Alvimopan: a peripheral acting μ-opioid-receptor antagonist used for the treatment of postoperative ileus

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Alvimopan is a peripherally acting μ-opioid-receptor antagonist that has been investigated for the treatment of postoperative ileus. Postoperative ileus, defined as a disruption in normal bowel motility, is a significant cause of morbidity and increased hospital costs for the surgical patient. The etiology of postoperative ileus is multifactorial and includes neurogenic, inflammatory and pharmacologic influences. Until this point, there has been no successful pharmacotherapy to treat bowel hypomotility following abdominal surgery. Alvimopan blocks the negative effects of opioids in the gastrointestinal tract without compromising central opioid-based analgesia. Alvimopan has been shown to significantly decrease the effect of narcotics on bowel function, hasten the return of bowel function and decrease hospital stay in the postsurgical patient, without affecting the analgesic effect of opioids. Alvimopan, at the time of writing, is not yet available for general use and is awaiting FDA approval. Currently, there is no FDA-approved pharmacologic agent for the treatment of postoperative ileus.

Keywords: ADL 8-2698, alvimopan, ileus, opioid antagonist, piperidines

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Postoperative ileus

Postoperative ileus (POI) is defined as an impairment of gastrointestinal (GI) motility after abdominal or other surgery and is characterized by abdominal distension, lack of bowel sounds, accumulation of gas and fluids in the bowel, and delayed passage of flatus and defecation [1,2]. It is considered a normal and inevitable response to laparotomy and other major surgical procedures under general anesthesia [1–3].

Patients with POI experience signs and symptoms such as nausea, vomiting, abdominal distension, bloating, lack of bowel sounds, delayed passage of flatus or stool, and abdominal cramping and pain [2,4–6]. POI can also lead to delayed mobilization following surgery and can impede resumption of normal fluid intake, thereby increasing the risk of more serious sequelae, including pulmonary complications, delayed wound healing, infection, and catabolism [2,4,7]. Consequently, such symptoms and complications can delay patient recovery. POI is a principal contributor to patient morbidity and prolonged hospitalization after surgery and a significant factor of hospital readmission and increased costs [2,4,8].

POI may affect all parts of the GI tract but with differential recovery of normal function [5,9]. Small intestine function generally normalizes first, often within several hours of surgery [2,5]. Gastric motility usually returns to normal within 24–48 h after surgery. The colon is the final portion of the GI tract to regain normal motility, which usually occurs within 48–72 h after surgery, but can take as long as 5 days [2,5,10,11]. Motility normalizes in the proximal colon first and then progresses to the transverse and left colon. Colonic dysfunction is most frequently the factor that limits resolution of POI [5,10].

In observational studies, the natural course of POI following abdominal surgery has been described [12]. It has been shown that, in patients undergoing abdominal surgery, most tolerate solid food and have a bowel movement by postoperative day 4. The majority of patients are discharged by postoperative day 6, but 24.4% require a prolonged hospital stay or readmission. The incidence of nausea is the highest on the day of surgery and decreased thereafter, whereas vomiting is uncommon on the day of surgery but increased slightly on postoperative days 1 to 6. The incidence of postoperative nasogastric tube insertion is highest on postoperative day 2 [12].

Mechanisms of postoperative ileus

At least three major mechanisms are involved in causing manipulation-induced POI – neurogenic, inflammatory and pharmacologic mechanisms [13]. Physiologically, this includes perioperative release of catecholamines [14], inhibitory effect of opiates on GI motility [15], reflex inhibition of motility by activation of the sympathetic nervous system through spinal

afferents [16], and release of a panel of mediators such as calcitonin-gene-related peptide (CGRP) [17], nitric oxide (NO) [18], vasointestinal polypeptide (VIP) [19] and substance P [19].

These different mechanisms are not seen to be independent of each other, but work cooperatively in causing POI. However, the importance of each contributing mechanism may vary over time, with considerable overlap and possible interactions. The duration of POI correlates with the degree of surgical trauma and is most extensive after colonic surgery. However, POI may develop after all types of major surgery [13].

Contribution of opioids to postoperative ileus

Of the three most prominent opioid receptor subtypes (μ, κ and δ) the μ-opioid receptor is the principal receptor involved in pain management with most currently marketed opioid analgesic drugs [20]. Opioids used in pain management maintain selectivity for the μ-opioid receptor at normal therapeutic doses. However, stimulation of the μ-opioid receptor also results in decreased GI motility [20,21]. High concentrations of opioid receptors have been found throughout the GI tract [20,22,23], and activation of these receptors by opioid analgesics has a direct local effect on bowel function [23–25].

Opioids are of major importance in the pathogenesis of POI as a result of their depressing effects on GI transit [26,27]. The GI effects of opioids are mediated primarily by receptors within the bowel, whereas spinal and cerebral opioid receptors play a minor role [26,28,29]. The receptor primarily involved in pain control and delay in GI transit is the μ-receptor [26,27]. Administration of the nonselective opioid antagonist naloxone reverses gut paralysis, but systemically absorbed naloxone enters the CNS with withdrawal or loss of analgesia [26,30]. The ratio between analgesic and constipating effect of morphine is approximately four to one, that is, four-times more morphine is needed to obtain an analgesic effect than to slow GI motility [26,30]. With repeated opioid administration for pain relief, tolerance to the analgesic effect subsequently develops; however, tolerance to the GI adverse effects does not develop [26,30].

Costs

POI adds considerably to hospital costs by prolonging hospital stay. One study demonstrated that POI has been associated with both a longer hospital stay (11.5 vs 5.5 days) and increased costs per patient (US$18,877 vs US$9460). It is estimated that total annual costs attributed to managing POI approaches $1.5 billion [31].

Treatments

Historical

Treatment of POI is largely supportive and historically has consisted of routine nasogastric intubation (NGT), intravenous hydration and bowel rest. In recent studies, however, extended NGT use has not been shown to provide a beneficial effect for the management of POI. Rather, NGT use beyond the day of surgery increases patient discomfort and may increase postoperative complications [12,32,33].

Pharmacologic treatments

Several pharmacological agents have been employed to resolve POI – propranolol [34–36], dihydroergotamine [37,38], neostigmine [39,40], erythromycin [41,42], cisapride [43–50], metoclopramide [51–54], cholecystokinin [55], ceruletide [56,57], and vasopressin [58], most with either limited effect or limited applicability because of adverse effects [26].

Epidurals

The advantages of postoperative epidural local anesthetics are many: superior pain relief allowing early mobilization; opioid-sparing thereby avoiding opioid-related adverse effects such as POI; and the important stress-reducing effects of epidural local anesthetics obtained by blocking of afferent input from the surgical wound [26]. Anesthetic agents administered via an epidural catheter have been found to decrease the duration of POI in several studies, possibly as a result of blockade of inhibitory sympathetic reflexes at the cord level [5]. In a review of ten studies comparing epidural anesthesia with systemic opiates, seven showed a faster return of bowel function in the epidural group [5]. The location of the epidural catheter is important, since successful blockade of inhibitory spinal reflexes is accomplished only with thoracic administration of the anesthetic agent [5].

Other

Other methods of reducing POI have also been somewhat effective in reducing POI. Perioperative administration of intravenous fluid in excess may contribute to POI, possibly by delaying GI motility as a result of the presence of edema in the intestinal wall. Studies have demonstrated decreased postoperative morbidity with the use of limited intravenous fluid administration protocols [26,59,60].

Minimally invasive surgery has also been effective in decreasing POI for a number of abdominal procedures. Laparoscopic colon surgery, when compared with open surgery, has been shown in a recent meta-analysis to lower perioperative mortality rates, lower wound complication rates, and decrease blood loss during surgery [61]. Other advantages of laparoscopic surgery appear to be decreased postoperative pain, decreased narcotic usage and earlier return of bowel function. This study also demonstrated no significant differences in overall and surgical complication rate, anastomotic leak rate, reoperation rate and oncologic clearance between open and laparoscopic procedures. It must be emphasized that, despite these results, not every patient is a candidate for a minimally invasive procedure [61,62].

Also, decreasing the amount of postoperative morphine usage with the administration of NSAIDs, such as ketorolac, has been shown to be effective in decreasing the duration of POI [63]. Similar results have been documented with COX-2 inhibitors, such as valdecoxib, but recent findings of cardiovascular (CV) side effects of COX-2 inhibitors has limited their usage [64].

Introduction to the compound

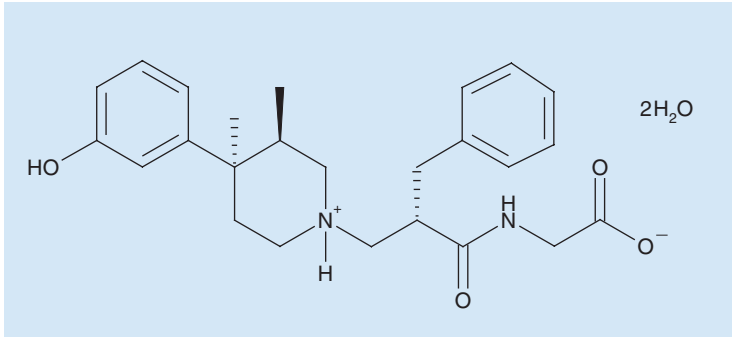
Chemistry

Alvimopan (ADL 8–2698) is a novel, peripherally restricted trans-3,4-dimethyl-4-(3-hydroxyphenyl) piperidine μ-opioid antagonist. ADL 8–2698 is a small, totally synthetic molecule ($C_{25}H_{32}N_2O_4{\cdot}2H_2O$) (**Figure 1**). Its moderately large molecular weight, zwitterioinic form, and polarity limit GI absorption and prevent penetration of the blood–brain barrier [20,65,66].

Pharmacodynamics

In vivo and *in vitro*, alvimopan is a potent antagonist of peripheral μ-receptors. Radioligand binding assays have confirmed the high affinity of Alvimopan for the μ-opioid receptor (K_i = 0.77 nmol/l) and lower affinities for the δ (K_i = 4.4 nmol/l) and κ (K_i = 40 nmol/l) receptors [20,65,66]. Alvimopan is more potent than naloxone (K_i = 3.7 nmol/l) as a μ-opioid receptor antagonist [20,66]. In animals, alvimopan antagonizes centrally mediated, morphine-induced analgesia only at relatively high doses, with very high plasma concentrations needed to cross the blood–brain barrier. After intravenous administration, alvimopan is approximately 200-times more potent at blocking peripheral verses central μ-receptors [20,66]. After oral administration, alvimopan is also highly active. Alvimopan was evaluated in animal studies to measure its peripheral and central μ-opioid receptor antagonist activities [20,65]. Peripheral antagonist activity was determined by the compound's ability to precipitate diarrhea in morphine-dependent mice, and its central antagonist activity was measured by determining its ability to antagonize morphine-induced analgesia. After oral administration, the dose calculated to produce diarrhea in 50% of the mice treated (ED_{50}) was 1.1 mg/kg, which was two-times greater than the ED_{50} of naloxone [20,66]. Alvimopan inhibited morphine-induced constipation in the mouse charcoal meal test without reversing analgesia. The drug prevented morphine-induced inhibition of transit for up to 8 h [20,66].

Figure 1. Alvimopan.



Pharmacokinetics & metabolism

In dogs, intravenous administration of alvimopan provided dose-dependent increases in peak plasma concentrations and plasma area under the concentration–time curve. However, as a result of poor systemic absorption, oral doses up to 100 mg/kg produced low plasma concentrations (mean C_{max} = 92.9 ng/ml), which resulted in an oral bioavailability of approximately 0.03%. The half-life of alvimopan is estimated to be approximately 10 min after intravenous administration in dogs and rabbits [20,66].

Alvimopan has been shown to be a peripherally restricted opioid antagonist that does not penetrate the CNS. Whole-body autoradiography studies in rats were conducted to determine the distribution of intravenous and oral alvimopan throughout the body [20]. After intravenous administration, alvimopan distributed to most parts of the body except the spinal cord and brain. Confirming autoradiographic studies have been reported [66], showing that most radiocarbon associated with an orally administered

dose of [14C] alvimopan is detected throughout the GI tract, much of it within the gut wall, with minimal evidence of distribution to the blood or other tissue in rats [20].

Clinical efficacy

Comparative data from clinical trials are shown in **Table 1** (GI-2 and -3 are 2- and 3- component composite end points comprising times to first tolerance of solid food, first bowel movement and first flatus).

Preliminary studies

Phase I and II studies were undertaken to test the safety and dosage efficacy in human subjects [67,68]. An early study performed on healthy volunteers demonstrated that ADL-8–2698 prevented the prolonged GI transit time associated with morphine administration. This study also demonstrated that analgesia and papillary constriction were unaffected by alvimopan administration [67]. Another study by Taguchi *et al.* demonstrated that alvimopan (6 mg dosage), when administered to patients undergoing either colorectal surgery or total hysterectomy, decreased median time to flatus from 70 to 49 h, decreased median time to first bowel movement from 111 to 70 h, and decreased median time to hospital discharge from 91 to 68 h. This study was somewhat limited due to the small, nonuniform patient population. Also, the majority of patients underwent total hysterectomy, which does not typically produce a prolonged ileus [68].

Phase III trials

In the first Phase III study by Delaney *et al.*, 449 patients in 40 US centers undergoing partial colectomy or simple or radical hysterectomy were randomized to receive alvimopan 6 mg (n = 152), alvimopan 12 mg (n = 146) or placebo (n = 153) orally 2 h before surgery and twice daily thereafter until discharge or for up to 7 days [69]. The primary efficacy end point, time to return of GI function, was a composite measure of passage of flatus or stool and the ability to tolerate solid food. Secondary end points included time until the hospital discharge order was written. Mean time to GI recovery was significantly reduced in patients treated with alvimopan 6 mg vs placebo (hazard ratio [HR]: 1.45; p = 0.003), with a smaller reduction seen with alvimopan 12 mg (HR: 1.28; p = 0.059). The mean time to GI recovery (GI-3) was 86.2 h for patients treated with alvimopan 6 mg, which was 14.1 h less than the mean recovery time for patients administered placebo (100.3 h).

Patients undergoing bowel resections seemed to benefit the most from receiving alvimopan and, alternately, primary end points for the alvimopan cohort patients undergoing simple hysterectomies were not significantly different from placebo. Overall, mean time to hospital discharge order being written was significantly accelerated in patients treated with alvimopan 6 mg (HR: 1.50; $p < 0.001$). Time to hospital discharge order written was significant in the alvimopan 6 mg group (108 vs 122 h placebo; $p < 0.001$), but not in the alvimopan 12 mg group (115 vs 122 h placebo; p = 0.17) [69]. The most common treatment-emergent adverse events across all treatment groups were nausea, vomiting and hypotension; the incidence of nausea and vomiting was reduced by 53% in the alvimopan 12 mg group [69].

In a study by Wolf *et al.*, 469 patients in 34 US centers undergoing bowel resection (n = 451) or radical hysterectomy (n = 18) met study criteria and were randomized to receive alvimopan 6 mg, alvimopan 12 mg or placebo orally more than 2 h before surgery, then twice daily until hospital discharge [70]. Time to recovery of GI function was accelerated for the alvimopan 6 mg (HR: 1.28; $p < 0.05$) and 12 mg (HR: 1.54; $p < 0.001$) groups with a mean difference of 15 and 22 h, respectively, compared with placebo. The time to hospital discharge order written was also accelerated in the alvimopan 12 mg group (HR: 1.42; p = 0.003) with a mean difference of 20 h compared with placebo. The incidence of adverse events was similar among treatment groups, as were the daily and maximum pain scores [70].

In a study by Hertzog *et al.*, alvimopan was evaluated in patients undergoing simple total hysterectomy in 519 women randomized to 12 mg alvimopan versus placebo twice daily for a minimum of 7 days [71]. Alvimopan significantly accelerated the time to first bowel movement (HR: 2.33; $p < 0.001$). Average time to first bowel movement was reduced by 22 h, with more frequent bowel movements and better bowel movement quality found in the treatment cohort. Unlike previous Phase III studies, alvimopan was given for a minimum of 7 days, regardless of hospital length of stay. Most common adverse events were nausea, vomiting and constipation, and less than 5% of patients discontinued use because of adverse events [71].

In a recent study by Viscusi *et al.*, patients undergoing open laparotomy (bowel resection, n = 418; hysterectomy, n = 197) were randomized to receive alvimopan 6 or 12 mg or placebo orally up to 2 h before surgery and then twice daily until hospital discharge (up to 7 days) [72]. Primary efficacy end point was time to GI recovery and hospital length of stay. Alvimopan was found to significantly shorten time to GI recovery for both 6 and 12 mg doses when the analysis was adjusted for covariates (sex and surgery duration), and was well tolerated [72].

The value of alvimopam in long-term relief of delayed bowel function in patients receiving narcotics for chronic pain management is less clear. Recent preliminary analysis of study 014, which is a Phase III, double-blind, placebo-controlled, 12-month study designed to evaluate the long-term safety and tolerability of alvimopan 0.5 mg twice daily in patients taking opioids for chronic noncancer pain and experiencing opioid-induced bowel dysfunction. This study enrolled 805 patients and randomized 2:1, with 538 patients receiving alvimopan and 267 patients receiving placebo. Patients were enrolled starting in August 2005 with completion of the study this year.

Preliminary results from this study showed an increased incidence of myocardial infarction (MI) and in all CV serious adverse events of alvimopam vs placebo (MI: 1.30 vs 0%; CV events: 2.60 vs 1.12%) (data from Adolor website). All of the CV events occurred in patients with known CV disease or who were at high risk for CV disease. The majority of adverse events occurred within the first 12 weeks of treatment.

This study also showed an imbalance in the incidence of benign and malignant neoplasms. A total of 15 neoplasms were reported in patients receiving alvimopam (2.8%) versus two in patients receiving placebo (0.7%). Four of the alvimopan patients (0.7%) and one placebo (0.4%) patient developed neoplasms considered serious events.

In the combined analysis of the POI studies there was no increase in MI or other CV adverse events.

As a result of these recent findings seen in the preliminary evaluation of data from this one specific study, the sponsoring companies have stopped ongoing studies in patients with chronic pain. A final decision regarding further testing will be made after a thorough analysis has been completed.

Current data suggest that, when available, dosing in POI patients should be 12 mg starting preoperatively and continued twice daily for up to 7 days postoperatively. At present there is no way to predict which patients are most likely to develop POI.

Postmarketing surveillance

Alvimopan at the time of writing is not yet available for general use and is awaiting FDA approval. Currently, there is no FDA-approved pharmacologic agent for the treatment of POI.

Safety & tolerability

Acute and subacute toxicology studies revealed that alvimopan has a large therapeutic index. Over a 30-day period, peak plasma levels in dogs were proportional to intravenous doses and exceeded 4000 ng/ml after a 2 mg/kg intravenous dose. Oral doses up to 200 mg/kg in rats and up to 100 mg/kg in dogs were evaluated in 6-month safety studies. Neither study revealed important toxicologic findings. In addition, no reproductive or developmental safety issues were identified in preliminary *in vitro* and *in vivo* studies in animals [23].

A Phase I ascending-dose study evaluated the clinical safety and dose-related side effects of alvimopan in 44 healthy volunteers. This single-center, double-blind, placebo-controlled trial began with a 3-week screening period, followed by a 4-day oral dosing period in which subjects were randomized to receive placebo (n = 5) or alvimopan 0.25, 0.5, 2.0, 6.0 or 18.0 mg three-times daily (n = 4, 11, 9, 9, and 6, respectively). The most common adverse events reported in healthy volunteers treated with ADL 8–2698 were dose related and included abdominal pain (31%), flatulence (31%) and diarrhea (21%). Nausea, polyuria and nervousness also were reported. Side effects were dose related and occurred infrequently at lower doses. No serious adverse events were reported. Abnormal laboratory values were reported in two patients; both patients had clinically significant elevations in liver function tests (aspartate aminotransferase, alanine aminotransferase, and lactic [acid] dehydrogenase; maximum increases of 2.5- to 4.0-times the upper limits of normal) that subsequently normalized without intervention. No dose-related hepatotoxicity was reported. Overall, this study confirmed that alvimopan is generally well tolerated at doses up to 54 mg daily over 4 days without occurrence of serious adverse events [23].

Table 1. Overview of Phase III alvimopan trials .

Authors	Design	Treatment groups	Primary end points	Secondary end points	Primary outcomes	Secondary outcomes	Ref.
Wolff *et al.* (2004)	DB, PC, R, MC, parallel-group trial, patients undergoing large or small bowel resection or radical hysterectomy	MITT population (n = 469): alvimopan 6 mg (n = 155) vs alvimopan 12 mg (n = 165) vs placebo (n = 149), PO 2 h prior to surgery, then b.i.d. until hospital discharge or up to 7 days	Time to recovery of GI function (GI-3)	Time to recovery of GI function (GI-2), time to hospital discharge, readiness for discharge, average daily postoperative opioid use, average daily pain scores, incidence of chest x-ray or NGT insertion postsurgery	Mean time to recovery of GI-3 decreased with alvimopan 6 mg (105 vs 120 h placebo; HR: 1.28; 95% CI: 1.00-1.64; $p < 0.05$) and 12 mg (98 vs 120 h placebo; HR: 1.54; 95% CI: 1.21-1.96; $p < 0.001$)	GI-2 faster with alvimopan 6 mg (113 vs 133 h placebo; HR: 1.38; 95% CI: 1.07-1.79; $p = 0.0013$) and 12 mg (105 vs 133 h placebo; HR: 1.67; 95% CI: 1.30-2.15; $p < 0.001$), time to discharge faster with alvimopan 6 mg (133 vs 146 h placebo; HR: 1.25;95% CI: 0.98 to 1.58; $p = 0.070$) and 12 mg (126 vs 146 h placebo; HR: 1.42; 95% CI: 1.12-1.79; $p = 0.003$, no meaningful differences in requirement for postoperative opioid use between all groups, postoperative VAS pain scores comparable between all groups, incidence of NGT insertion reduced with alvimopan 6 mg (8.4 vs 14.8% placebo) and 12 mg (4.8 vs 14.8% placebo; $p = 0.004$)	[70]
Delaney *et al.* (2005)	DB, PC, R, MC, patients undergoing bowel resection, radical or simple hysterectomy	MITT population (n = 424): alvimopan 6 mg (n = 141) vs alvimopan 12 mg (n = 138) vs placebo (n = 145), PO 2 h prior to surgery, then b.i.d. until hospital discharge or up to 7 days	Time to recovery of GI function (GI-3)	Time to recovery of GI function (GI-2), time to hospital discharge, readiness for discharge, average daily postoperative opioid use, average daily pain scores, incidence of chest x-ray or NGT insertion postsurgery	Mean time to recovery of GI-3 decreased with alvimopan 6 mg (86.2 vs 100.3 h placebo; HR: 1.45;95% CI: 1.13 to 1.85; $p = 0.003$) and 12 mg (92.8 vs 100.3 h placebo; HR: 1.28; 95% CI: 0.99-1.64; $p = 0.059$)	GI-2 faster with alvimopan 6 mg (99.5 vs 114.7 h placebo; HR: 1.46; 95% CI: 1.11-1.93; $p = 0.007$) and 12 mg (104.2 vs 114.7 h placebo; HR: 1.31; 95% CI: 0.99-1.73; $p = 0.057$), time to discharge faster with alvimopan 6 mg (108 vs 122 h placebo; HR: 1.5; 95% CI: 1.18-1.90; $p < 0.001$) and 12 mg (115 vs 122 h placebo; HR: 1.18; 95% CI: 0.93-1.50; $p = 0.17$), readiness for discharge faster with alvimopan 6 mg (96.6 vs 112.1 h placebo; HR: 1.61; 95% CI: 1.21-2.15; $p < 0.001$) and 12 mg (98.2 vs 112.1 h placebo; HR: 1.54; 95% CI: 1.15-2.06; $p = 0.004$), no significant differences in requirement for postoperative opioid between all groups, VAS pain scores comparable between all groups, incidence of chest X-ray or NGT insertion comparable between all groups	[69]

AE: Adverse event; b.i.d.: Twice daily; BM: Bowel movement; CI: Confidence interval; DB: Double-blinded; GI: Gastrointestinal; HR: Hazard ratio; MC: Multicenter; MITT: Modified intent-to-treat; NGT: Nasogastric tube; PC: Placebo-controlled; PO: Orally; POI: Postoperative ileus; R: Randomized; TEAE: Treatment-emergent adverse events; VAS: Visual analog scale.

Table 1. Overview of Phase III alvimopan trials (cont.)..

Authors	Design	Treatment groups	Primary end points	Secondary end points	Primary outcomes	Secondary outcomes	Ref.
Viscusi *et al.* (2005)	DB, PC, R, MC parallel-group trial, patients undergoing bowel resection or abdominal hysterectomy	Safety population (n = 665): alvimopan 6 mg (n = 220) vs alvimopan 12 mg (n = 222) vs placebo (n = 224), PO 2 h prior to surgery, then b.i.d. until hospital discharge or up to 7 days. MITT population (n = 615; no further MITT subgroup n values provided)	Time to recovery of GI function (GI-3)	Time to recovery of GI function (GI-2), time to hospital discharge, readiness for discharge, first flatus, first BM, first tolerance of solid food, postoperative pain scores, opioid consumption, severity of GI symptoms, and incidence of postoperative insertion of NGT	Mean time to recovery of GI-3 decreased with alvimopan 6 mg (97.7 vs 105.2 h placebo; HR: 1.24; 95% CI: 1.01–1.53; p = 0.037) and 12 mg (95.3 vs 105.2 h placebo; HR: 1.26; 95% CI: 1.03–1.54; p = 0.028) when adjusted for covariates	GI-2 faster with alvimopan 6 mg (109.8 vs 126.2 h placebo; HR: 1.40; 95% CI: 1.11–1.76; p = 0.005) and 12 mg (112.5 vs 126.2 h placebo; HR: 1.36; 95% CI: 1.07–1.72; p = 0.012), time to discharge order written faster with alvimopan 6 mg (112.0 vs 126.2 h placebo; HR: 1.36; 95% CI: 1.12 to 1.66; p = 0.002) and 12 mg (111.0 vs 126.2 h placebo; HR: 1.30; 95% CI: 1.07–1.59; p = 0.010) (all data adjusted for covariates). No meaningful differences in requirement for postoperative opioid use between all groups, postoperative VAS pain scores comparable between all groups, incidence of NGT insertion reduced with alvimopan 6 mg (6.0 vs 8.2% placebo) and 12 mg (5.5 vs 8.2% placebo) and incidence of postoperative CXR lower with alvimopan 6 mg (7.3 vs 11.2% placebo) and 12 mg (12.5 vs 17.1% placebo).	[72]
Herzog *et al.* (2006)	DB, PC, R, MC parallel-group trial, patients undergoing simple total abdominal hysterectomy	Safety population (n = 519): alvimopan 12 mg (n = 413) vs placebo (n = 106), PO >2 h prior to surgery, then b.i.d. for 7 days	Safety and tolerability of alvimopan	Time to recovery of GI function (GI-3, GI-2), first postoperative BM, flatus, toleration of solid food, time to discharge order written	The most common TEAE's were GI related and had a similar incidence in the alvimopan and placebo groups. The proportion of patients with >1 TEAE's (alvimopan, 96.1%; placebo 94.3%) or serious AE's (alvimopan 5.6%; placebo 6.6%) was similar between treatment groups	No significant differences in time to GI-3 recovery (53.5 vs 55.4 h placebo, HR, 1.16; p = 0.18), toleration of first solid food (49.9 vs 5.1.5 h placebo, HR: 1.09; p = 0.46), or written hospital discharge order (66.3 vs 68.6 h placebo, HR: 1.31; p = 0.27). Alvimopan significantly accelerated GI-2 recovery compared with placebo (112.2 vs 92 h placebo, HR: 2.23; p < 0.001), a difference that was primarily driven by time to first BM (69.4 vs 91.6 h placebo, HR: 2.33; p < 0.001). Alvimopan also significantly accelerated time to first flatus (42.4 vs 46.7 h placebo, HR: 1.26; p = 0.039). Opioid consumption and VAS pain scores were comparable between alvimopan and control groups.	[71]

AE: Adverse event; b.i.d.: Twice daily; BM: Bowel movement; CI: Confidence interval; DB: Double-blinded; GI: Gastrointestinal; HR: Hazard ratio; MC: Multicenter; MITT: Modified intent-to-treat; NGT: Nasogastric tube; PC: Placebo-controlled; PO: Orally; POI: Postoperative ileus; R: Randomized; TEAE: Treatment-emergent adverse events; VAS: Visual analog scale.

Table 1. Overview of Phase III alvimopan trials (cont.)..

Authors	Design	Treatment groups	Primary end points	Secondary end points	Primary outcomes	Secondary outcomes	Ref.
Wolff *et al.* (2007)	Pooled, post-hoc analysis of data from above four R, DB, PC, parallel-group, MC trials (12 mg dose only)	MITT population (n = 1409): alvimopan 12 mg (n = 714) vs placebo (n = 695), PO >30 min preoperatively and b.i.d. until hospital discharge	Overall POI-related morbidity, defined as postoperative NGT insertion or experiencing complications of POI such as anastomotic leak and TEAE's such as nausea, vomiting, abdominal bloating and distension	N/A	Alvimopan patients were less likely to experience overall POI-related morbidity compared with placebo (alvimopan 12 mg, 7.6%; placebo, 15.8%; odds ratio: 0.44 [0.30–0.62]; $p < 0.001$). Decreased requirement for NGT insertion in alvimopan 12 mg group (6.6%) vs placebo (11.5%) $p = 0.001$. Opioid comsumption was comparable between alvimopan and placebo groups.	N/A	[73]

AE: Adverse event; b.i.d.: Twice daily; BM: Bowel movement; CI: Confidence interval; DB: Double-blinded; GI: Gastrointestinal; HR: Hazard ratio; MC: Multicenter; MITT: Modified intent-to-treat; NGT: Nasogastric tube; PC: Placebo-controlled; PO: Orally; POI: Postoperative ileus; R: Randomized; TEAE: Treatment-emergent adverse events; VAS: Visual analog scale.

Aside from the localized GI side effects (abdominal cramps, diarrhea, nausea, vomiting) experienced by some chronic opioid patients receiving apparently supramaximal doses (3 mg/kg or higher) of alvimopan, no other serious adverse events were reported in initial Phase I and Phase II studies of patients treated with alvimopan for opioid bowel dysfunction or POI [23].

A recent *post-hoc* analysis by Wolff *et al.* of the four alvimopan Phase III trials has been completed [73]. This analysis demonstrated that patients receiving alvimopan 12 mg were less likely to experience POI-related morbidity than patients receiving placebo (odds ratio: 0.44; $p < 0.001$) and that fewer patients receiving alvimopan (alvimopan: 7.6%; placebo: 15.8%) experienced POI-related morbidity. There was also a lower incidence of postoperative NGT insertion, and other GI-related adverse events on postoperative day 3 to 6 in the alvimopan group than the placebo group. Opioid consumption was comparable between the two groups [73].

Regulatory affairs

Alvimopan is still in clinical trials and is not US FDA approved. There are no currently available, FDA-approved pharmacologic treatments for POI.

Conclusion

Alvimopan is a novel μ-receptor opioid antagonist that may offer the first effective pharmacologic treatment for POI. It has minimal systemic absorption and does not cross the blood–brain barrier and, therefore, does not appear to affect the analgesia provided by narcotic pain medication. It has been shown to be safe and effective in blocking the intestinal effects of opioids and speeding the recovery of peristalsis in postoperative patients. Additionally, owing to its opioid-blocking effects, it is currently being investigated for the treatment of chronic opioid-induced bowel dysfunction in patients with chronic pain [74].

Expert commentary & future perspective

Healthcare expenditure now accounts for nearly 15% of the gross national product. Hospitals and physicians continue to deal with payment reductions and will soon need to adapt to 'Pay for Performance' to supplement these falling payments for care. Increased efficiency and decreased length of stay are two important and potentially controllable remaining areas where there is significant room for improvement.

POI is a natural result of any major operative procedure. Even those procedures where limited or no contact with the bowel occurs can result in POI. Ileus is often seen in patients after total joint replacement, trauma or any painful situation where narcotic pain medicine is administered.

Although proponents of minimally invasive procedures claim a lower incidence of POI as well as shorter hospitalizations there will always be a significant percentage of those patients who will develop POI. There will also be patients who still require major open procedures for many intraabdominal problems. They will all require pain medications (usually a narcotic) and as a result will be subject to the development of POI.

Goldstein *et al.* analyzed coded hospital records available from 160 hospitals nationally to develop an assessment tool regarding the costs of POI. Considering extra days of hospitalization for POI after abdominal-related operations, they showed that costs attributed to POI were US$1.46 billion per year. This study did not take into account the lost productivity from the national workforce or the personal loss of productive time for the patient [31]. It is clear that reduction of the incidence of POI would be beneficial to the patient as well as to the overall expenditure for healthcare and loss of worker productivity. We anticipate that, in at least those patients undergoing major abdominal surgery, a relatively short course of alvimopam will be beneficial in decreasing the risk for POI. Although the studies have some degree of heterogeneity (inclusion of both hysterectomy and colon resection patients) the reduction of duration of POI remains just under 1 day. Although this may seem insignificant, when considering the cost savings to hospitals under diagnosis-related group (DRG) payments and the potential to have an available bed for another DRG patient has significant positive financial impact on a hospital's bottom line. The cost of a short course of alvimopan (which has yet to be determined) will need to be factored into a final validation of the clinical impact and cost–benefit analysis.

Although the results from the recent 014 trial (for patients taking opioids for chronic noncancer pain and experiencing opioid-induced bowel dysfunction) [Adolor, Pers. Comm.] are somewhat disappointing it is our belief that there will be a

Executive summary

- Postoperative ileus (POI) is common after abdominal and nonabdominal operations, but there has been no effective pharmacologic therapy for the prevention of POI up to this time.
- Alvimopan is a peripherally acting μ-opioid receptor antagonist that blocks the adverse effects of narcotics on bowel motility while preserving analgesia in the postsurgical patient.
- Alvimopan has been shown to have a favorable side-effect profile very similar to placebo.
- Alvimopan may have a role in the treatment of opioid-induced bowel dysfunction.

significant role for alvimopam in the setting of avoidance of postoperative ileus. Adolor plans to submit a complete response to the November 2006 approvable letter from the FDA, which we anticipate will be looked at favorably for FDA approval.

Disclosure

James Weese was a principal investigator in Adolor 14CL302 "A multicenter Phase III double-blind placebo controlled parallel study of ADL8–2698 in opioid-induced postoperative bowel dysfunction/postoperative ileus." He is also a consultant for data review for Adolor.

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