ORIGINAL ARTICLE

Gastrointestinal Tract Recovery in Patients Undergoing Bowel Resection

Results of a Randomized Trial of Alvimopan and Placebo With a Standardized Accelerated Postoperative Care Pathway

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Objective: To investigate the efficacy and safety of alvimopan, 12 mg, administered orally 30 to 90 minutes preoperatively and twice daily postoperatively in conjunction with a standardized accelerated postoperative care pathway for managing postoperative ileus after bowel resection.

Design, Setting, and Patients: This multicenter, randomized, placebo-controlled, double-blind, phase 3 trial enrolled adult patients undergoing partial bowel resection with primary anastomosis by laparotomy and scheduled to receive intravenous, opioid-based, patient-controlled analgesia. A standardized accelerated postoperative care pathway including early ambulation, oral feeding, and postoperative nasogastric tube removal was used to facilitate gastrointestinal (GI) tract recovery in all of the patients.

Main Outcome Measures: The primary end point was time to GI-2 recovery (toleration of solid food and first bowel movement). Secondary end points included time to GI-3 recovery (toleration of solid food and first flatus or bowel movement), hospital discharge order written, and actual hospital discharge. Postoperative length of hospital stay based on calendar day of hospital discharge order written, opioid consumption, and overall postoperative ileus–related morbidity were recorded.

Results: Alvimopan, 12 mg, was well tolerated and significantly accelerated GI-2 recovery, GI-3 recovery, and actual hospital discharge compared with a standardized accelerated postoperative care pathway alone (hazard ratio = 1.5, 1.5, and 1.4, respectively; $P < .001$ for all). Time to hospital discharge order written as measured by hazard ratio (1.4) and by postoperative calendar days (mean for alvimopan, 5.2 days; mean for placebo, 6.2 days) was also accelerated. Opioid consumption was comparable between groups, and alvimopan was associated with reduced postoperative ileus–related morbidity compared with placebo.

Conclusions: Alvimopan, 12 mg, administered 30 to 90 minutes before and twice daily after bowel resection is well tolerated, accelerates GI tract recovery, and reduces postoperative ileus–related morbidity without compromising opioid analgesia.

Trial Registration: clinicaltrials.gov Identifier: NCT00205842

Arch Surg. 2008;143(11):1098-1105

MORE THAN 330 000 PATIENTS undergo bowel resections in the United States each year, and virtually all experience postoperative ileus (POI), an interruption of bowel function after surgery.[1-3] Postoperative ileus is characterized by the inability to tolerate a solid diet, delayed passage of flatus and formed stool, pain and abdominal distention, nausea, vomiting, and accumulation of gas or fluids in the bowel.[3-5] The causes of POI are multifactorial and include surgical manipulation, inflammatory response, inhibitory neural reflexes, and the secretion of endogenous opioids within the gastrointestinal (GI) tract.[6-8] Moreover, although opioid analgesia is considered the standard of care for relief of moderate to severe pain, opioids can bind to μ-opioid receptors in the GI tract, extending the duration of POI and further delaying GI tract recovery.[9-11] Postoperative ileus is associated with increased postoperative morbidity, reduced patient satisfaction, and increased length of hospital stay (LOS).[6,7,12-16] Moreover, POI-related increases in LOS and use of resources translate into increased costs for the health care system.[17]

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Attempts to reduce the duration of POI have prompted the implementation of various strategies including accelerated postoperative care pathways. Reports of numerous multimodal regimens have been published with a variety of outcomes.[2,18-21] Some GI tract recovery protocols enacted to reduce LOS have resulted in increased rates of readmission, and certain advanced surgical approaches and anesthetic care pathways may not be feasible for all patients and institutions.[22,23] Early postoperative removal of the nasogastric tube, early feeding, and prompt ambulation have each demonstrated clinical benefits in accelerating GI tract recovery but have not been associated with increased risk of rehospitalization and are easily implemented in a variety of settings.[24-27] In previous POI trials of alvimopan, an oral peripherally acting μ-opioid receptor antagonist, these approaches were combined, standardized, and used across all treatment groups as follows: nasogastric tube removal no later than noon on postoperative day 1, liquid diet and ambulation on postoperative day 1, and solid food by postoperative day 2.[28-30] As a result, the placebo groups for the bowel resection population had reduced times to hospital discharge when compared with national averages but still experienced delayed GI tract recovery and postoperative morbidity.[15]

The alvimopan clinical studies represent the first randomized, large-scale, placebo-controlled clinical trials to investigate pharmacologic management of POI. In 3 previous studies, alvimopan in conjunction with a standardized accelerated postoperative care pathway (described earlier) reduced time to GI tract recovery compared with the pathway alone in patients who underwent laparotomy.[28-30] Although the results favored alvimopan across studies, the statistical significance, dose response, and magnitude of treatment effect were somewhat inconsistent. This may have been the result, in part, of the mixed surgical populations (bowel resection and total abdominal hysterectomy) with varying clinical recovery enrolled in these trials. Moreover, these studies used a dosing regimen of 2 or more hours preoperatively with which it may be difficult to comply because patients are not always in the preoperative holding area in that time frame. However, pharmacokinetic studies and a post hoc analysis have suggested that alvimopan can be administered as early as 30 minutes before surgery without affecting treatment efficacy.[31] Our study was undertaken to confirm this hypothesis and to help address some of these remaining issues. This article reports the results of a recent double-blind, placebo-controlled, randomized, multicenter trial of alvimopan, 12 mg, administered 30 to 90 minutes preoperatively and twice daily postoperatively in conjunction with a standardized accelerated postoperative care pathway in patients who underwent small- or large-bowel resection.

METHODS

PATIENTS

Adult patients (aged ≥18 years) undergoing laparotomy for partial small- or large-bowel resection with primary anastomosis who were scheduled for postoperative pain management with intravenous, opioid-based, patient-controlled analgesia were eligible. Patients were excluded from eligibility if they were pregnant; were currently using opioids or receiving an acute course of opioids (>3 doses) less than 1 week before study entry; were experiencing complete bowel obstruction; were undergoing total colectomy, colostomy, ileostomy, or ileal pouch–anal anastomosis; or had a history of total colectomy, gastrectomy, gastric bypass, short bowel syndrome, or multiple previous abdominal operations performed by laparotomy. All of the patients were provided with a written informed consent form that was approved by each institutional review board.

STUDY DESIGN AND TREATMENT

This was a randomized, multicenter, double-blind, placebo-controlled, phase 3b trial conducted at 55 centers in the United States (study ^{14}CL314). Institutional review board approval was obtained at each investigational site. Patient randomization was stratified by sex and site. Information regarding race was collected for covariate efficacy analysis. The classification categories for race included white, black, Hispanic, Asian, Native American, or other. After informed consent was obtained, an interactive voice response system was used to obtain blister card assignment of alvimopan or placebo. All study treatment was blinded, although blinding could be broken if necessary for patient safety. If unblinding occurred, the sponsor was immediately notified. Patients received oral alvimopan, 12 mg, or identical placebo (two 6-mg capsules with a sip of water) 30 to 90 minutes before surgery and then twice daily (according to the individual twice-daily hospital dosing interval) until hospital discharge or for up to 7 postoperative days.

A standardized accelerated postoperative care pathway was used to facilitate GI tract recovery in all of the patients: if the nasogastric tube was kept in place after surgery, it was removed by noon on the first postoperative day before the first dose of study medication was administered; a liquid diet was offered and ambulation was encouraged on postoperative day 1; and solid food was offered on postoperative day 2. The individual primary investigators determined readiness for discharge.

ASSESSMENTS

Efficacy analyses were based on the modified intent-to-treat (MITT) population (all randomized and treated patients who received the protocol-specified surgery and had ≥1 efficacy evaluation). Efficacy was assessed until hospital discharge or for a maximum of 10 postoperative days. Safety analyses were based on the safety population, defined as all treated patients who had any safety evaluation data. Safety was assessed based on all adverse events (AEs) up to 14 days after the last dose of study medication, clinical evaluation, and laboratory testing. Treatment-emergent AEs were defined as any AE occurring after the first dose of study medication and within 7 days of the last dose of study medication. Serious AEs were recorded for up to 30 days after the last dose of study medication; a serious AE was defined as an AE that resulted in death, persistent or substantial disability, prolonged hospitalization, or readmission; was immediately life threatening; or required intervention to prevent permanent impairment or damage.

EVALUATIONS

The primary end point was time to GI-2 recovery (representing resolution of POI), a composite assessment that measured upper (toleration of solid food) and lower (first bowel movement [BM]) GI tract recovery, with time to achieve GI-2 recovery based on the last event to occur. Time to tolerate solid food was defined as the time of solid food ingestion without significant nausea or vomiting for 4 hours. Secondary support-

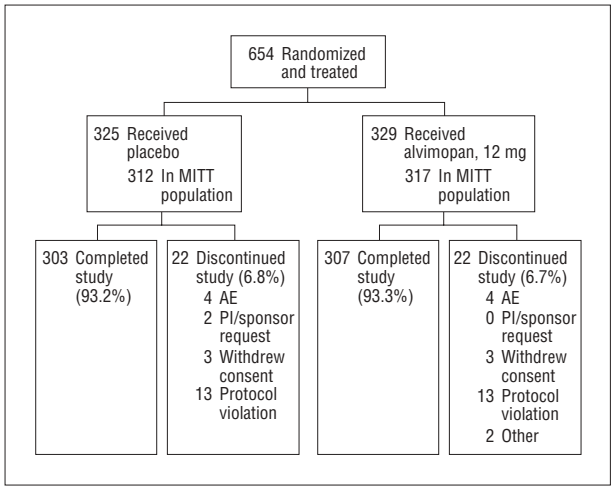

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram. This schematic illustrates the study design for patient randomization, treatment, and disposition. MITT indicates modified intent-to-treat; AE, adverse event; and PI, principal investigator.

ive end points included time to GI-3 recovery (first toleration of solid food and first flatus or BM), hospital discharge order (DCO) written, and actual date and time of hospital discharge. Patients were assessed for end points twice daily by the individual principal investigators or qualified designees by speaking with the patient and confirming the assessment by record review. Postoperative length of hospital stay (LOS) was a supportive analysis of the prespecified secondary end point of DCO written and was measured from the calendar day after surgery to the calendar day of DCO written. Information about the incidence of POI-related morbidity was collected. Overall POI-related morbidity was a prespecified exploratory analysis and included postoperative nasogastric tube insertion, complications of POI, complications of POI resulting in prolonged LOS, and complications of POI resulting in readmission. For the purposes of this analysis, overall POI-related morbidity was composed of postoperative nasogastric tube insertion or complications of POI. Complications of POI comprised serious AE reports of POI, paralytic ileus, or small-intestinal obstruction resulting in prolonged LOS or readmission 7 days or sooner after initial hospital discharge. Total opioid consumption was measured in morphine sulfate equivalents (MSEs). Safety was monitored with continuous AE reporting, clinical safety laboratory evaluations, and vital sign measurements. Investigators assessed all abnormal laboratory results as either clinically significant or not clinically significant based on their opinion.

STATISTICAL ANALYSIS

It was estimated that a sample size of 660 patients (1:1 randomization) would achieve 90% power to detect a difference in GI-2 recovery between groups assuming the hazard ratio (HR) between alvimopan and placebo was 1.46. Time-to-event data were analyzed using Cox proportional hazard models to generate HRs and associated 95% confidence intervals (CIs), and the Wald χ^2 test was used to calculate the nominal *P* values for comparisons between groups. Magnitude of treatment effect was represented by the differences in Kaplan-Meier means that graphically could be expressed as the area between the 2 Kaplan-Meier curves, and the 95% CIs of the Kaplan-Meier mean difference were calculated using normal approximation. For binary outcomes, *P* values assessing odds ratios for alvimopan compared with placebo were calculated with Fisher exact test. Associated 95% CIs were calculated using normal approximation. For opioid consumption, least-squares means (MITT population) were compared and *P* values were calculated from an analysis of variance model. Fisher exact test was used to evaluate AE rates between treatment groups for events with incidence of more than 2% in any treatment group. All of the statistical analyses were performed using SAS statistical software version 9.1 or higher (SAS Institute Inc, Cary, North Carolina).

RESULTS

PATIENTS

Patient recruitment began June 9, 2004, and patient follow-up was completed by December 20, 2005. Of the 654 patients randomized and treated, all were included in the safety population and 629 were included in the MITT population. Less than 4.0% of patients (12 patients in the alvimopan group and 13 patients in the placebo group) were excluded from the MITT population. Reasons for exclusion included non–protocol-specified surgery, no efficacy evaluations, and no surgery performed. Twenty-two patients in each group discontinued the study, with 1.2% of patients discontinuing because of AEs (**Figure 1**). The mean patient age was 59.8 years, and the majority of patients (83.6%) were white (**Table 1**). The most common reasons for surgery were colon cancer (35.6%) and diverticular disease (15.9%). The majority of patients (91.6%) underwent large-bowel resection.

All of the patients were scheduled for postoperative management with a standardized accelerated postoperative care pathway. Three hundred twenty-two patients (99.1%) in the placebo group and 324 patients (98.5%) in the alvimopan group had their nasogastric tube removed by noon on postoperative day 1. Study medication was not administered when a nasogastric tube was in place.

EFFICACY

Alvimopan significantly accelerated time to the primary end point in the MITT population (GI-2 recovery) (HR=1.5; 95% CI, 1.29-1.82; $P<.001$). The primary analysis was also performed in the randomized population (N=654) with similar results. Moreover, alvimopan accelerated time to GI-3 recovery (HR=1.5; 95% CI, 1.23-1.71), DCO written (HR=1.4; 95% CI, 1.19-1.65), and actual hospital discharge (HR=1.4; 95% CI, 1.18-1.63) ($P<.001$ for all). The mean time to GI-2 recovery was accelerated by 20 hours (0.8 days) to 92 hours (3.8 days) in the alvimopan group from 112 hours (4.7 days) in the placebo group (**Figure 2**). Furthermore, alvimopan also accelerated the mean time to GI-3 recovery by 16 hours (placebo, 98 hours), DCO written by 18 hours (placebo, 138 hours), and actual hospital discharge by 17 hours (placebo, 141 hours). Alvimopan accelerated the mean time to the individual components of the composite end points by 9 hours for toleration of solid food, 16 hours for first BM, and 10 hours for first flatus. A review of the DCO written and actual discharge data revealed that most patients left the hospital within 4 hours from the time the DCO was written.

Patients in the alvimopan group remained in the hospital (based on DCO written) for a shorter duration than patients in the placebo group (**Figure 3**), and the mean

Table 1. Patient Demographics and Baseline Surgery Characteristics in Safety Population

Characteristic	Placebo (n=325)	Alvimopan, 12 mg (n=329)	Total (N=654)
Age			
Mean (SD), y	59.6 (13.6)	59.9 (14.4)	59.8 (14.0)
Patients aged ≥65 y, No. (%)	127 (39.1)	126 (38.3)	253 (38.7)
Race, No. (%)			
White	275 (84.6)	272 (82.7)	547 (83.6)
Black	30 (9.2)	36 (10.9)	66 (10.1)
Hispanic	14 (4.3)	15 (4.6)	29 (4.4)
Asian	4 (1.2)	5 (1.5)	9 (1.4)
Native American	1 (0.3)	0	1 (0.2)
Other	1 (0.3)	1 (0.3)	2 (0.3)
Female, No. (%)	165 (50.8)	164 (49.8)	329 (50.3)
BMI			
Mean (SD)	28.8 (6.1)	28.0 (6.5)	28.4 (6.3)
Patients with BMI ≥30, No. (%)	116 (35.7)	102 (31.0)	218 (33.3)
Primary reason for surgery, No. (%)[a]			
Colon cancer	103 (33.0)	121 (38.2)	224 (35.6)
Diverticular disease	54 (17.3)	46 (14.5)	100 (15.9)
Stoma reversal with resection	39 (12.5)	46 (14.5)	85 (13.5)
Intestinal polyps	44 (14.1)	31 (9.8)	75 (11.9)
Crohn disease	18 (5.8)	23 (7.3)	41 (6.5)
Rectal cancer	23 (7.4)	18 (5.7)	41 (6.5)
Rectal prolapse	6 (1.9)	4 (1.3)	10 (1.6)
Intestinal fistula	1 (0.3)	4 (1.3)	5 (0.8)
Small-bowel cancer	1 (0.3)	3 (0.9)	4 (0.6)
Other	23 (7.4)	21 (6.6)	44 (7.0)
Surgery type, No. (%)[a]			
Large-bowel resection	290 (92.9)	286 (90.2)	576 (91.6)
Left	185 (59.3)	174 (54.9)	359 (57.1)
Right	105 (33.7)	112 (35.3)	217 (34.5)
Small-bowel resection	22 (7.1)	31 (9.8)	53 (8.4)
Overall surgery duration, mean (SD), h[a]	2.0 (1.1)	2.0 (1.1)	2.0 (1.1)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] Reported in the modified intent-to-treat population (placebo, n=312; alvimopan, 12 mg, n=317).

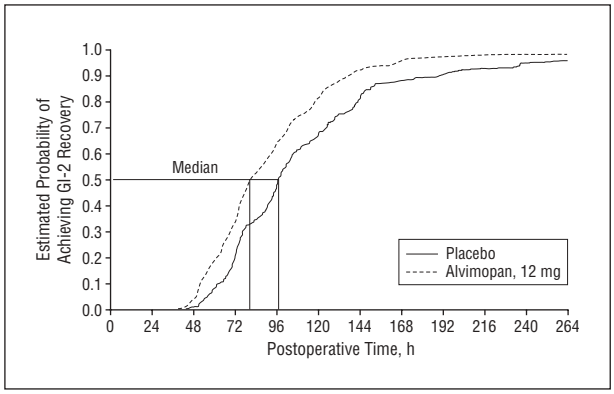

Figure 2. Kaplan-Meier cumulative probability of GI-2 recovery (time to first toleration of solid food and first bowel movement) (modified intent-to-treat population). The mean difference between alvimopan and placebo is represented by the difference in the area between the 2 curves; the mean (95% confidence interval) difference was –19.8 (–27.6 to –11.9) hours.

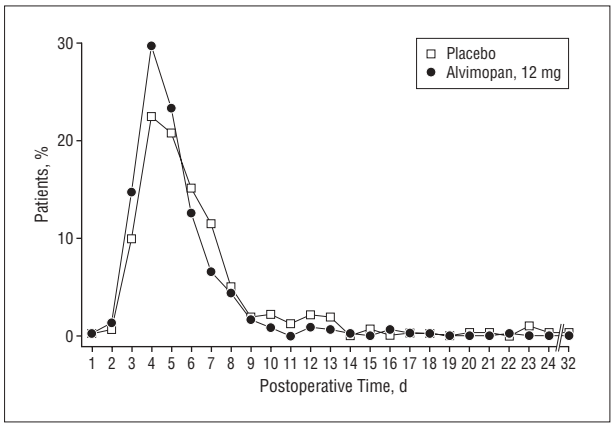

Figure 3. Hospital discharge by day (modified intent-to-treat population).

postoperative LOS was significantly shorter (1 full calendar day) for patients who received alvimopan compared with patients who received placebo (alvimopan, 5.2 days; placebo, 6.2 days; $P<.001$). The greatest numbers of patients were discharged on days 4 and 5 for both groups (alvimopan, 53.0%; placebo, 43.2%). Furthermore, compared with patients who received alvimopan, significantly more patients who received placebo remained in the hospital (did not have a DCO written) for 7 postoperative days or longer (alvimopan, 18.0%; placebo, 30.8%; $P<.001$).

POSTOPERATIVE MORBIDITY

Overall POI-related morbidity was less likely to occur in patients treated with alvimopan compared with placebo (odds ratio=0.42; 95% CI, 0.23-0.74; $P=.002$). Moreover, patients who received alvimopan as compared with patients who received placebo were less likely to experience the components of overall POI-related morbidity, POI-related complications (odds ratio=0.25; 95% CI, 0.09-0.60; $P<.001$) and postoperative nasogastric tube insertion (odds ratio=0.56; 95% CI, 0.29-1.04; $P=.06$). Fewer than half as many patients in the alvimopan group compared with the placebo group experienced overall POI-related morbidity: 21 of 317 patients (6.6%) in the alvimopan group compared with 45 of 312 patients (14.4%) in the placebo group (**Figure 4**). Nineteen patients (6.0%) in the alvimopan group compared with 32 patients (10.3%) in the placebo group had postoperative nasogastric tube insertion. Compared with patients in the alvimopan group, 5.1% more patients in the placebo group experienced complications of POI resulting in prolonged stay (alvimopan, 1.3%; placebo, 6.4%). The POI-related hospital readmission rates within 7 days of discharge (alvimopan, 0.9%; placebo, 1.9%) and overall hospital readmission rates within 10 days of discharge (alvimopan, 5.0%; placebo, 6.1%) were comparable between groups. The rate of anastomotic leak was low and comparable between groups (alvimopan, 1.5%; placebo, 1.8%).

OPIOID CONSUMPTION

The mean (SD) opioid consumption was similar between groups in the preoperative period (alvimopan, 16.5

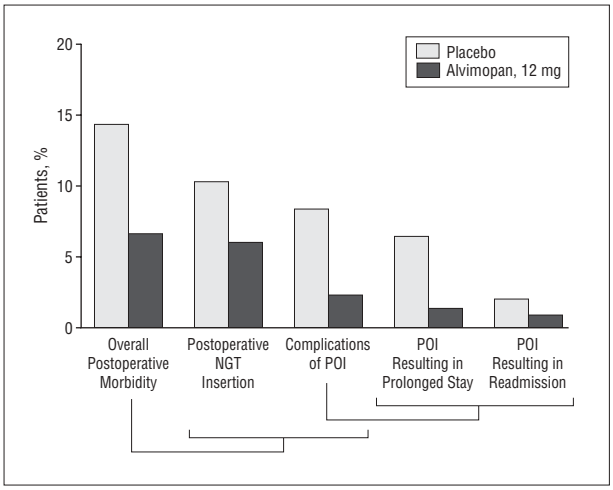

Figure 4. Postoperative ileus (POI)–related postoperative morbidity (modified intent-to-treat population). NGT indicates nasogastric tube.

Table 2. All Treatment-Emergent Adverse Events Reported in 10% of Patients or More in Safety Population

	Patients, No. (%)	
Adverse Event[a]	Placebo (n=325)	Alvimopan, 12 mg (n=329)
Nausea	215 (66.2)	190 (57.8)
Abdominal distention	66 (20.3)	58 (17.6)
Hypokalemia	36 (11.1)	49 (14.9)
Vomiting	80 (24.6)	46 (14.0)
Pruritus	41 (12.6)	45 (13.7)
Pyrexia	69 (21.2)	41 (12.5)
Hypertension	34 (10.5)	36 (10.9)
Insomnia	36 (11.1)	35 (10.6)
Urine output decreased	37 (11.4)	33 (10.0)
Tachycardia	35 (10.8)	27 (8.2)
Postoperative ileus	51 (15.7)	24 (7.3)

[a] Adverse events were collected up to 14 days after the last dose of study medication.

[15.1] MSEs; placebo, 16.6 [15.1] MSEs; $P=.99$), the intraoperative period (alvimopan, 31.0 [30.6] MSEs; placebo, 29.5 [31.9] MSEs; $P=.54$), and the postoperative period (alvimopan, 185.3 [188.3] MSEs; placebo, 219.3 [259.0] MSEs; $P=.06$).

SAFETY RESULTS

Almost all of the patients reported 1 or more treatment-emergent AEs (alvimopan, 95.7%; placebo, 95.4%). The overall incidence of treatment-emergent AEs was similar between groups (**Table 2**). The 3 most commonly reported treatment-emergent AEs were nausea (alvimopan, 57.8%; placebo, 66.2%; $P=.003$), vomiting (alvimopan, 14.0%; placebo, 24.6%; $P<.001$), and abdominal distention (alvimopan, 17.6%; placebo, 20.3%; $P=.42$). Forty patients (12.2%) in the alvimopan group and 62 patients (19.1%) in the placebo group reported 1 or more treatment-emergent serious AEs. Two patients in each group died during the study, but no serious AEs that resulted in death (electromechanical dissociation, anastomotic leak and septic shock, GI tract hemorrhage, and hepatic and acute renal failure) were considered related to the study drug.

Similar clinically significant shifts in biochemical liver test results were reported in both treatment groups, with changes observed in 1.6% of patients in both groups for any parameter. Vital sign measurements were comparable between groups.

COMMENT

Prior investigations have demonstrated that alvimopan can significantly accelerate GI tract recovery after bowel resection, but surgical populations and optimal dosing and timing parameters had not been fully defined.[28-30] Our analysis confirmed that alvimopan, 12 mg, dosed 30 to 90 minutes preoperatively and twice daily postoperatively in conjunction with a standardized accelerated postoperative care pathway significantly accelerates upper and lower GI tract recovery and reduces postoperative LOS and POI-related morbidity without compromising opioid analgesia in patients undergoing bowel resection. Indeed, patients in the placebo group treated with the standardized accelerated postoperative care pathway continued to experience delayed GI tract recovery and postoperative morbidity, which could be minimized further by adding alvimopan to their recovery protocol.

There are a number of differences between this study and previously published clinical trials of alvimopan for the management of POI. One difference was the inclusion of only patients undergoing laparotomy for segmental bowel resection with primary anastomosis and, as a result, the evolution of a more objective and appropriate primary end point (GI-2 recovery) compared with prior trials, which used a 3-component composite assessment (GI-3 recovery) that measured upper (toleration of solid food) and lower (passage of flatus or BM) GI tract recovery. Time to first flatus may also be a less objective end point than time to first BM because a patient must be conscious and willing to report it.[32] Therefore, the GI-2 recovery end point (toleration of solid food and passage of BM) may provide a more objective assessment of upper and lower GI tract recovery and represents a more appropriate measure of alvimopan treatment effect in the bowel resection population. In this trial, time to GI-2 recovery was primarily driven by time to first BM as in general this was the later occurring of the 2 components of GI-2 recovery.

Previous pharmacokinetic modeling suggested that the alvimopan plasma concentration after a single dose of alvimopan, 12 mg, would achieve or exceed the dissociation constant for μ-opioid receptor antagonism within 0.5 hour and remain sufficiently high for longer than 6 hours after administration.[31] This trial demonstrates that an administration schedule of 30 to 90 minutes preoperatively and twice daily postoperatively is also effective. The preoperative dosing window in this study provides a convenience benefit compared with the dosing regimens in prior phase 3 trials. The current dosing window allows for administration of alvimopan at a time when

patients are under medical observation in preparation for surgery and receiving other medications. These data plus the previous alvimopan data support a wide preoperative dosing window (30 minutes to 5 hours) that provides more flexibility in actual surgery start times without concern for a loss of efficacy.[28-31]

In previous trials, 2 doses (6 mg and 12 mg) of alvimopan were studied.[28-30] In a pooled analysis of these trials, GI tract recovery appeared faster in patients who received 12 mg of alvimopan compared with patients who received 6 mg of alvimopan.[33] Our trial supports that alvimopan 12-mg dosing is efficacious in the bowel resection population.

Consistent with previous reports, some degree of acceleration of GI tract recovery compared with national averages may be achieved with accelerated postoperative recovery protocols alone.[28-30] Indeed, in our study, in patients who received the protocol-specified standardized accelerated postoperative care pathway alone (placebo group), postoperative LOS was shorter (6.2 days) than national averages (10-14 days according to 2003 national statistics) that are derived from hospitals where these recovery protocols may or may not be used.[1] Moreover, in this trial, both GI-2 recovery and time to DCO written reported in the placebo group are shorter than reported in a previous alvimopan trial comprising mostly patients undergoing bowel resection (study ^{14}CL313).[30] Patients in our trial achieved GI-2 recovery 0.8 day earlier and DCO written 0.2 day earlier than patients in the study reported by Wolff et al,[30] perhaps reflecting greater acceptance and implementation of accelerated postoperative care pathways with time. Treatment with alvimopan provided clinically meaningful benefits despite the shorter times to GI tract recovery and discharge in placebo groups in this trial.

Although GI-2 recovery and time to hospital discharge were accelerated by less than 24 hours, this translated to a reduction in postoperative LOS of 1 full calendar day in the alvimopan group compared with LOS in the group receiving the standardized accelerated postoperative care pathway alone (alvimopan, 5.2 days; placebo, 6.2 days). Shorter LOS may translate into meaningful benefits to patients and cost savings for the health care system and could result in a reduced chance of patients contracting nosocomial infections and in increased patient satisfaction.[34-36] Indeed, in a pooled economic analysis (not including the price of alvimopan) of the first 3 alvimopan efficacy trials, overall costs associated with patients in the alvimopan group were $1443 less than costs for patients in the placebo group.[37] Although not assessed in this trial, shorter LOS may lead to reduced costs for occupancy of beds, monitoring requirements, and nursing support.

Previous alvimopan trials measured overall (all-cause) postoperative morbidity; however, POI-related morbidity was not specifically examined.[28-30] Alvimopan reduced POI-related morbidity compared with placebo in our study. This is a more specific measure of how alvimopan may influence patient recovery compared with general postoperative morbidity measures. Importantly, complications of POI resulting in prolonged LOS were significantly less likely to occur in patients treated with alvimopan compared with placebo: 5.1% more patients in the placebo group had these complications compared with the alvimopan group. The LOS is correlated with morbidity, and prolonged LOS may be especially important in the elderly, who are more at risk for in-hospital mortality.[38,39] Additionally, the incidence of postoperative nasogastric tube insertion, which may reflect GI tract symptoms that are not manageable with supportive care, was reduced in our trial, although not significantly. Postoperative nasogastric tube insertion is associated with increased rates of postoperative morbidity, and any reduction in its use may minimize further postoperative morbidity or reflect reduced GI tract morbidity.[26]

In conclusion, this trial confirms and extends the results of previous US efficacy trials.[28-30] Alvimopan, 12 mg, administered as early as 30 to 90 minutes before and twice daily after bowel resection is well tolerated, accelerates GI tract recovery, shortens postoperative LOS, and reduces POI-related morbidity without compromising opioid analgesia or increasing patient risk. This study adds to the body of literature reporting the GI tract recovery benefit of alvimopan in conjunction with a standardized accelerated postoperative care pathway.[28-30]

Accepted for Publication: August 6, 2007.
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Financial Disclosure: Dr Delaney has been a consultant to and has received research grants from Adolor Corp and GlaxoSmithKline. Dr Wolff has served on the medical advisory board of Adolor Corp. Drs Du and Techner, Ms Cherubini, and Mr Cucinotta are employees of Adolor Corp. Dr Fort is an employee of and has stock options with Adolor Corp.
Funding/Support: This study was supported by Adolor Corp, Exton, Pennsylvania, and GlaxoSmithKline, Philadelphia, Pennsylvania.

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Tran, MD, Alhambra, California; Mississippi Baptist Medical Center, Jackson; International Research Associates, LLC, and Baptist Hospital of Miami, Miami; Christus St Joseph Hospital, Houston, Texas; Shands Hospital at the University of Florida, Shands Medical Plaza, and Shands Hospital Pharmacy, Gainesville; Oschner Clinic Foundation, New Orleans, Louisiana; Atlanta Colon and Rectal Surgery, Atlanta, Georgia; ARS Clinical Trials, Powder Springs, Georgia; St Joseph's Hospital of Atlanta, Atlanta; Bend Memorial Clinic and St Charles Medical Center, Bend, Oregon; Lehigh Valley Hospital and KSRR, PC, Allentown, Pennsylvania; Baystate Medical Center and Baystate Surgical Associates, Springfield, Massachusetts; Akron General Medical Center, Akron, Ohio; Melbourne Internal Medical Associates, MIMA, Century Research Associates, Holmes Medical Center, and Melbourne Internal Medicine Associates, Melbourne, Florida; and The Surgical Clinic of Central Arkansas and Baptist Health Medical Center–Little Rock, Little Rock.

Additional Contributions: Gary Koch, PhD, University of North Carolina, Chapel Hill, and Robert Woolsen, PhD, Medical University of South Carolina, Charleston, provided statistical review of the manuscript. Amy Rachfal, PhD, ProEd Communications, Inc, Beachwood, Ohio, provided medical editorial assistance with the manuscript.

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