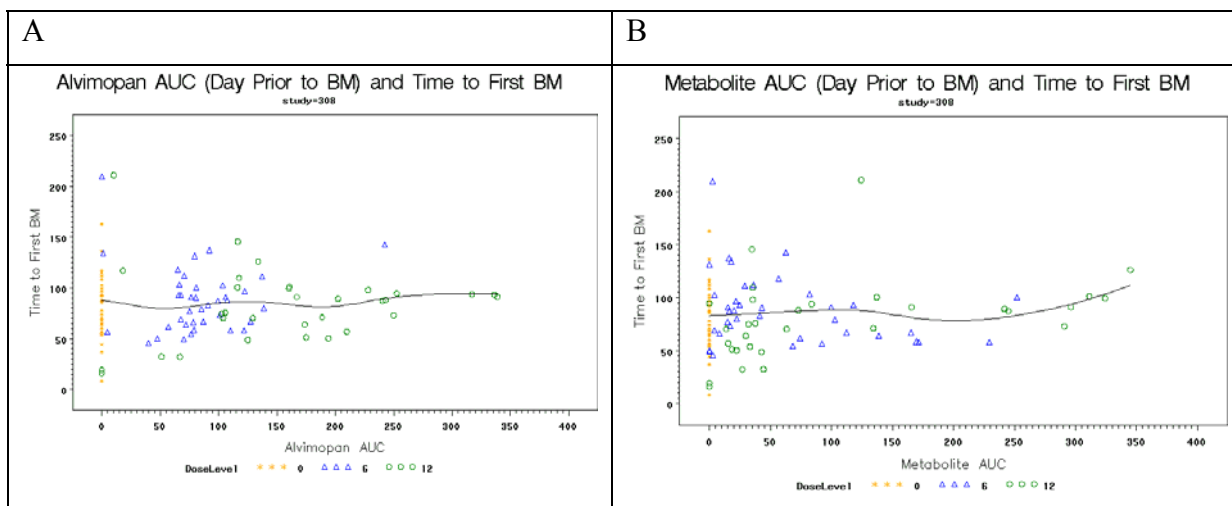
The potential exposure-response relationship was difficult to demonstrate because:

- POI increases the residence time of alvimopan in the GI tract, which leads to a greater potential for absorption and metabolism (i.e., higher plasma metabolite concentrations), which might explain a weak, apparently paradoxical, exposure-response relationship in some subjects.

- Nonpharmacological factors, such as wakefulness of the subject and social appropriateness of the timing, and non-opioid–related factors, such as inflammation, may increase variability in the time to first BM, preventing demonstration of an exposure-response relationship.

- The concentrations observed, when related to the hypothetical target, K_i, were generally in the therapeutic range for the majority of subjects through the entire study period. Concentrations above this range may not yield any improvement (measured as a decreased time to BM). In addition, if exposure is only at the extremes of the concentration-response relationship, such a relationship may be difficult to demonstrate.

12.5.3   Exposure Response for AEs of Special Interest

The exposure-response relationship for the AEs of special interest was evaluated in POI and in OBD separately.

12.5.3.1   Exposure Response for CV AEs in POI

The AUC of alvimopan and metabolite was estimated based on population PK analysis. The AUC was plotted in those with and without the AE of special interest (e.g., CV AE). These

plots were based on data from 393 patients in Studies 14CL308 and GSK001, with 11 subjects with CV AEs having had at least 1 concentration available for analysis. These data are illustrated in Figure 12.5-3.

In Figure 12.5-3, note that for data presented as a box plot with median, 25th and 75th percentile are within the box. Vertical lines represent the 5th and 95th percentile. Dots represent individuals outside the 5th to 95th percentile. The category "None" represents those POI patients with no CV AEs (n = 382); CV SAE represents those POI patients with CV AE, including five patients who received alvimopan 6 mg and six patients who received alvimopan 12 mg.

For alvimopan, at first glance, it appears that the AUC on day 3 is higher in those receiving alvimopan 6 mg that experienced a CV AE than those not experiencing a CV AE; this trend was not seen for those receiving alvimopan 12 mg. However, one must keep in mind that the box plot only represents five patients receiving alvimopan 6 mg. Thus, the value at the 95th (580 ng•hr/mL) percentiles represent one subject (GSK001, #598); this subject had one high concentration and four concentrations that were within those predicted based on dose; thus, this AUC appears to be driven by the single high sample and may be artificially high. All other exposures are seen in either the 6- or 12-mg group of patients who did not experience a CV AE. When keeping the low subject numbers in mind, the other values all appear to show no difference in alvimopan exposure between those with and without a CV AE. There does not appear to be any difference in metabolite AUC between those that experienced a CVAE and those that did not experience a CV AE.

12.5.3.2   Exposure Response for AEs of Special Interest in OBD

For the OBD population, AUC values were not available for patients in GSK014. Thus, plasma concentrations from patients experiencing an AE of special interest were plotted against the median (and 5th and 95th percentile) plasma concentrations expected over time, based on dose. Data from 1017 patients receiving doses of 0.5 or 1 mg once or twice daily in GSK011, GSK012, GSK014, GSK008, and GSK684 were eligible to be included in this analyses. The data were consistent across doses, so only data from the 0.5-mg BID dose is shown.

Figure 12.5-4 illustrates that the majority of plasma concentrations observed in those patients who experienced CV AEs are within the 5th to 95th percentile of expected plasma concentrations. Overall, CV AEs do not appear to be explained by higher exposure to alvimopan or metabolite and there is unlikely to be an exposure-response relationship for this AE.

The plasma concentrations of alvimopan and metabolite in those patients experiencing an AE of special interest, overlayed with the expected plasma concentration-time profile, are given in Figure 12.5-5 and Figure 12.5-6 for neoplasm and fractures, respectively . As for CV AEs, the majority of plasma concentrations observed in those patients who experienced either a neoplasm or a fracture are within the 5th to 95th percentile of expected plasma concentrations. Neoplasms and fractures are not explained by higher exposure to alvimopan or metabolite, and there is unlikely to be an exposure-response relationship for these AEs.

Figure 12.5-3   AUC on Day 3 for POI Patients Who Had Experienced a CV AE and for Those Not Experiencing a CV AE

Alvimopan AUC on Day 3, 6 mg	Alvimopan AUC on Day 3, 12 mg
Metabolite AUC on Day 3, 6 mg	Metabolite AUC on Day 3, 12 mg

Figure 12.5-4   Alvimopan (A) and Metabolite (B) AUC in OBD Patients Receiving Alvimopan 0.5mg BID Who Experienced vs. Those Who Did Not Experience a CV AE[1,2]
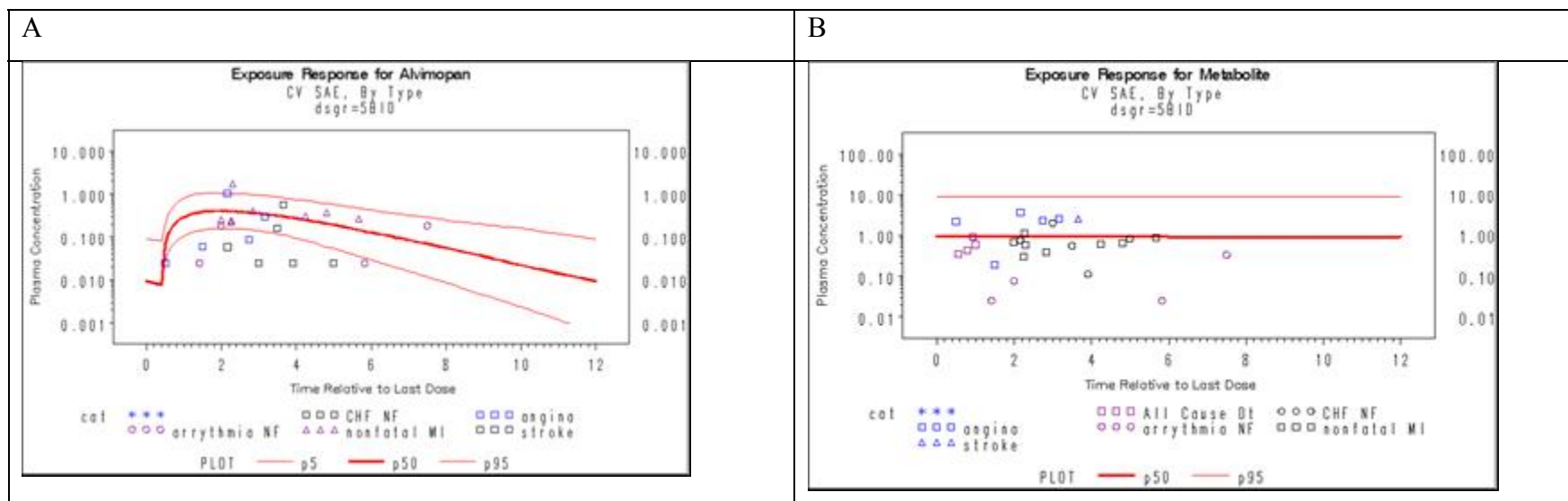
1 Data presented as a box plot with median, 25th and 75th percentile within the box. Vertical lines represent the 5th and 95th percentile. Dots represent individuals outside the 5th to 95th percentile.

2 All Cause Dt = death due to all causes (n=2 from Study SB767905/008, metabolite only); stroke = subjects experiencing stroke (n=1); arrhythmia NF = subjects experiencing a nonfatal arrhythmia (n=4); angina = subjects experiencing angina (n=1); nonfatal MI = subjects experiencing a nonfatal myocardial infarction (n=3); CHF-NF = subjects experiencing nonfatal congestive heart failure (n=1).

Figure 12.5-5   Alvimopan (A) and Metabolite (B) AUC in OBD Patients Receiving Alvimopan 0.5mg BID Who Had a Neoplasm vs. Those Who Did Not[1,2]
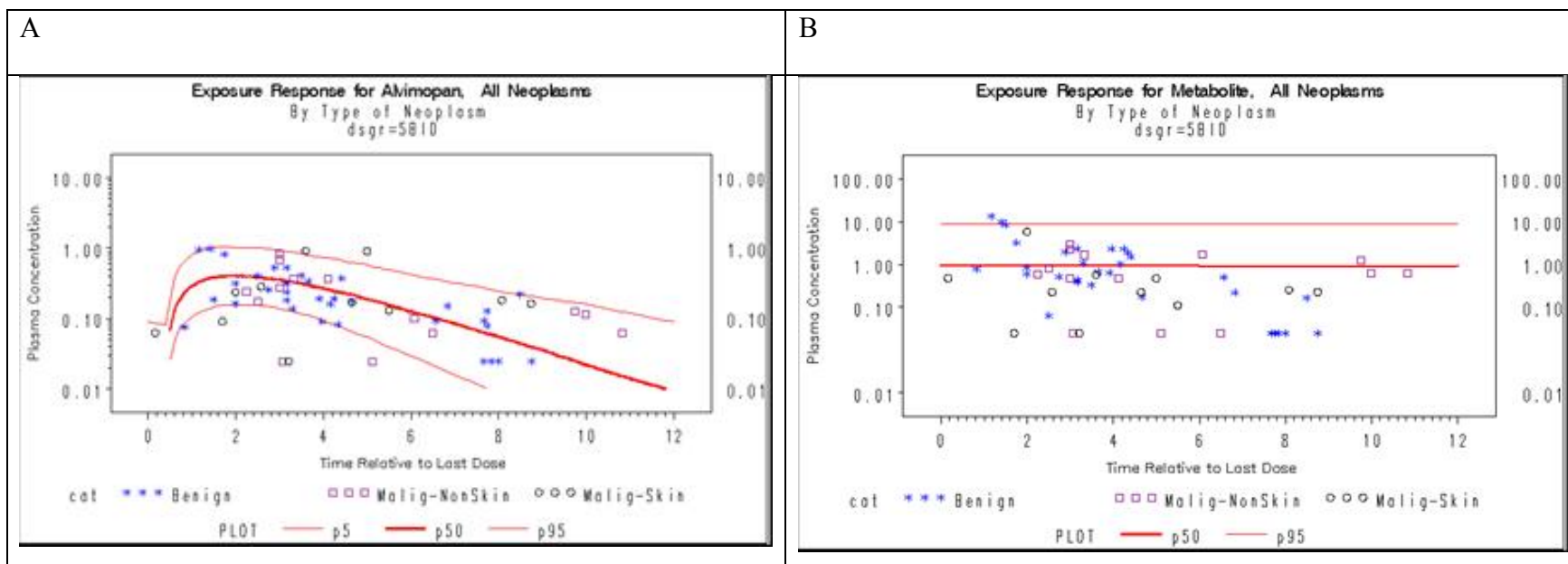
1 Data presented as a box plot with median, 25th and 75th percentile within the box. Vertical lines represent the 5th and 95th percentile. Dots represent individuals outside the 5th-95th percentile.

2 Malig-NonSkin = those patients with malignant cancer that are not considered skin cancers (n=6); Malign-Skin = skin cancers (n=4); Benign = benign neoplasms (n=7); no neoplasm = those with no neoplasm.
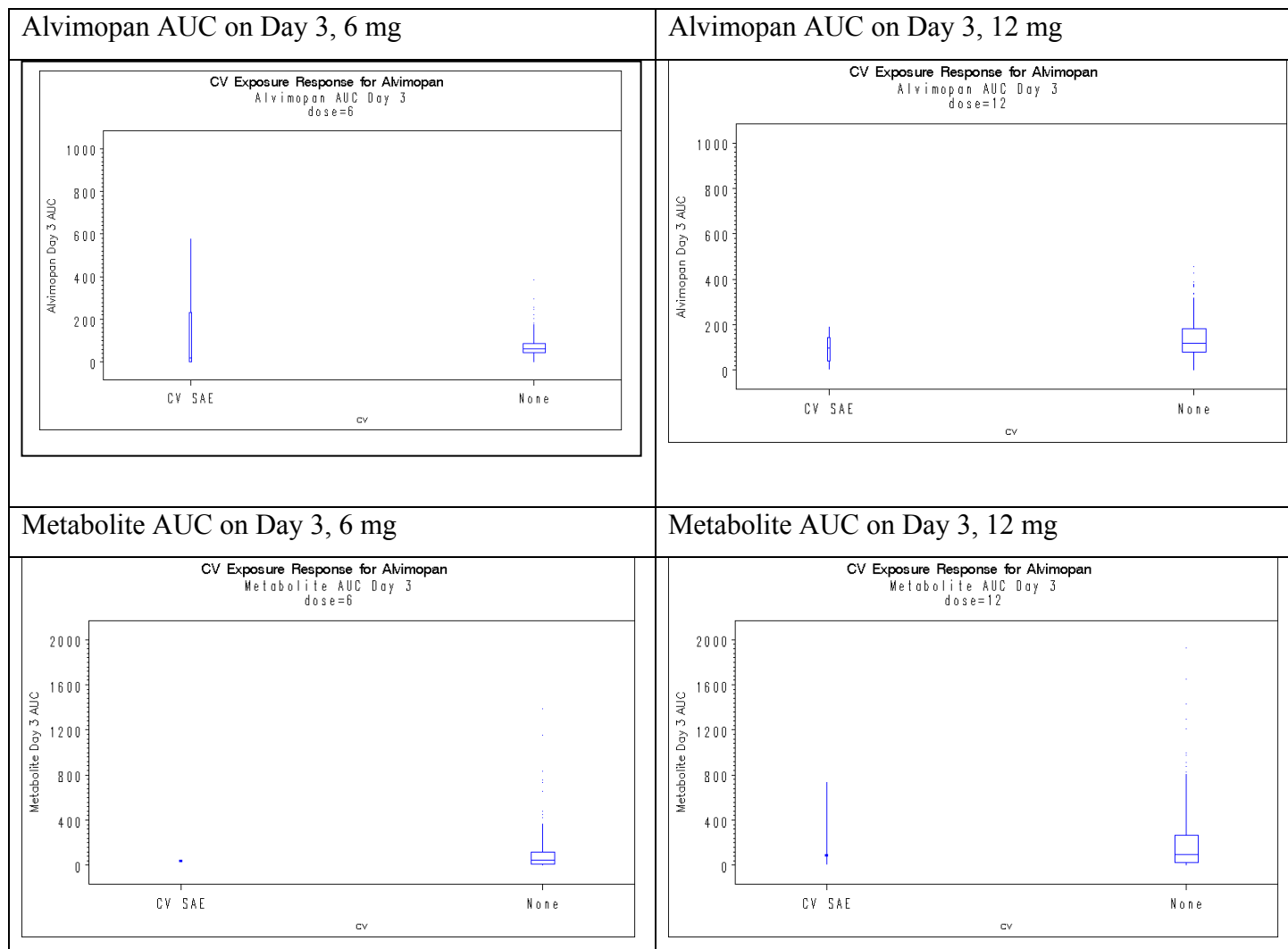
Figure 12.5-6   Alvimopan (A) and Metabolite (B) AUC in OBD Patients Receiving Alvimopan 0.5mg BID Who Experienced vs. Those Who Did Not Experience a Fracture[1,2]
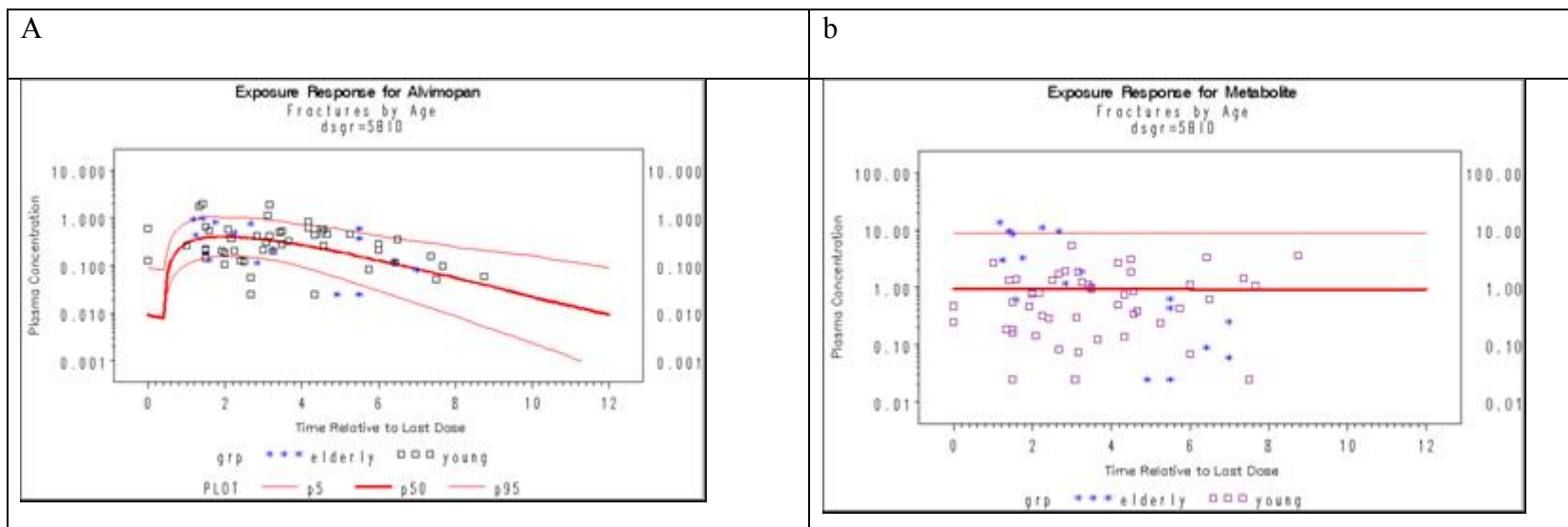
1 Data presented as a box plot with median, 25th and 75th percentile within the box. Vertical lines represent the 5th and 95th percentile. Dots represent individuals outside the 5th to 95th percentile.

2 Fracture = those with a fracture at any time throughout treatment (n=8); no fracture = those with no fracture.

12.6 Summary of Methodology and Results From Thorough QTc Study

12.6 Summary of Methodology and Results From Thorough QTc Study

This was a randomized, placebo-controlled trial conducted to evaluate the effect of single and multiple oral doses of alvimopan on QT interval as assessed by triplicate 12-lead electrocardiograms (ECGs) in adult healthy male and female subjects, using moxifloxacin as a positive control. Eligible subjects were randomly allocated to one of four treatment groups:

- Alvimopan 6 mg BID (Days 1 to 7; morning dose only on Day 7)

- Alvimopan 24 mg BID (Days 1 to 7; morning dose only on Day 7)

- Moxifloxacin 400 mg once (Day 1 only)

- Placebo BID (Days 1 to 7; morning dose only on Day 7)

The primary endpoint was QTcF interval as assessed by 12-lead ECG measured by the change from baseline at the 2-hour post dose time point on Day 1 and 7 hours and 12 hours post dose on Day 7. Secondary endpoints were QTcB interval, QT interval, and heart rate as assessed by 12-lead ECGs and the PK parameters of alvimopan and its major metabolite. Only results for QTcF interval are presented below.

A total of 162 subjects completed the study as planned (approximately 40 per group). A summary of point estimates and 90% CIs for change from baseline in QTcF at 2 hours post dose on Day 1, at 2 hours post dose on Day 7, and at 12 hours post dose on Day 7 are shown in Table 12.6-1.

Table 12.6-1   Summary of Point Estimates and 90% Confidence Intervals for Change From Baseline in QTcF

Comparison	Point Estimate	90% Confidence Interval
2-hr Post-dose on Day 1		
Alvimopan 6 mg BID–Placebo	0.35	(-3.65, 4.35)
Alvimopan 24 mg BID–Placebo	0.37	(-3.67, 4.41)
Moxifloxacin 400 mg–Placebo	9.77	(5.76, 13.78)
2-hr Post-dose on Day 7		
Alvimopan 6 mg BID–Placebo	-0.42	(-5.27, 4.44)
Alvimopan 24 mg BID–Placebo	2.84	(-2.14, 7.81)
12-hr Post-dose on Day 7		
Alvimopan 6 mg BID–Placebo	3.04	(-1.17, 7.25)
Alvimopan 24 mg BID–Placebo	-0.46	(-4.79, 3.87)

Note: The between-subject standard deviation for QTcF on Day 1 at 2 hours was 11.0 msec, on Day 7 at 2 hours was 13.0 msec, and on Day 7 at 12 hours was 11.3 msec.
BID = twice daily; h = hour.

Overall, these results indicate that based on change from baseline in QTcF for both alvimopan 6 mg BID and alvimopan 24 mg BID, an effect greater than 10 msec can be ruled out because the upper limit of the 90% CI is less than 10 msec.

With respect to individual changes from baseline, the number of subjects with changes in QTcF of 30 to 60 msec was approximately similar in the alvimopan and placebo treatment groups on Days 1 and 7; a higher frequency of subjects in the moxifloxacin treatment group had changes in QTcF of 30 to 60 msec on Day 1, which is as expected given the inclusion of moxifloxacin as a positive control for its known effects on QTc.

Only 1 incidence of a change from baseline in QTcF of > 60 msec was observed in a female subject at the alvimopan 6-mg BID dose level. This subject had a maximum change in QTcF of 61 msec, with a baseline QTcF of 399 msec and a QTcF of 460 msec on Day 7 at 18 hours post-dose. Concentrations of alvimopan at this time were less than 10% of peak concentrations, while the metabolite concentrations at this time were similar to the maximum concentrations. In this particular subject, the concentration of the metabolite (2.17 ng/mL) at 16 hours was much lower than the median C_{max} (4.3 ng/mL) for the 6-mg dose and less than 1/10 the median C_{max} (35.3 ng/mL) for the 24-mg dose. It is, therefore, very unlikely that this change is related to either alvimopan or its metabolite, given the isolated nature of the finding and the lack of similar observations at the alvimopan 24-mg BID dose level.

The overall conclusion using standard statistical approaches and PK/PD modeling suggest that, at oral doses up to 24 mg BID for 7 days, alvimopan did not cause clinically significant QTc prolongation and, therefore, within this dose range, has a low risk of affecting cardiac conduction.

12.7   Patient Narratives for AEs of Interest—OBD Population

12.7 Patient Narratives for AEs of Interest—OBD Population

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12.7.1   *OBD Patients With Myocardial Infarctions*

12.7.1.1   Patient GSK014-000759: Grade 3 MI

This 71-year-old male subject was enrolled in a blinded study for the treatment of opioid-induced bowel dysfunction. The subject received oral investigational product twice per day from 04 Oct 2005.

The subject was randomized to alvimopan 0.5 mg capsules twice daily.

Medical conditions at the time of the event included chronic obstructive pulmonary disease, ischemic heart disease and osteoarthritis. The subject was an ex-smoker.

On 11 Nov 2005, 38 days after the start of investigational product, the subject developed a grade 3 or severe MI. The subject was hospitalized. Treatment with investigational product was discontinued and the subject was withdrawn from the study. The event resolved on 18 Nov 2005. The investigator considered that there was no reasonable possibility that the MI may have been caused by investigational product.

Diagnostic results: Echocardiogram revealed a non-ST elevation MI. Angiogram showed complex coronary artery disease.

Investigator comments: Patient telephoned surgery to inform myself that he had been admitted to (hospital name deleted) on 11 Nov 2005, suffering from severe chest pain. He indicated that he had been informed that he had had a myocardial infarction. Patient states he had angiogram and an echocardiogram. Doctor in hospital stopped patient's study drug. Discharge letter says non ST elevation myocardial infarct and complex coronary artery disease on angio.

Additional information obtained from the site by Clinical: Subject receiving opioids (Coproxamol [propoxyphene/acetaminophen, total daily dose of propoxyphene = 260 mg]) for 18 years for osteoarthritis. Concurrent medications include aspirin (prevention of heart attack), simvastatin (hyperchol.), terbutaline, and budesonide (COPD), tamsulosin (urinary flow obstruction), Enzira (flu prophylaxis - 29 Oct 2005). CRF: Obese (BMI=38.2), no history of DM but glucose intolerance noted June 2005, hypercholesterolemia diagnosed June 05, history of stable exertional angina prior to MI elucidated during hospitalization, not previously divulged to PCP.

Family history positive for DM Type II and CAD.

Electrocardiogram (ECG): Inferolateral ST depression, Troponin +

Echocardiogram: Mild LVH and mild MR

Catheterization Report: Diffuse, triple vessel CAD

The subject was noted to have a good recovery from the MI. Poor PTCA candidate, referred for CABG evaluation.

12.7.1.2   Patient GSK014-805: Grade 3 Inferior ST Elevation MI

This 75-year-old female subject was enrolled in a blinded study for the treatment of opioid-induced bowel dysfunction. The subject received oral investigational product twice per day from 19 Oct 2005 to 12 Jan 2006.

The subject was randomized to alvimopan 0.5 mg capsules twice daily.

The subject's past medical history included ocular hypertension. Medical conditions at the time of the event included chronic obstructive pulmonary disease, hypercholesterolemia, hypertension and osteoarthritis. The subject was a smoker.

On 12 Jan 2006, 85 days after the start of investigational product, the subject developed a grade 3 or severe inferior ST elevation MI. The subject was hospitalized. Treatment with investigational product was discontinued on 12 Jan 2006 and the subject was withdrawn from the study. The event resolved on 17 Jan 2006. The investigator considered that there was no reasonable possibility that the inferior ST elevation MI may have been caused by investigational product.

Diagnostic results: 14 Jan 2006—C-reactive protein 32 mg/L (reference range: less than 10), troponin I 9.88 ug/L (reference range: less than 0.04).

Investigator comments: Patient admitted to hospital due to chest pain 12 Jan 2006 pm. Patient discharged from hospital 17 Jan 2006—Inferior ST elevation MI diagnosed. Reperfused with Streptokinase-referred to Cardiac rehabilitation

Additional information obtained from the site by Clinical: Osteoarthritis x 13 years treated with opioids for the same period (dihydrocodeine/acetaminophen, 80 mg/d dihydrocodeine since 2002). Concurrent medications include: omeprazole and peptac (dyspepsia), salbutamol and salmeterol (COPD), aspirin (prophylaxis for cardiovascular event), verapamil and bendrofluazide (HTN), Xalatan eye drops (ocular HTN), Arthrotec (osteoarthritis), metoclopramide (nausea). CRF: Smoker (40/d), not diabetic, no family history of ischemic heart disease noted, mildly obese (BMI= 30.6), ultimately discharged on atorvastatin, though hypercholesterolemia not noted previously.

On 12 Jan 2006, the subject was admitted to the hospital due to chest pain. ECG—inferolateral ST elevation, Troponin +. Echocardiogram and cardiac catheterization results not available. "Good recovery" noted on discharge summary. Work-up by cardiologist Mar 2005 concluded non-ischemic disease with a normal resting ECG: stress ECG not performed. Subsequent episode of chest pain described during a review performed Jul 2005 also described as non-ischemic.

12.7.1.3   Patient GSK014-807: Grade 2 MI

This 75-year-old female subject was enrolled in a blinded study for the treatment of opioid-induced bowel dysfunction. The subject received oral investigational product twice per day from 12 Dec 2005.

The subject was randomized to alvimopan 0.5 mg capsules twice daily.

Medical conditions at the time of the event included aortic incompetence, atrial fibrillation, current smoker, transient cerebral ischemia, and worsening of heart failure.

On 11 Jan 2006, 30 days after the start of investigational product, the subject developed a grade 2 or moderate MI. The subject was hospitalized. Treatment with investigational product was discontinued and the subject was withdrawn from the study. The event resolved on 20 Jan 2006. The investigator considered that there was no reasonable possibility that the MI may have been caused by investigational product.

Diagnostic results: 02 Jan 2006—Echocardiogram revealed a dilated and severely hypokinetic left ventricle. The mitral valve leaflets were thickened with severe mitral regurgitation into a dilated atrium. The aortic valve leaflets were also thickened, but there was no stenosis and regurgitation was mild. The right ventricle was also dilated with good function and moderate to severe tricuspid regurgitation. There was no moderate pulmonary hypertension. Jan 2006 (exact date unknown)—Troponin was 0.08.

Investigator comments: Attended surgery with right shoulder pain, very breathless. With orthopnea & bilateral ankle edema. Bradycardic and irregular pulse, pulse=40. BP=150/70. Admitted to Glasgow Royal Infirmary. Patient discharged 17 Jan 06.

Diagnosis: Patient had positive troponin, congestive cardiac disease, atrial fibrillation, severe mitral regurgitation, hypertension, severe LV systolic dysfunction. Beta blockers withdrawn and loop diuretic introduced.

Additional information obtained from the site by Clinical: Subject receiving opioids (tramadol 300mg/d) since Mar 2001 for osteoarthritis. Additional past medical history includes HTN. Concomitant medications include: Atrovent and salbutamol (COPD), digoxin (aortic valve dysfunction), paracetamol (osteoarthritis), Clopidogrel (prophylaxis following TIA), pravastatin (hypercholesterolemia), ranitidine (dyspepsia), amlodipine and bendrofluazide (hypertension).

CRF: Obese (BMI=33.1), non-diabetic smoker with hypercholesterolemia. Additional significant cardiac history included CHF and valvular heart disease. No family history of ischemic heart disease noted.

On 11 Jan 2006, the subject was admitted to the hospital for worsening dyspnea and ankle edema. Troponin +, ECG results unavailable, no cardiac catheterization results available. Bradycardia was noted (HR=40). Echocardiogram: Severe MR, thickened leaflets, dilated LA, thickened AV leaflets, mild AR, no stenosis, moderate-severe TR, moderate PH.

12.7.1.4   Patient GSK014-1818: Grade 3 Acute MI

This 93-year-old female subject was enrolled in a blinded study for the treatment of opioid-induced bowel dysfunction. The subject received oral investigational product twice per day from 23 Jan 2006.

The subject was randomized to alvimopan 0.5 mg capsules twice daily.

The subject's medical history included ischemic heart disease and hypertension.

On 20 Mar 2006, 56 days after the start of investigational product, the subject developed a grade 3 or severe acute MI. The subject was hospitalized treated with an unspecified "pressor". Treatment with investigational product was discontinued and the subject was withdrawn from the study. The subject died on 21 Mar 2006 due to acute MI. It was unknown whether an autopsy was performed. The investigator considered that there was no reasonable possibility that the acute MI may have been caused by investigational product.

Investigator comments: Patient was admitted to hospital because of dyspnea on 20 Mar 2006. In some minutes sudden asystolia occured. After reanimation and intubation supportive therapy was started. ECG and troponin test proved MI. After 12 hours on 21.03.2006 patient died. ECG: Date: 20.03.2006; Result: Tachycardy, V1-4:2-3 mm ST elevation, rS complex. Troponin test: Date: 20.03.2006; Result: Elevated: 0,634ng/mL

Additional information obtained from the site by Clinical: Osteoarthritis x 9 years treated with opioids (tramadol, 300mg/d) for 16 months. Concomitant medications include: co-renitec and felodipine (HTN), Nitroderm TTS (ischemic heart disease), aspirin (cardiovascular prophylaxis), and humacarpin (glaucoma).

CRF: Non-obese (BMI=26.4). Patient was admitted to hospital on 20 March 2006 because of dyspnea, which had been worsening for 1 week. Soon after arrival, the patient experienced cardiac arrest. After resuscitation and intubation, supportive therapy was started. Twelve hours after presentation to the hospital, the patient died.

Additional information received on 28 Jul 2006 from a translated copy of the final medical report: History could not be taken from the subject. The subject's medical history, as told by a relative, also included diabetes mellitus, which was controlled by diet for several years. Additional concomitant medications to those previously noted included Furon 40 mg every other day, Amlodipin 1 x 5mg, and Betaloc ZOK 2 x 50mg. At admission, the subject's blood pressure was 140/80 and her heart rate was 98 beats/min (pulse was regular and even). Additional laboratory test results from 20 Mar 2006: CPK 113 U/L, serum sodium 134 mmol/l, and serum potassium 4.3 mmol/l.

12.7.1.5   Patient GSK014-17641: Grade 3 Transmural MI and Grade 3 CAD

This 68-year-old male subject was enrolled in a blinded study for the treatment of opioid-induced bowel dysfunction. The subject received oral investigational product twice per day from 03 Nov 2005.

The subject was randomized to alvimopan 0.5 mg capsules twice daily.

Medical conditions at the time of the event included arthritis, depression, and insulin-dependent diabetes mellitus.

On 17 Feb 2006, 106 days after the start of investigational product, the subject developed a grade 3 or severe transmural MI and grade 3 or severe coronary artery disease. The subject was

hospitalized and treated with clopidogrel bisulphate, aspirin, metoprolol, and simvastatin. Treatment with investigational product was interrupted. The MI resolved on 20 Feb 2006, and the coronary artery disease resolved on 08 Mar 2006. The investigator considered that there was no reasonable possibility that the transmural MI and coronary artery disease may have been caused by investigational product.

Diagnostic results: 17 Feb 06—Inital ECG NSR with T wave abnormalities inferior leads. Cath/angioplasty showed right coronary artery (RCA) 85-90% occlusion; left main normal; left anterior descending (LAD) 75-85% occlusion; left circ. 85% occlusion; left ventricle (LV) apical hypokinesis with normal ejection fraction (EF). Stent emergently placed in RCA and posterior descending branch. LAD and left circ. were scheduled 2 weeks out. Recheck of RCA stents on 03/01/06 showed excellent results of 10%. Left circ. was stented on 03/03/06.

Lab results:
17 Feb 2006 at 15:30—Creatine kinase (CK) 252, CK-MB 6.2, %MB 2.5, brain natriuretic peptide (bnp) 270, Troponin I 0.40, D Dimer less than 200.
8 Feb 2006 at 01:40—CK 212, CKMB 10.9, %MB 5.1.
18 Feb 2006 at 07:59—CK 367, CKMB 38.0, %MB 10.4.
20 Feb 2006 at 05:45—CK 205, CKMB 9.4, %MB 4.6, Troponin I 2.13.
01 Mar 2006 at 15:20—Troponin I 0.13.
01 Mar 2006 at 23:56—CK 156, CKMB 3.8, %MB 2.4, Troponin I 0.12.
02 Mar 2006 at 08:35—CK 155, CKMB 3.9, %MB 2.5.
03 Mar 2006 at 14:45—CK 115, CKMB 3.8, %MB 3.3.
06 Mar 2006 at 22:45—CK 196, Troponin I 0.22.
07 Mar 2006 at 15:15—CK 140, CKMB 3.5, %MB 2.5.
07 Mar 2006 at 20:00—Troponin I 0.31.
08 Mar 2006 at 06:00—Troponin I 0.30.
08 Mar 2006 at 11:55—Troponin 0.2.

Investigator comments: 20 Feb 2006—Patient called to inquire and be reminded of rescue laxative guideline. Patient reports that he was admitted to hospital for angina on 17 Feb 2006. He had 3 cardiac stents placed. He was discharged home on 20 Feb 2006 without any further symptoms. Study medication was interrupted from 2/17 PM dose to 2/20 AM dose. Patient to resume study medication with 2/20 PM dose. Patient called the morning of 21 Feb 2006 to report bowel pattern had returned to his normal pattern since beginning study medication. No further cardiac symptoms. Readmitted for scheduled stent and angioplasty on 01 Mar 2006. Patient discharged 4 Mar 2006. On 6 Mar 2006 the patient experienced chest discomfort with dyspnea. He returned to the emergency room (ER) and a balloon dilatation was performed. He was kept in the hospital for 2 days. No changes were made to the new medications ordered on 17 Feb 2006. Per the patient, the cardiologist was informed of study participation and not concerned. 3 May 2006—Patient states most recent check by cardiologist and stress test were good. To follow up in 6 months. Pt. denies further cardiac symptoms since discharge on 8 May 2006. Per Principal Investigator, patient was not taking any relavent medications contributing to this SAE event.

Additional information received from the site by Clinical: Shoulder pain treated with opioids and NIDDM since Jul 1989 effectively treated with oral hypoglycemics. Using opioids for 3 years, but has only had "general joint pain" primary pain condition for 12 weeks, thus opioids taken for the primary pain conditions is 12 weeks. Methadone 20 mg since 2004 for maintenance and oxycodone 15 mg for breakthrough.

CRF: DM+, non-obese, non-smoker, no prior CAD history, low cholesterol (41 HDL, 32 LDL, Total lipid 82), family history not assessed.

On February 17, 2006, patient had acute onset severe angina at rest. Admitted to hospital with findings of ECG with T wave inversion in inferior leads. Enzymes show peak CPK within 24 hours (367), MB fraction 38 (10.4%), and a Troponin increased from 0.4 at baseline to 2.13.

Echocardiogram: Apical LV hypokinesis with normal EF. Catheterization Report: Patient found to have extensive CAD [RCA 80-90% long seg mid-obstruction, PDA 95% long seg obstruction, LM normal, LAD - small caliber vessel, 75-85% mid course obstruction, LCx 85% mid portion obstruction, Post Lat - branches totally occluded]

Patient had the RCA stented emergently and then returned 2 weeks later for the placement of two additional stents.

Based upon the conclusion of the investigator & the patient's cardiologist that the event was not related to study drug, the patient was allowed to resume investigational drug treatment 3 days post event and has been without report of additional angina.

12.7.1.6   Patient GSK014-18321: Grade 3 MI

This 48-year-old male subject was enrolled in a blinded study for the treatment of opioid-induced bowel dysfunction. The subject received oral investigational product twice per day from 11 Oct 2005.

The subject was randomized to alvimopan 0.5 mg capsules twice daily.

Medical conditions at the time of the event included obesity, coronary artery disease, and hypertension.

On 30 Jan 2006, 111 days after the start of investigational product, the subject developed a grade 3 or severe MI. The subject was hospitalized and treated with atorvastatin calcium, clopidogrel bisulphate, aspirin, metoprolol, digoxin, warfarin sodium, quinapril and hydrochlorothiazide. Treatment with investigational product was interrupted. The event resolved on 30 Jan 2006. The investigator considered that there was no reasonable possibility that the myocardial infarction may have been caused by investigational product.

Investigator comments:

Diagnostic results: ECG 30 Jan 2006 abnormal = acute MI, ECG 2 Feb 20006 = abnormal, inferior infarct, left heart catheterization 30 Jan 2006, temporary pacer and an intra-aortic balloon pump 30 Jan 2006, blood transfusion 4 units 30 Jan 2006.

Narrative remarks: The SC met with the subject for month 6 visit at which time he reported that he had an MI on 30 Jan 2006. He was at home felt arm pain followed by syncope. His wife called EMS. He was admitted to the hospital and underwent a cardiac cath with 2 stents placed on 31 Jan 2006. The subject was discharged home on 2/7/06. He then had another stent placed on 13 Mar 2006 and was discharged on 14 Mar 2006. The subject has completely recovered from the MI and stent surgeries and wishes to continue in the study.

Additional information received from the site by Clinical: Failed back syndrome x 20 years receiving opioids for same interval (methadone 50mg/d since 2000). Additional past medical history includes HTN x 26 years and spinal fusion procedure 16 January 06. Concomitant medications included losartan, HCTZ, diltiazem, Mobic, amitriptyline, fosamax, monopril, atenolol, Lyrica, and gabapentin.

CRF: Non-smoker, obese (BMI=32.1), normal lipid profile per history (though discharged on atorvastatin), family history unknown.

Subject apparently was diagnosed with ischemia and was sent for cardiac catheterization on 1/31. Two stents were placed at that time, and the patient had another stent placed on 13 Mar 2006, though it is currently unknown if that procedure was elective or emergent.

The investigator first found out about these events during an Apr 2006 clinic visit for Study GSK014. Treatment with investigational product was interrupted with original incident, though the patient wishes to continue in the study.

Additional information obtained from medical records submitted to GSK by the site on 12 May 2006:

Diagnostic results: ECG revealed ST elevations in the inferior and posterior leads. Laboratory tests on 30 Jan 2006: Troponin I 13.7 ng/mL (range less than 0.5), CKMB 12.3 ng/mL (range less than 5.3), triglycerides 157 mg/dL (range 30 - 200), cholesterol 134 mg/dL (range 50 - 200), HDL cholesterol 31 mg/dL (range 29 - 61), VLDL cholesterol 31 mg/dL (range 0 - 40), LDL cholesterol 72 mg/dL (range 62 - 178), cholesterol ratio 4.3. Laboratory tests on 05 Feb 2006: Troponin I 5.00 ng/mL (range less than 0.20), CPK 36 U/L (range less than 171). The subject had a history of hyperlipidemia. Additional treatment of the event included unspecified antithrombotic agents. The subject underwent a left heart catheterization and was found to have severe, two-vessel disease with a total, mid RCA occlusion and a 90% ostial first diagonal lesion. The subject was also found to be in cardiogenic shock with CT heart block. He received a temporary pacer and an intra-aortic balloon pump, and was placed on multiple pressors. While in the ICU, the subject also developed new onset atrial fibrillation. Discharge medications included aspirin, Lipitor, Plavix, metoprolol, digoxin, Coumadin, quinapril, hydrocholorothiazide and methadone.

12.7.1.7   Patient GSK014-18322: Grade 1 Heart Attack

This 62-year-old female subject was enrolled in a blinded study for the treatment of opioid-induced bowel dysfunction. The subject received oral investigational product twice per day from 28 Oct 2005 to 03 Jan 2006.

The subject was randomized to alvimopan 0.5 mg capsules twice daily.

Medical conditions at the time of the event included hyperlipidemia, hypertension, and peripheral vascular disease. The subject was a smoker (15 cigarettes per day).

On 01 Jan 2006, 65 days after the start of investigational product, the subject developed a grade 1 or mild heart attack. The subject was hospitalized. The subject was treated with heparin, clopidogrel bisulphate and metoprolol tartrate. Treatment with investigational product was discontinued on 03 Jan 2006 and the subject was withdrawn from the study. The event resolved on 06 Jan 2006. The investigator considered that there was no reasonable possibility that the heart attack may have been caused by investigational product.

Diagnostic results: Laboratory results on 04 Jan 2006—Troponin I 21.9, creatine kinase (CK) 423, triglycerides 260, high-density lipoprotein (HDL) 23, risk ratio 5.48, glucose 154, hematocrit 36.7. Coronary angiography was done on 03 Jan 2006; results were not provided. EKG on 04 Jan 2006 revealed a T wave abnormality.

Investigator comments: The subject phoned the SC on 17 Jan 2006 and reported that she will be withdrawing consent due to a mild heart attack. The subject reported having chest pains on 1 Jan 2006 but thought it was indigestion. She finally went to the ER on 1/3/06 and test showed that she had had a mild heart attck on 1 Jan 2006. Although she is fine now, she does not want to take any medications that are investigational. Hospital records are pending. The subject has an appointment for early term visit. Hospital records showed that the subject had undergone a successful percutaneous transluminal coronary angioplasty with stent placement on 3 Jan 2006.

Additional information received by the site from Clinical: Reflex sympathetic dystrophy and DJD of the spine x 10 years treated with opioids x 9 years (Oxycontin 40 mg/d since Jun 2005). Past medical history notable for hypertension since 1987, hypercholesterolemia since 2002, and peripheral arterial disease. Concomitant medications included furosemide, verapamil, gabapentin, ezetemide, alprazolam.

CRF: Smoker (10-20/d), mild obesity (BMI=29.1). Additional relevant history included hypercholesterolemia and peripheral arterial disease. No history of DM, unknown family history.

On 03 Jan 2006, the subject presented with a 4-day history of waxing and waning chest discomfort described as burning and tightness. ECG: Q waves in V1, V2 with 1-2 mm ST elevations and flipped T-wave. CK MB and Troponin both +. No echocardiogram results available. Catheterization report: Critical LAD lesion.

Patient underwent emergent stenting procedure, based on angiogram results, and apparently has done well post discharge. Patient elected to withdraw from the study on 6 Jan 2006.

12.7.1.8   Patient GSK011-000973: Acute MI

This 55-year-old male subject was enrolled in a blinded study for the treatment of opioid-induced bowel dysfunction. The subject's medical history included MI, percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass x 2, chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), controlled hyperlipidemia, controlled hypertension, and bilateral leg pain. The investigator noted that although the subject's history was significant for CAD, he had been stable since 1997. The subject currently smokes cigarettes (1.5 packs per day) and has a 52.5 pack/year history of smoking. He had not used alcohol since 2000. Concomitant medications included atenolol for hypertension, clopidogrel for peripheral vascular disease, and oxycodone for bilateral leg pain.

The subject received oral blinded trial medication from 22 Oct 2003. The subject was randomized to oral alvimopan capsules 0.5 mg once daily for three days, followed by alvimopan 1 mg once daily. On 29 Oct 2003, 1 week following the initiation of investigational product, the subject presented to the ER due to shortness of breath that began on 26 Oct 2003, and which progressed each day thereafter. The subject also reported that on 28 Oct 2003, he had burning in his chest which was relieved with two nitroglycerin tablets. He was diagnosed with a COPD exacerbation and treated in the ER with albuterol/atrovent nebulizers and nasal oxygen. The dyspnea improved. The investigator did not consider the COPD exacerbation to be serious, and reported that the subject's pulmonary symptoms were related to the cardiac event. Relevant test results included an abnormal ECG with ST depression. An ECG conducted prior to study enrollment (on 06 Dec 2002), showed an RSR prime pattern with non-specific T wave changes in Lead III. The subject also had elevated cardiac enzymes (creatine phosphokinase = 194U/L, creatine phosphokinase MB = 5.6ng/ml, troponin = 3.39ng/ml). A chest x-ray revealed cardiomegaly and congestive heart failure (CHF) with interstitial edema and small bilateral pleural effusion. The subject was admitted to the hospital for the evaluation and treatment of an acute MI. Treatment with investigational product was continued. The subject underwent percutaneous coronary intervention (PCI) on the saphenous vein graft (SVG) to the right coronary artery. Additional treatment included a heparin drip, nasal oxygen, the administration of an ACE-inhibitor (not specified) and concomitant medication adjustment (also not specified). He remained hemodynamically stable with no recurrent pain. The event resolved on 01 November 2003, and he was discharged from the hospital the same day. On 11 Dec 2003, the subject was examined by his primary care provided and was noted to be stable. The investigator considered there was not a reasonable possibility that the serious adverse event, acute MI, may have been caused by the investigational product. The subject's previous cardiac history was cited as a possible cause.

12.7.1.9   Patient GSK012-006053: CHF and MI

This 91-year-old female subject was enrolled in a blinded study for the treatment of opioid-induced bowel dysfunction. The subject received oral investigational product twice per day from 01 Feb 2006.

The subject was randomized to placebo capsules.

The subject's recent past medical history included bilateral ankle swelling from 06 Mar 2006 to 29 Mar 2006. Medical conditions at the time of the event included hypertension. Concomitant medications included diltiazem hydrochloride and hydrochlorothiazide.

On 20 Apr 2006, 78 days after the start of investigational product, the subject developed grade 2 or moderate CHF and a grade 1 or mild subendocardial MI. The subject was hospitalized. Treatment with investigational product was interrupted on 20 Apr 2006. The events resolved on 02 May 2006. The investigator considered that there was no reasonable possibility that the CHF and subendocardial MI may have been caused by investigational product.

Diagnostic results: 20 Apr 2006—Chest x-ray revealed mild cardiomegaly. Troponin I: 0.21 ng/ml at 11:40, 0.23 ng/ml at 13:55, 0.24 ng/ml at 17:35 (reference range 0 - 0.04ng/ml). An ECG revealed normal sinus rhythm, left atrium enlargement, left axis deviation, old septal infarct, and no acute changes.

Investigator comments: On 20 Apr 2006, subject had shortness of breath, chest pressure, nausea and vomiting and diaphoresis. EMS was activated, she was then taken to a local hospital where she is currently admitted for CHF and sub-endocardial MI. The subject was given diuretics, B-blocker, and NTG tabs. On 2 May 2006 subject was discharged from the hospital.

12.7.1.10 Patient GSK013-009983: Coronary Artery Stenosis and MI

This 47-year-old male subject was enrolled in a blinded study for the treatment of opioid-induced bowel dysfunction. The subject received oral investigational product twice per day from 28 Nov 2005.

The subject was randomized to placebo capsules.

The subject's past medical history included coronary stent placement. Medical conditions at the time of the event included angina pectoris, atherosclerotic cardiovascular disease, diabetes, hiatal hernia, hyperlipidemia, hypertension, multiple sclerosis, obesity, peptic ulcer disease, and reflux esophagitis. The subject was a smoker.

On 01 Feb 2006, 65 days after the start of investigational product, the subject developed grade 3 or severe coronary artery stenosis and a grade 3 or severe possible MI. The subject was hospitalized and the events were life-threatening. He underwent coronary artery stent placement and was treated with nitroglycerine. Treatment with investigational product was discontinued and the subject was withdrawn from the study. The events resolved on 01 Feb 2006. The investigator considered that there was no reasonable possibility that the coronary artery stenosis and possible MI may have been caused by investigational product.

Diagnostic results: Cardiac catheterization—Left main was normal, showed myocardial bridge, circumflex normal; right coronary artery 100% stenosis of the posterolateral branch. It was unknown whether these findings were similar to a previous catheterization performed in 1991. Chest x-ray was normal. 2-D echocardiogram—Evidence of pericardial effusion. Ultrasound of abdomen—5 cm area of increased echogenicity in the region of the right lobe of liver. Computed tomography was unremarkable. Lab studies on 01 Feb 2006 revealed potassium 3.0 mEq/L (reference range 3.5 - 5.1), creatine 1.1 mg/dL (reference range 0.6 - 1.3), creatine phosphokinase 26 U/L (reference range 21 - 232), creatine phosphokinase MB 0.6 ng/ml (reference range 0 - 3.6), and troponin < 0.04 ng/ml. Labs at discharge were unremarkable.

Investigator comments: Subject has coronary heart disease since 1991. Had three coronary stents placed in 1991 and 2 stents placed in 2005. Patient had crushing chest pain at home and as he had previously had same condition Mother called 911. Patient was taken to hospital ER where he was thought to have "acute inferior wall MI" and was taken to the cath lab. While in cath lab patient was in V. Tach and defibrillated X 1. He had 2.75 x 20mm Taxux drug-eluting stent to the distal RCA with a 2.0 x 15 PTCA to the side branch through struts placed. Patient did not go into cardiac arrest, but was defibrillated one time for ventricular tachycardia.

12.7.2   *OBD Patients With Malignant Neoplasms*

12.7.2.1   Patient GSK014-3233: Nontuberculosis Mycobacterium With Lung Cavitations And
               Rib Involvement, Lung Cancer

Subject 3233 was an 81-year-old Asian male, BMI = 26, with a 60-year history of smoking, who was treated with propoxyphene (stable 130 mg oral total daily dose) and tramadol (200 mg oral total daily dose) as scheduled maintenance opioid therapy for relief of neuralgia. At study entry the subject had suffered from this condition for 2 years and had received opioid therapy for 1 year, including the current opioid therapy, with < 1 year at stable dose.

Subject 3233 began investigational product on 09 Jan 2006, was > 80% compliant with taking investigational product, and had completed approximately 4 months of the 12-month treatment period when he stopped taking investigational product due to the serious adverse event of lung cancer. The subject received investigational product for 133 days with no interruptions, with a treatment stop date of 21 May 2006. The date of withdrawal from the study was 23 Jun 2006.

The subject was randomized to alvimopan 0.5 mg capsules twice daily.

Six months prior to starting on study, the subject presented with chronic cough and hemoptysis and was admitted to the hospital where he stayed for 2 weeks. A chest CT showed a 4.3-cm cavitary lesion with attachment to the right anterolateral chest wall with rib destruction. Sputum cytology was negative. The subject refused operation and lung biopsy. He was treated with 4 months of anti-tuberculosis therapy. The diagnosis recorded in the subject's medical chart at the clinic site was nontuberculosis mycobacterium with lung cavitations and rib involvement.

A serious adverse event of lung cancer was reported on 21 May 2006, 133 days after start of investigational product. This was diagnosed at an outlying hospital, and the subject himself was not informed by family of the diagnosis. A confirmatory cancer pathology report was not provided to GSK. The neoplasm in question had not been diagnosed prior to participation in the study. The subject was withdrawn from study and any further outcome was unknown.

Non-opioid concomitant medications included ambroxol hydrochloride as an expectorant for sputum removal, celecoxib and gabapentin for neuralgia, and lorazepam for insomnia.

12.7.2.2   Patient GSK014-3553: Squamous Cell Carcinoma of the Lung

Subject 3553 was a 61-year-old Caucasian male, BMI = 26, smoker (average of 20 cigarettes/day), treated with oxycodone (stable 30 mg oral total daily dose) as scheduled maintenance opioid therapy for relief of arthritis pain. At study entry the subject had suffered from this condition for 2 years and had received opioid therapy for 2 years, including the current opioid therapy for 2 years, with < 1 year at stable dose. The subject used oxycodone (5-20 mg oral total daily dose) for breakthrough pain.

Subject 3553 began investigational product on 17OCT05, was > 80% compliant with taking his investigational product, and had completed the majority of the study, composed of a 1-week screening period, 12-month treatment period, and 2-week follow-up period, when he withdrew due to the adverse event of squamous cell carcinoma after approximately 11 months on treatment. The subject received investigational product for 330 days with no interruptions, with a treatment stop date of 11SEP06.

The subject was randomized to alvimopan 0.5 mg capsules twice daily.

A serious adverse event of squamous cell carcinoma of the right lung was reported on 13 Jul 2006, 270 days after the start of investigational product. The carcinoma was detected as an incidental finding when the subject had a routine chest x-ray done on 13 Jul 2006 as part of preoperative workup for elective surgery of umbilical hernia repair done on 14 Jul 2006. The chest x-ray showed an apparent cavitating abnormality in the right middle lobe. A CT scan done 22 Aug 06 showed a large cavitating lesion in the right middle lobe with a couple nodular densities in the right lung and a smaller cavitating lesion in the lower lobe. CT-guided fine-needle aspiration biopsy done on the right lung on 07 Sep 2006 confirmed a diagnosis of squamous cell carcinoma with pulmonary metastases. A copy of the confirmatory diagnostic reports from the Aug 06 CT scan and Sep 2006 biopsy were provided to GSK. The neoplasm in question had not been diagnosed prior to participation in the study. The event was considered unresolved and the investigational product was discontinued on 11 Sep 2006 and the subject was withdrawn from the study. No further follow-up on the subject's course of disease was provided to GSK.

The subject had a history of severe chronic lung disease with numerous hospitalizations treated with bronchodilators and high-dose corticosteroid intermittently. In addition, per the subject's physician, Subject 3553 had been diagnosed with adenocarcinoma of the prostate in 1994 (no

pathology report available). There was no documented recurrence of this cancer. The subject's physician reiterated that the current squamous cell carcinoma was a primary tumor and not as a result of metastasis from the prostate cancer.

Non-opioid concomitant medications included alendronate sodium for prevention of glucocorticoid-induced osteoporosis, allopurinol and colchicine for gout, bisacodyl for constipation, citalopram hydrobromide for depression, ipratropium, montelukast sodium, salbutamol, salmeterol xinafoate + fluticasone propionate, sodium chloride, and terbutaline sulfate for asthma, moxifloxacin for increasing chest congestion due to COPD, omeprazole for gastroesophageal reflux disease, prednisone for arthritis pain, chest congestion, COPD and gout exacerbation, sulfamethoxazole + timethoprim for COPD exacerbation, tetracycline for acute bronchitis, and tiotropium bromide for COPD.

12.7.2.3   Patient GSK014-3555: Squamous Cell Carcinoma of the Larynx

Subject 3555 was a 74-year-old Caucasian female, BMI = 26, smoker for 50+ years, treated with oxycodone (stable 25 mg oral total daily dose) as scheduled maintenance opioid therapy for relief of back pain. At study entry the subject had suffered from this condition for 30 years and had received opioid therapy for 8 years, including the current opioid therapy for 5 years, with 1 year at stable dose. The subject used oxycodone (5 mg and 30 mg oral total daily dose) for breakthrough pain.

Subject 3555 began investigational product on 20 Oct 2005, was > 80% compliant with taking her investigational product, and successfully completed the study composed of a 1-week screening period, 12-month treatment period, and 2-week follow-up period. The subject received investigational product for 362 days with no interruptions, with a treatment stop date of 16 Oct 2006.

The subject was randomized to alvimopan 0.5 mg capsules twice daily.

A serious adverse event of squamous cell carcinoma of the larynx was reported with an onset date of 01 Sep 2006, 316 days after the start of investigational product. The series of events which led to this diagnosis was as follows. The subject saw her family doctor on 01 Sep 2006 with complaint of a lump on her right anterior neck. The size was reported as 2.5 cm; the lesion was not mobile. The subject had no complaints of discomfort and no difficulty swallowing. A needle biopsy of the lymph node at the right anterior neck was done on 17 Oct 06 and found to have malignant cells present. CT of the neck on 24 Oct 2006 showed enlarged nodes in the right neck, the largest being 2.1 cm with some necrosis and also mild thickening of the laryngeal mucosa outline. A chest CT showed no findings of malignancy in the thorax, although two tiny granulomas were noted. The biopsy of the arytenoid mucosa on the right showed poorly differentiated squamous carcinoma, with tumor growth in large sheets of squamoid cells, with an active mitotic rate. The bulk of the submucosa was extensively infiltrated. The biopsy report dated 31 Oct 2006 indicated that malignant cells were present in the lymph node of the right anterior neck. The subject had her month 12 visit done on 16 Oct 2006 with the last dose of study medication taken that same day. The follow-up visit was 01 Nov 2006. Copies of

oncology clinic note reports were provided to AGSK. The neoplasm in question had not been diagnosed prior to participation in the study. The event was considered unresolved on the AE report form. An oncology clinic report provided to GSK dated 27 Dec 2006 indicated that the subject was receiving chemotherapy and radiotherapy for her squamous cell carcinoma of the larynx, described as locally advanced throat cancer.

The subject had a history of hypertension for ~40 years as well as angioedema for ~3 years.

Non-opioid concomitant medications included acetylsalicylic acid for chronic back pain, benadryl, hydroxyzine hydrochloride, and prednisone for recurrent angioedema, bisacodyl for constipation, hydrochlorothiazide and metoprolol tartrate for hypertension, methylprednisolone as prophylaxis for possible allergy to radiographic dye, and salbutamol for upper respiratory infection.

12.7.2.4   Patient GSK014-7846: Non-Small Cell Lung Cancer

Subject 7846 was a 57-year-old Caucasian male, BMI = 28, smoker, treated with methadone (stable 15 mg oral total daily dose) for back pain. At study entry the subject had suffered from this condition for 16 years and had received opioid therapy for 16 years, including the current therapy for 1 year at stable dose. Hydrocodone (40 mg oral total daily dose) and morphine (6 mg intramuscular total daily dose) were used for breakthrough therapy.

Subject 7846 began investigational product on 29 Nov 2005, was > 80% compliant with taking his investigational product, and successfully completed the study composed of a 1-week screening period, 12-month treatment period, and 2-week follow-up period. The subject received investigational product for 364 days with no interruptions, with a treatment stop date of 27 Nov 2006.

The subject was randomized to placebo capsules twice daily.

On 16 Jan 2007, 50 days following his last dose of investigational product, subject was found to have a right lower lobe nodule. Chest x-ray was performed as part of screening for participation in a clinical trial. A follow-up chest CT on 06 Feb 2007 showed a 1.9-cm right lower lobe nodule. CT-guided needle biopsy of this lesion on 23 Feb 2007 showed poorly differentiated non-small cell carcinoma. A bone scan on 05 Mar 2007 and CT of the head and abdomen performed on 08 Mar 2007 found no evidence of metastases. A PET scan on 09 Mar 2007 revealed intensity and hypermetabolic focus in the lateral right lower lobe corresponding with the pulmonary mass seen on CT scan. There was also metabolic right hilar and subcarinal lymphadenopathy. The tumor was staged T1, N2, M0 (III-A). The consultation notes of 27 Mar 2007 indicate that there were recommendations for chemotherapy and radiation therapy. The subject was referred for oncology recommendations. No updates provided since that time.

The subject's past medical history was otherwise notable for COPD, Type II diabetes, coronary artery disease (S/P CABG), peripheral arterial disease (S/P profundoplasty), and nephrectomy for nephrolithiasis. While on study, the subject suffered adverse events related to a vascular

procedure. None of the adverse events were related to investigational product, nor was the dose of investigational product changed. No serious adverse events were reported.

Non-opioid concomitant medications included acetylsalicylic acid for his heart condition, allopurinol for gout, amitriptyline hydrochloride, etodolac, felodipine, and lidocaine for back pain, bisacodyl as rescue laxative therapy, cefpodoxime proxetil, moxifloxacin, piperacillin sodium + tazobactam sodium, and vancomycin for an infection in the iliac region, citalopram hydrobromide for depression, clopidogrel bisulfate as a blood thinner, diphenhydramine hydrochloride for cough, furosemide and metoprolol for hypertension, guaifenensin + dextromethorphan for cough, ipratropium for asthma, levothyroxine for hypothyroidism, nicotinic acid and simvastatin for high cholesterol, and omeprazole for gastroesophageal reflux disease.

12.7.2.5   Patient GSK014-8523: Metastatic Prostate Cancer

Subject 8523 was a 68-year-old male, BMI = 31, former smoker (one pack per day from 1956 to 2002), treated with morphine (stable 90 mg oral extended-release total daily dose) as scheduled maintenance opioid therapy for relief of degenerative disk disease pain. At study entry the subject had suffered from this condition for 15 years and had received opioid therapy for 2 years, including the current morphine therapy for 2 years with less than 1 year at stable dose. The subject also used hydrocodone (20 mg oral total daily dose) for breakthrough therapy.

Subject 8523 began investigational product on 15 Nov 05, was > 80% compliant with taking his investigational product, and had completed < 2 months of the 12-month treatment period when he withdrew from the study due to the adverse event of prostate cancer. The subject received investigational product for 45 days with no interruptions, with a treatment stop date of 29 Dec 2005.

The subject was randomized to placebo capsules twice daily.

The subject developed severe pneumonia and exacerbation of pre-existing chronic obstructive pulmonary disease (COPD) on 29 Dec 2005 and was admitted to the hospital. Upon chest x-ray for these conditions "ivory vertebrae" were noted, suggestive of metastatic prostate disease. Bone scan and magnetic resonance imaging (MRI) on 30 Dec 2005 showed multiple lesions consistent with metastatic neoplastic disease. Prostate-specific antigen (PSA) was measured and shown to be elevated at 148.8, and a presumptive diagnosis of metastatic prostate cancer was made and reported as a serious adverse event on 31 Dec 2005, 47 days after the start of investigational product. The subject was discharged from the hospital on 03 Jan 2006. A copy of the medical report documenting the late Dec 2005 findings and indicating start of treatment for prostate cancer was received by GSK. The subject expired 05 Feb 2006 due to prostate cancer and complications from metastases.

Additional medical conditions included COPD, acontractile bladder, and hyperlipidemia.

Non-opioid concomitant medications included acetylsalicylic acid for heart prophylaxis, bicalutamide, leuprolide and zoledronic acid for metastatic prostate cancer, ergocalciferol +

calcium as a health supplement, fluoxetine hydrochloride for anxiety, gemfibrozil and lovastatin for hyperlipidemia, lansoprazole for gastroesophageal reflux, levosalbutamol hydrochloride, salbutamol, salmeterol xinafoate + fluticasone propionate, and tiotropium bromide for COPD, meloxicam for osteoarthritic spine, and zolipidem tartrate for insomnia.

12.7.2.6   Patient GSK014-16803: Squamous Cell Lung Carcinoma

Subject 16803 was a 63-year-old Caucasian male, BMI = 25, non-smoker, treated with fentanyl (stable 1200 mcg transdermal) as scheduled maintenance opioid therapy for relief of back pain. At study entry the subject had suffered from this condition for 15 years and had received opioid therapy for 15 years, including the current opioid therapy for 7 years, with 5 years at stable dose. The subject used hydromorphone (24 mg oral total daily dose) and morphine (60 mg oral total daily dose) for breakthrough therapy.

Subject 16803 began investigational product on 07 Dec 2005, was > 80% compliant with taking investigational product, and had completed < 2 months of the 12 month treatment period when he withdrew due to the serious adverse event of squamous cell carcinoma.. The subject received investigational product for 55 days with no interruptions, with a treatment stop date of 30 Jan 2006.

The subject was randomized to placebo capsules twice daily.

A serious adverse event of squamous cell carcinoma of the right lung was reported on 24 Jan 2006, 49 days after the start of investigational product. The neoplasm in question had not been diagnosed prior to participation in the study. Events leading up to this diagnosis were as follows. After enrollment into the study, the subject informed the investigator that he had a spot on the lung for several years and was getting annual x-ray follow-up exams. vAn x-ray done after study start indicated that the spot had enlarged. A PET scan done 19 DEC 2005, 12 days after start of investigational product, showed increased uptake consistent with inflammation or tumor. At the suggestion of the primary care physician, the subject subsequently had a lung biopsy which revealed squamous cell carcinoma. A confirmatory cancer pathology report received by GSK documented the squamous cell carcinoma from a fine-needle biopsy that was performed 17 Jan 2006. The event was not resolved at time of reporting and the subject withdrew from the study.

Non-opioid concomitant medications included acetylsalicylic acid for prophylaxis, carvedilol and lisinopril for hypertension, celecoxib for inflammation, citalopram hydrochloride for depression, ezetimibe for hyperlipidemia, gabapentin for back pain/spasms, lovastatin, and simvastatin + ezetimibe for hyperlipidemia, omeprazole for gastroesophageal reflux disease, paracetamol + caffeine + butalbital for headaches, tizanidine for sleep and multivitamin for prophylaxis.

12.7.2.7   Patient GSK014-18857: Melanoma

Subject 18857 was a 77-year-old Caucasian female, BMI = 43, non-smoker, treated with oxycodone (stable 30 mg oral total daily dose) as scheduled maintenance opioid therapy for relief of back pain. At study entry the subject had suffered from this condition for 3 years and had received opioid therapy for 3 years, including the current opioid therapy for 3 years at stable dose. The subject used morphine (30 mg oral extended-release total daily dose) for breakthrough pain.

Subject 18857 began investigational product on 13 Jan 2006, was > 80% compliant with taking her investigational product, and successfully completed the study comp0sed of a 1-week screening period, 12-month treatment period, and 2-week follow-up period. The subject received investigational product for 357 days with no interruptions, with a treatment stop date of 04 Jan 2007.

The subject was randomized to placebo capsules twice daily.

A non-serious adverse event of right ear melanoma was reported in the subject report form with an onset date of 06 Jul 2006, 175 days after the start of investigational product.

The subject presented 26 Apr 2006 with a painful right ear lesion that had been present for 2 months from which she had been able to express fluid and blood. A physical exam showed a 4 x 4 mm purplish fluctuant lesion. Clinical impression was of a cyst or a neoplasm. The lesion was lanced with minimal fluid expressed. The subject was advised to apply hot compresses. On 05 May 2006 the subject was seen again and the lesion was unchanged. The plan was for a dermatological referral. Per subject report to the study coordinator, the lesion was removed on an outpatient basis and the diagnosis was of "melanoma." No pathology or surgical reports have been provided to GSK. Subsequent clinic reports through Apr 2007 did not refer to the lesion. HEENT exams do not note any ear findings.

A non-serious adverse event of a left breast lump was reported as an incidental finding on 11 Jan 2007, 364 days after the start of the investigational product. The neoplasm in question had not been diagnosed prior to participation in the study. Findings upon mammogram and ultrasound were negative and there was no further evaluation. No confirmatory pathology report was provided to GSK. No further follow-up has been reported to GSK. The event was considered unresolved in the subject report form.

Non-opioid concomitant medications included acetylsalicylic acid for heart health, amitriptyline hydrochloride as a sleep aid, calcium and multivitamins for health maintenance, escitalopram oxalate for depression, folic acid, methotrexate, and prednisone for rheumatoid arthritis, glucosamine for joint health, and rosuvastatin calcium and valsartan for hypertension.

12.7.2.8   Patient GSK011-1374: Pancreatic Carcinoma

Subject 1374 was a 64-year-old black female, BMI = 17, treated with codeine for the last 17 years (stable dose of 240 mg total daily dose last 17 years) as scheduled maintenance opioid

therapy for rheumatoid arthritis. Subject 1374 was a smoker (~21 cigarettes per week). On 9 Aug 2004, 4 days after initiating treatment with Investigational Product, the subject was admitted to the hospital after developing severe abdominal pain. On the day of admission, a CT scan of the abdomen resulted in a diagnosis of inoperable pancreatic cancer. Emergency endoscopic retrograde cholangiopancreatography (ERCP) was performed and a stent was placed in the biliary tree. Cell washings were taken for further diagnosis of the mass; results were not available at the time of reporting. The subject was started on dimenhydrinate (Gravol), pethidine (Demerol), heparin, and an unspecified intravenous antibiotic. The subject was withdrawn from the study, and the event recorded as resolved with sequelae. The investigator considered the pancreatic cancer to be life-threatening and unrelated to the investigational product. A pathology report was not received by GSK.

The investigator reported that the subject was subsequently lost to follow-up.

Other medical conditions notable included polio, osteoporosis, depression, anemia, and headache.

Non-opioid concomitant medications included Tylenol #3, prednisone (Apo-prednisone), meloxicam, methotrexate for rheumatoid arthritis; didrocal, CaCO3, Vitamin D for osteoporosis; folic acid (Apo-folic) for prophylaxis; lorazepam for insomnia; colace for chronic constipation; and Celexa for depression.

12.7.2.9   Patient GSK011-2077: Adenocarcinoma of the Lung

Subject 2077 was a 63-year-old Caucasian male, BMI = 30, treated with oxycodone for the last 9 years (stable dose of 40 mg total daily dose last 10 months) as scheduled maintenance opioid therapy for relief of neuralgia. Subject 2077 had a history of tobacco abuse (70 cigarettes per week) but stopped smoking since Apr 2004.

The subject had a pulmonary cancer, but no thoracic cancer in 1994 for which he was operated. Consequently, the subject had no tumor and no recidivation had occurred. In Feb 2003, the subject had increasing shortness of breath, which resolved by 07 Mar 2003 and was considered related to an exacerbation of COPD. In Apr 2004, the subject again developed increasing shortness of breath. A chest X-ray was negative at this stage, and the symptom was considered as a worsening of concurrent condition of COPD and recorded as a non-serious AE. The subject also reported increasing tiredness which was attributed to the COPD exacerbation.

On 10 Sep 2004, 229 days following initiation of Investigational Product (approximately 6 months after completing study), the subject developed increasing shortness of breath, pain, and loss of weight. A chest X-ray and CT scan showed a left lung tumor with intrapulmonary metastases bilaterally. The subject was hospitalized and the event was considered disabling and life threatening. A bronchial lavage revealed non small cell carcinoma with bilateral metastasis. Pain was managed with morphine, diclofenac and fentanyl. Chemotherapy was initiated with cisplatin and etoposide from 27 Sep 2004 to 10 Oct 2004, and again from 18 Oct 2004 to

25 Oct 2004. A third cycle was omitted because of poor general condition. A further chest X-ray of 10 Nov 2004 showed stable disease, and no progression.

On further follow-up, the investigator reported there was no reasonable causal relationship between the occurrence of a bronchial carcinoma and the investigational product. The event had not resolved at the time of reporting.

Other medical conditions included COPD, pulmonary cancer (1994), sinus tachycardia, arterial hypertonia, adipositas, sleep apnea syndrome, and ankle edema.

Non-opioid concomitant medications included Enalapril and HCT-CT for hypertension; Metoprolol for tachycardia; Neurontin for pain; Salbuterol DA and Pulmicort DA for COPD.

12.7.2.10 Patient GSK012-824: Colon Cancer

Subject 824 was a 55-year-old Caucasian male, BMI = 26, treated with tramadol for the last 3 years (stable dose of 400 mg total daily dose last 1 year) as scheduled maintenance opioid therapy for relief of visceral pain. Subject was a non-smoker. The subject's past medical history also included darker stools, sigmoid colon cancer (1998), and sigmoidectomy. The subject was not known to have metastatic disease prior to the onset of the study. On 5 Apr 2006, 106 days after the start of the investigational product, the subject, a non-smoker, developed a neoplasm of the cecum. The day before, the subject reported seeing dark blood during defecation and dark, but not black, stools. A colonoscopy revealed a bleeding tumor in the cecum. The subject was treated with 5-fluorouracil and leucovorin and underwent a right hemi-colectomy. Histopathological examination of biopsies taken during the colonoscopy and hemi-colectomy revealed tubular colon adenocarcinoma with metastases in 1/13 lymph nodes and one metastatic focus in the omentum. This appears to have been a second malignancy. A pathology report was not received by GSK, however procedural reports revealed a tumor of ascending colon, 5 cm in diameter, causing concentric narrowing of the intestinal lumen.

The event occurred after the investigational product had been discontinued and was unresolved at the time of reporting.

Other medical conditions included anemia.

Non-opioid concomitant medications included Gripex (paracetamol) for flu; Ibuprom Max for headache; Polopiryna S for fever, headache, and sore throat; Manti for heartburn; calcium for subfebrile body temperature; and Falvit for anemia.

12.7.2.11 Patient GSK012-6483: Chronic Lymphocytic Leukemia

Subject 6483 was a 51-year-old Caucasian female, BMI = 29, treated with Duragesic patch for the last 6 years (stable dose of 2400 mg total daily dose last 5 years) as scheduled maintenance opioid therapy for relief of peripheral neuropathy. The subject was a non-smoker. Opioid breakthrough therapy was percocet (30 mg). On 2 Mar 2006, the subject, suffered undisclosed

symptoms of chronic lymphocytic leukemia (CLL). This diagnosis had not been made prior to the study; however, the Principal Investigator had been watching the patient in anticipation of development of CLL. The Principal Investigator believed that this was an adverse event and not a pre-existing condition.

The event was not resolved at the time of reporting.

Subject 6483 was randomized and received alvimopan 0.5 mg twice daily from 20 Dec 2005 to 17 Mar 2006.

Other medical conditions included mitral valve prolapse, depression, anxiety, symptoms of menopause, insomnia, and gastritis.

Non-opioid concomitant medications included, Norpace for mitral valve prolapse; Ativan and Xanax for anxiety; Neurontin for neuropathy; Progesterone for hormone replacement therapy; Trazadone for depression and headaches; Ambien for insomnia; Provigil for increased energy; Aciphex for gastritis; and Remeron for depression.

12.7.2.12 Patient GSK012-10092: Breast Cancer

Subject 10092 was a 72-year-old Caucasian female, BMI = 37, treated with MS Contin for the last 13 months (stable dose of 30 mg total daily dose last 13 months) as scheduled maintenance opioid therapy for relief of back pain. The subject has taken other, unspecified opioids for back pain for the past 10 years. Subject was a non-smoker. The subject was not known to have neoplastic disease prior to the onset of the study. On 14 Mar 2006 an adverse event of breast cancer was reported. The subject was admitted to the hospital for a lumpectomy and lymphectomy after tc-99m scan showed sentinel nodes as well as in situ ductal cancer. A confirmatory pathology report was provided to GSK. The diagnosis was in situ carcinoma that was focally present, nuclear grade 3, necrosis present, less than 1% of the tumor. Biopsy of the left axillary contents via dissection yielded metastatic ductal carcinoma involving 15 of 23 lymph nodes. The investigator considered that there was no reasonable possibility that the breast cancer may have been caused by investigational product.

Medical history includes high blood pressure, irregular heart beat, shortness of breath, recent URI, asthma, COPD/emphysema, bronchitis, back pain, neck pain, headaches, arm or leg weakness/numbness, fibromyalgia, arthritis, gastric reflux, stomach ulcers, dentures.

Additional opioid medications included MSIR, morphine, Lortab, Dilaudid, fentanyl, Percocet.

Non-opioid concomitant medications included Nexium and Prevacid for GERD; Singulair, Spiriva, Advair, Albuterol, and Prednisone for asthma; Hyzaar for hypertension; Fosamax for osteoporosis; Lexapro for depression; Benadryl for atopic dermatitis; Tylenol Sinus and Tylenol PM for headache; aspirin for back pain; Augmentin for breast infection; Ambien for insomnia; Nuprin and Tylenol for arthritis; coral calcium, Vitamin D, Vitamin C, and magnesium for nutritional supplementation; lactated ringers and TC 99M for breast cancer; NaCl 0.9%,

Marcaine 0.25%, Tobramycin, Zofran, Hydralazine, Ancef, Propofol and Seconal for left wrist fracture.

12.7.2.13 Patient GSK013-905: Breast Cancer

Subject 905 was a 46-year-old Caucasian female, BMI = 26, treated with morphine for the less than 1 year (stable dose of 100 mg total daily dose last 2 months) as scheduled maintenance opioid therapy for relief of failed back pain.

Subject 905, a non-smoker, presented with breast cancer on 3 May 2006. The subject had a history of fibroadenoma since 2000, with annual mammography as follow up. On 28 Apr 2006, the subject underwent a mammogram and biopsy; the biopsy results showed ductal infiltrative cancer. On 21 Jun 2006, the subject underwent a tumorectomy and axillary emptying with radiotherapy to be scheduled. No confirmatory pathology report has been made available to GSK. The event resolved on 21 Jun 2006.

Subject 905 was randomized and received alvimopan 0.5 mg twice daily from 3 Mar 2006 to 26 May 2006.

Non-opioid concomitant medications included alprazolam for anxiety, amitriptyline and pregabalin for neuropathic pain, and lansoprazole for gastritis.