Alvimopan for postoperative ileus

HEATHER R. BREAM-ROUWENHORST AND MATTHEW A. CANTRELL

Postoperative ileus is a temporary impairment in gastrointestinal (GI) motility. Though considered an inevitable complication of abdominal and pelvic surgeries, postoperative ileus may also occur after nonabdominal surgeries, such as thoracic and orthopedic procedures. The duration of ileus depends on the part of the GI tract affected; recovery times for the small intestine and stomach are generally 0–24 and 24–48 hours, respectively, while the colon may take 48–72 hours to recover. Alvimopan is a selective \( \mu \)-opioid receptor antagonist with no central nervous system activity. When orally administered after partial small- or large-bowel resection in patients with primary anastomosis, alvimopan shortened the return of bowel function and time to discharge by approximately one day without compromising analgesia. Alvimopan was not shown to be beneficial on these same outcomes after hysterectomy and has not been studied in other surgical populations. Alvimopan is generally well tolerated, with the frequency of adverse events being similar to placebo when used postoperatively for one week or less. Long-term studies of alvimopan in opioid-induced bowel dysfunction have shown an association with adverse cardiovascular outcomes, neoplasms, and fractures. Because of these concerns, the Entereg Access Support and Education program was developed. The recommended dosage of alvimopan is 12 mg administered with a sip of water 30 minutes to five hours before surgery, followed by 12 mg twice daily beginning the day after surgery for a maximum of seven days, 15 total doses, or until discharge. There is a limited amount of pharmacoeconomic analysis concerning alvimopan. Alvimopan, a peripherally acting \( \mu \)-opioid receptor antagonist, is a novel agent for the treatment of postoperative ileus. It appears to decrease the duration of postoperative ileus and hospitalization by approximately one day, theoretically offsetting its acquisition costs. Unresolved long-term safety issues, a limited indication, and its restricted-access program are likely to hinder its widespread use in the surgical population.

Index terms: Alvimopan; Dosage; Drug administration; Drug interactions; Hospitals; Ileus; Mechanism of action; Opiate antagonists; Pharmacoeconomics; Pharmacokinetics; Postoperative complications; Toxicity

ing. In severe cases, postoperative ileus may contribute to aspiration; furthermore, due to decreased oral intake, patients may become catabolic, increasing the risk of complications. While postoperative ileus is often a transient complication of surgery, recovery may take three to five days or even longer in some instances, often making postoperative ileus the rate-limiting step in recovery. The associated costs of postoperative ileus are clinically important to both patients and payers, as the condition has been shown to more than double inpatient hospitalization costs and significantly increase the length of hospital stay. Postoperative pain control nearly always includes opioid analgesia, which contributes to the development of postoperative ileus. The three main subtypes of opioid receptors include μ, κ, and δ. Although all opioid receptors are involved in analgesia, the μ-receptor is the primary receptor targeted for the pharmacologic treatment of pain. All opioid receptors belong to the same 7-transmembrane G-protein-coupled receptor family and retain selectivity for specific ligands; however, there is overlap among the three classes with respect to their pharmacologic binding profiles. Opiate receptors are distributed throughout the GI tract and assist in GI motility, secretion, and transportation of electrolytes. Localization of these receptors in the GI tract near interneurons, secretomotor neurons, and the interstitial cells of Cajal—the pacemaker cells for GI motility—aids in carrying out these aforementioned biological functions (Figure 1).
Despite opioids’ beneficial effects for acute pain, the drugs decrease gastric motility, inhibit propulsion of the small and large intestine, delay transit time, cause constipation, and increase fluid absorption from bowel contents. Thus, the GI effects of opioids, coupled with the effects of surgical procedures, place patients at further risk of postoperative ileus. The development and recent approval by the Food and Drug Administration (FDA) of labeling for alvimopan (Entereg marketed by Adolor and GlaxoSmithKline), a peripheral μ-opioid receptor antagonist, may represent an advance in the treatment of postoperative ileus.

Pharmacology

Alvimopan, a novel peripherally acting μ-opioid receptor antagonist, is an N-substituted-trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine. Substitution of the piperidine ring at the 3-position accounts for its ability to antagonize opioid receptors. Alvimopan has a high affinity for μ-opioid receptors (dissociation constant \( K = 0.77 \) nmol/L) and lower affinities for κ- and δ-receptors (\( K = 40 \) and 4.4 nmol/L, respectively). Alvimopan is a more potent μ-opioid receptor antagonist than naloxone and has not shown affinity for adrenergic \( \alpha_1, \alpha_2, \) or \( \beta \); dopamine D1 or D2; serotonin 5-HT; histamine H1; benzodiazepine; \( \gamma \)-aminobutyric acid; or muscarinic receptors. Penetration of the drug through the blood-brain barrier is poor due to its large molecular weight, zwitterionic form, and polarity. When administered intravenously, alvimopan demonstrates a 200-fold greater selectivity for peripheral μ-opioid receptors relative to those in the central nervous system (Figure 1).

The binding affinities of alvimopan, its biologically active metabolite (ADL 08-0011), and another recently approved peripherally acting μ-opioid receptor antagonist, methylaltrexone, have been studied in vitro at opioid receptor subtypes using both morphine-dependent and morphine-naive animal and human models. Both alvimopan and its metabolite demonstrated a 10-fold greater selectivity for μ-opioid receptors relative to human δ-opioid receptors and guinea pig κ-opioid receptors. Moreover, alvimopan and ADL 08-0011 both demonstrated greater affinity for human μ-opioid receptors relative to methylaltrexone. After morphine exposure, spontaneous ileal activity was greater with alvimopan and its metabolite relative to methylaltrexone. The clinical significance of the differing pharmacologic profiles among these agents remains to be elucidated. Several analogues of alvimopan are currently being investigated, with at least one such lysine analogue demonstrating the highest selectivity for peripheral μ-opioid receptors currently reported. Alvimopan provides a novel treatment approach for patients with postoperative ileus, since GI motility may be improved without compromising central analgesic effects of concomitantly used systemic opioids.

Pharmacokinetics

Absorption and distribution. It was originally hypothesized that the clinical effects of alvimopan were entirely mediated locally and that systemic absorption did not occur. While it is now known that systemic absorption does occur, oral bioavailability in humans is estimated at only 6%. After five days of therapy with alvimopan 12 mg orally twice daily, the mean ± S.D. peak plasma concentration (\( C_{max} \)) was 10.98 ± 6.43 ng/mL with a time to reach peak concentration (\( t_{max} \)) of 1.5–3 hours. Plasma alvimopan concentrations are dose dependent up to 18 mg. The basic pharmacokinetic parameters of alvimopan are summarized in Table 1. The plasma concentration–time profile of alvimopan has been described by a two-compartment model with first-order absorption and a lag.

Interindividual variability in plasma concentration appears to be greater with ADL 08-0011 relative to the parent compound as demonstrated by the mean ± S.D. \( C_{max} \) for ADL 08-0011 with standard dosing (35.73 ± 35.29 ng/mL). The \( t_{max} \) for this metabolite does not occur until 36 hours after alvimopan administration.

Concentrations of both alvimopan and its metabolite are 1.9- and 1.4-fold greater in surgical patients, respectively, relative to healthy volunteers, though the difference is not thought to be clinically important. Food decreases the bioavailability of alvimopan and its metabolite 18% and 25%, respectively, and the preoperative dose of alvimopan should be administered while fasting.

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Alvimopan</th>
<th>ADL 08-0011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ( t_{1/2} ) (hr)</td>
<td>10–17</td>
<td>10–18</td>
</tr>
<tr>
<td>Median ( t_{max} ) (hr)</td>
<td>2</td>
<td>36</td>
</tr>
<tr>
<td>Absolute oral bioavailability (%)</td>
<td>6†</td>
<td>NA</td>
</tr>
<tr>
<td>Mean ± S.D. ( C_{max} ) (ng/mL)</td>
<td>10.98 ± 6.43</td>
<td>35.73 ± 35.29</td>
</tr>
<tr>
<td>Mean ± S.D. volume of distribution (L)</td>
<td>30 ± 10</td>
<td>NA</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>80</td>
<td>94</td>
</tr>
</tbody>
</table>

*Information not available.
†Bioavailability 1.9-fold higher in surgical patients.
‡At steady state.

Am J Health-Syst Pharm—Vol 66 Jul 15, 2009 1269
Alvimopan has a mean ± S.D. volume of distribution of 30 ± 10 L, and both alvimopan and ADL 08-0011 bind albumin in plasma, averaging 80% and 94%, respectively. The clinical significance of alvimopan’s propensity to displace highly protein-bound drugs is not currently known.

**Metabolism and excretion.** Alvimopan is converted to its active metabolite, ADL 08-0011, via amide hydrolysis in the gut as a result of microbial activity, not by hepatic metabolism. Cytochrome P-450 (CYP) isoenzyme metabolism and secondary elimination pathways such as glucuronidation or sulfation are not involved in alvimopan metabolism. Biliary secretion is thought to be the primary pathway for alvimopan elimination, with renal excretion accounting for approximately 35% of its clearance. Once alvimopan is converted to ADL 08-0011, it undergoes systemic absorption and first-order elimination. The metabolite is eliminated unchanged in the feces and in the urine, along with other glucuronidated conjugates. The mean terminal half-lives of alvimopan and its metabolite after multiple doses are similar, ranging from 10 to 18 hours.

Recently, the pharmacokinetics of alvimopan and ADL 08-0011 in both healthy subjects and clinical trial participants was reported. Among several small combined studies totaling 719 participants, the mean age was 51.5 years (range, 18–89 years). Most (66%) were undergoing laparotomy at the time of study entry. The pharmacokinetic parameters of alvimopan did not change in the presence of several covariates, including weight, sex, renal function, concomitant acid-blocker use, and preoperative gut decontamination with neomycin and erythromycin. Covariates that lowered concentrations of ADL 08-0011 included preoperative oral antibiotics (lowered by 80%) and acid blockers (lowered by 50%). The former can be explained by the fact that alvimopan is metabolized by gut microflora, resulting in a decreased turnover to the equipotent metabolite. It can be hypothesized that lower plasma concentrations result from acid-blocker use because of the increased pH and subsequent change in gut microflora. The lowered metabolite concentration is not thought to be clinically important, as the efficacy of alvimopan is not altered in patients receiving either of these medication classes.

Because the overall bioavailability of ADL 08-0011 is more affected by antibiotics and acid suppressants than is alvimopan but the medication retains its efficacy, two plausible explanations exist: (1) the metabolite has little clinical significance to the efficacy of alvimopan, or (2) as suggested by Camilleri, alvimopan’s efficacy is not dependent on systemic absorption, and its effects are simply a function of local action in the GI tract. Given that the overall bioavailability of alvimopan is low, the latter seems most likely at this time. Furthermore, in the aforementioned study, there were specific geographic pharmacokinetic differences, with patients in the United States exhibiting higher plasma concentrations when compared to the non-U.S. population. These differences are likely due to regional variability in gut microflora and not to specific genetic differences. The clinical significance of these pharmacokinetic differences remains to be elucidated.

**Use in geriatric patients.** The bioavailability and oral clearance of alvimopan decrease with age; however, this appears to be of minor clinical significance. Alvimopan has been studied in a nonsurgical elderly population with a mean ± S.D. age of 72.7 ± 4.6 years and a mean ± S.D. creatinine clearance (CLcr) of 68 ± 11 mL/min. Although plasma alvimopan concentrations are increased in patients age 70 years or older relative to younger patients, no dosing adjustment is needed.

**Use in pregnancy and lactation and in children.** Alvimopan is in FDA pregnancy category B. Reproductive studies in rats with oral doses of alvimopan 68–136 times the recommended human dose and in rabbits with oral doses 5–10 times the recommended human dose found that fertility was not impaired and no fetal harm occurred. No studies have been conducted with pregnant women.

Lactating rats have been found to excrete alvimopan and its metabolite in milk. No studies in lactating women have been conducted.

To date, trials assessing the safety and efficacy of alvimopan in children have not been conducted.

**Use in renal insufficiency.** The pharmacokinetic variables of alvimopan do not appear to be altered as a result of renal function, given that its primary clearance is via biliary excretion. However, the study suggesting this conclusion was conducted in a nonsurgical population with a mean age of 28.4 years receiving a single 12-mg dose of alvimopan. Furthermore, the mean CLcr among the 24 subjects was 62.4 mL/min; however, this value did include patients with mild, moderate, or severe renal dysfunction. In patients with moderate renal impairment (CLcr, 31–50 mL/min) or severe renal impairment (CLcr, ≤30 mL/min), exposure to the metabolite was twofold to fivefold higher than in patients with no or mild renal impairment. The manufacturer stated that patients with severe renal dysfunction may be at higher risk for adverse effects, including diarrhea, GI pain, and cramping, presumably due to metabolite accumulation. Alvimopan has not been studied in patients with end-stage renal disease and should not be used in this patient population. Patients with mild-to-moderate renal disease do not require dosage adjustments.
Use in hepatic insufficiency.

Although alvimopan is not metabolized in the liver, the manufacturer has reported the potential for higher plasma drug levels in patients with hepatic impairment. Exposure to alvimopan is approximately 2-fold higher in patients with mild-to-moderate hepatic impairment (Child-Pugh class A to B). Dosage adjustment is not required in these patients, but alvimopan should not be used in patients with severe hepatic impairment (Child-Pugh class C). In patients with severe hepatic impairment, the $C_{\text{max}}$ of alvimopan may be increased up to 10-fold.

Pharmacodynamics

A pooled post hoc analysis of five randomized, double-blind, placebo-controlled, Phase III trials analyzed the effect on alvimopan outcomes of several covariates, including age, sex, and race, using Cox proportional hazard models. The primary endpoint was the return of both upper and lower GI functions (termed GI-3) as defined by when the last of the following occurred: first toleration of solid food, passage of first flatus, and passage of the first bowel movement. Patients over age 65 years achieved the primary endpoint later than did younger patients (hazard ratio [HR] = 0.883, $p < 0.05$), and males were slower to recover relative to females (HR = 0.914, $p < 0.05$). Race also seemed to be a factor, as Caucasians recovered faster than non-Caucasians (HR = 1.142, $p < 0.05$). Regardless of demographics, alvimopan was associated with a 12-hour faster GI recovery compared with placebo. The authors concluded that alvimopan was effective in accelerating GI recovery across diverse patient populations.

Alvimopan was shown to selectively prevent morphine-related adverse GI effects without affecting analgesia in patients receiving the opiate in a two-part, double-blind, crossover study in healthy volunteers. Morphine prolonged the mean ± S.D. baseline GI transit time from 69 ± 33 minutes to 103 ± 37 minutes ($p = 0.05$). However, the administration of alvimopan decreased these morphine-induced changes in GI transit time to almost baseline levels (76 ± 30 minutes). In the second part of this study, morphine was associated with reduced visual analogue scale (VAS) pain scores, and administration of alvimopan did not blunt this response. Furthermore, pupil size did not significantly increase in patients receiving alvimopan after receiving morphine, further highlighting the peripheral effects of alvimopan.

Clinical efficacy: Postoperative ileus

Taguchi et al. In a Phase II trial, Taguchi et al. studied the effects of alvimopan in patients age 18–78 years undergoing partial colectomy ($n = 15$) and simple or radical total abdominal hysterectomy (TAH) ($n = 63$). Patients were randomized in a 1:1:1 ratio to placebo or alvimopan 1 or 6 mg given two hours before surgery and then twice daily until the first of the following events occurred: bowel movement, hospital discharge, or seven days. Postoperative pain control was achieved via opioid patient-controlled analgesia (PCA). A liquid diet was introduced on postoperative day 1 if bowel sounds were heard, and diet and activity were advanced as tolerated. The primary study outcomes were time to passage of first flatus, time to the first bowel movement, and time until the patient was ready for discharge. Compared with placebo, alvimopan 6 mg reduced the time to first flatus from 70 to 49 hours ($p = 0.03$), time to the first bowel movement from 111 to 70 hours ($p = 0.01$), and time until discharge readiness from 91 to 68 hours ($p = 0.03$). Outcomes in patients receiving the 1-mg dose were not significantly better than with placebo. Cumulative opioid use and pain scores did not differ among groups. Nausea occurred less frequently in the alvimopan 6-mg group. In addition, the frequency of vomiting was 23%, 26%, and 0% in the placebo, alvimopan 1-mg, and alvimopan 6-mg groups, respectively.

North American Phase III trials.

Nearly all Phase III manufacturer-funded trials of alvimopan published to date have had a similar design. Each was a randomized, double-blind, placebo-controlled, parallel-group, multicenter trial conducted in North America. Patients were at least 18 years of age, underwent a partial small or large bowel resection with primary anastomosis or TAH under general anesthesia, and received postoperative pain management with opioid-based PCA. Patients receiving intrathecal or epidural pain control were excluded, as were those recently receiving opioid analgesics (within the last one to four weeks, depending on the study protocol). All patients were scheduled to have their nasogastric tubes removed at the end of surgery or no later than noon on postoperative day 1, encouraged to walk on postoperative day 1, offered liquids on postoperative day 1, and offered solid food on postoperative day 2. Placebo or alvimopan 6 or 12 mg was administered by mouth at least two hours before surgery and then twice daily, starting on postoperative day 1 and continuing until hospital discharge or for a maximum of seven days. The primary efficacy endpoint was GI-3. A secondary but less subjective efficacy endpoint that also determined both upper and lower GI recovery times was GI-2, which was when the latter of the following occurred: first toleration of solid food and time to the first bowel movement. GI-2 was likely reported more accurately as time to GI-3 may have been compromised by patients’ embarrassment to report flatus and variability in its definition. The results of these studies are summarized in Table 2.
clinical review alvimopan

Wolff et al. 31 studied alvimopan in 510 patients age 20–89 years, 96% of whom underwent bowel resection. Both the primary GI-3 and secondary GI-2 endpoints were reached 15–28 hours earlier with alvimopan compared with placebo, depending on the dose of alvimopan and endpoint used. Treatment effects were more pronounced with alvimopan 12 mg, allowing for discharge orders to be written a mean of 20 hours sooner than with placebo (p = 0.003). The placebo and alvimopan 6-mg groups did not differ significantly with respect to time of discharge orders.

Postoperative opioid use was identical in the placebo and alvimopan 12-mg groups but 24% higher in the alvimopan 6-mg group. The placebo group had a higher frequency of nasogastric tube insertion (14.8%) versus the alvimopan 6-mg group (8.4%) and the 12-mg group (4.8%); this difference was significant between the alvimopan 12-mg and placebo groups (p = 0.004).

Postoperative ileus was reported as a treatment-emergent adverse effect less often with alvimopan (8.3% in the 6-mg group, p = 0.043; 6.3% in the 12-mg group, p = 0.004) than with placebo (15.8%). Nausea, vomiting, hypokalemia, pruritus, and abdominal distention were also more commonly reported with placebo.

Wolff and colleagues 31 studied alvimopan in 510 patients age 20–89 years, 96% of whom underwent bowel resection. Both the primary GI-3 and secondary GI-2 endpoints were reached 15–28 hours earlier with alvimopan compared with placebo, depending on the dose of alvimopan and endpoint used. Treatment effects were more pronounced with alvimopan 12 mg, allowing for discharge orders to be written a mean of 20 hours sooner than with placebo (p = 0.003). The placebo and alvimopan 6-mg groups did not differ significantly with respect to time of discharge orders.

Postoperative opioid use was identical in the placebo and alvimopan 12-mg groups but 24% higher in the alvimopan 6-mg group. The placebo group had a higher frequency of nasogastric tube insertion (14.8%) versus the alvimopan 6-mg group (8.4%) and the 12-mg group (4.8%); this difference was significant between the alvimopan 12-mg and placebo groups (p = 0.004).

Postoperative ileus was reported as a treatment-emergent adverse effect less often with alvimopan (8.3% in the 6-mg group, p = 0.043; 6.3% in the 12-mg group, p = 0.004) than with placebo (15.8%). Nausea, vomiting, hypokalemia, pruritus, and abdominal distention were also more commonly reported with placebo.

Delaney et al. 32 studied alvimopan in 451 patients age 18–80 years undergoing partial colectomy with primary anastomosis or simple or radical TAH. Alvimopan 6 mg significantly decreased the times to GI-3 and GI-2; the alvimopan 12-mg and placebo groups did not differ significantly for these endpoints. In the subset of patients who underwent simple TAH, the mean time to GI recovery did not statistically differ between the placebo and alvimopan groups. Discharge orders were written a mean difference of 14 hours sooner with alvimopan 6 mg compared with placebo.

Table 2.

Phase III Trials of Alvimopan in Postoperative Ileus

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Type of Surgery (% Pts)</th>
<th>Alvimopan Dose (mg) (No. Pts)</th>
<th>Time to Outcome After Surgery (hr)</th>
<th>Tolerance of First Solids</th>
<th>First Flatus</th>
<th>First Bowel Movement</th>
<th>Discharge Order Written</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>LBR (84), SBR (12), rTAH (4)</td>
<td>Placebo (149)</td>
<td>GI-3</td>
<td>GI-2</td>
<td>Tolerance of First Solids</td>
<td>First Flatus</td>
<td>First Bowel Movement</td>
</tr>
<tr>
<td>32</td>
<td>BR (67.5), sTAH (21.6), rTAH (7.1)</td>
<td>Placebo (153)</td>
<td>100.3</td>
<td>115</td>
<td>89</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>33</td>
<td>BR (70.5), rTAH (16), s TAH (14)</td>
<td>Placebo (224)</td>
<td>105.2</td>
<td>126.2</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>34</td>
<td>LBR (NR), SBR (NR)</td>
<td>Placebo (312)</td>
<td>98</td>
<td>112</td>
<td>82</td>
<td>79</td>
<td>96</td>
</tr>
<tr>
<td>35</td>
<td>LBR (95), SBR (5)</td>
<td>Placebo (229)</td>
<td>92.6</td>
<td>109.5</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>39</td>
<td>sTAH (100)</td>
<td>Placebo (106)</td>
<td>55.4</td>
<td>92</td>
<td>51.5</td>
<td>46.7</td>
<td>91.6</td>
</tr>
</tbody>
</table>

aGI-3 = latest of events among (1) tolerance of solid food, (2) passage of first flatus, and (3) first bowel movement, GI-2 = latter of events between (1) tolerance of first solid food and (2) first bowel movement, LBR = large-bowel resection, SBR = small-bowel resection, rTAH = radical total abdominal hysterectomy, NR = not reported, sTAH = simple total abdominal hysterectomy.

bAlvimopan was given orally before surgery and twice daily after surgery for up to seven days.

cData from modified intent-to-treat population (i.e., all randomized patients who underwent protocol-specified surgery, took at least one dose of study drug, and had an efficacy assessment).

dSignificantly different from placebo result (p < 0.05).

eTime to event as compared with placebo (actual times not reported).

fData from McKay LW, GlaxoSmithKline, personal communication, 2008 May 27.
tive daily opioid use was 20% higher in the alvimopan 12-mg group than with placebo and alvimopan 6-mg groups; however, pain scores did not differ among the groups. The investigators did not think that the greater opioid use in the alvimopan 12-mg group was related to the study drug or that it was clinically significant.

Postoperative nasogastric tube insertion occurred in 6.9% of the placebo group, 2.1% of the alvimopan 6-mg group, and 7.2% of the alvimopan 12-mg group. Nausea was reported in 68%, 64%, and 58.9% of the placebo and alvimopan 6- and 12-mg groups, respectively; vomiting was reported in 32%, 25.3%, and 15.1%, respectively (p < 0.001). The rates of postoperative ileus did not significantly differ among groups. The authors attributed the apparent lack of effect of the 12-mg alvimopan dose to the higher dropout rate (26.7%) due to adverse GI events in that group. Hence, more censored observations were recorded in the 12-mg group compared with the placebo (20.9%) and 6-mg (15.8%) groups, possibly resulting in the lack of efficacy seen in the analysis.

Viscusi et al. Viscusi et al.33 randomized 666 patients age 20–93 years in a 1:1:1 ratio to receive alvimopan 6 or 12 mg or placebo. Approximately 70% of patients underwent bowel resection. Alvimopan 12 mg (but not 6 mg) differed significantly from placebo for the primary endpoint of GI-3. Once adjusted for significant covariates of surgery duration and sex, both doses significantly shortened the time to the primary endpoint versus placebo. Both alvimopan doses were significantly superior to placebo in achieving GI-2. In the modified intent-to-treat population (i.e., all randomized patients who had a bowel resection or TAH, took at least one dose of the study drug, and had an efficacy assessment), alvimopan 6 and 12 mg shortened the time to achievement of the primary endpoint by a mean of 7.5 hours (95% confidence interval [CI], −17.7 to 2.7) and 9.9 hours (95% CI, −20.4 to 0.6), respectively, compared with placebo (mean time to primary endpoint of 105.2 hours).

Neither alvimopan dose significantly shortened the time to tolerance of solid food, or passage of flatus. However, alvimopan did significantly shorten the time to the first bowel movement and time to written discharge order compared with placebo. The mean daily opioid doses and VAS pain scores were similar among all groups. Postoperative nasogastric tube insertion occurred more commonly with placebo (8.2%) versus alvimopan (6.0% with 6 mg and 5.5% with 12 mg). Postoperative ileus, nausea, and vomiting occurred at least 5% more frequently with placebo than with alvimopan.

Ludwig et al. A double-blind, placebo-controlled, parallel-group, multicenter, North American trial by Ludwig et al.34 randomized patients (mean ± S.D. age, 60 ± 14 years) in a 1:1 fashion to alvimopan 12 mg or placebo orally 30–90 minutes before surgery, specifically small- or large-bowel resection with primary anastomosis. Study medication was continued postoperatively in twice daily doses starting on postoperative day 1 and continued to be administered up to seven days. The primary efficacy endpoint was time to GI-2, which was achieved approximately 20 hours sooner with alvimopan compared with placebo. Other pertinent study endpoints are shown in Table 2. The mean quantity of opioid use was similar between groups. Drug-related adverse events, nausea (8.5% versus 10.2%), vomiting (1.8% versus 3.7%), and abdominal distention (2.1% versus 2.5%) occurred less frequently with alvimopan than placebo (McKay LW, GlaxoSmithKline, personal communication, 2008 May 27).

European trial. A multinational, European, randomized, double-blind, placebo-controlled, parallel-group, Phase III trial,35 similar to trials conducted in North America,31–34 randomized patients undergoing partial small- or large-bowel resection with primary anastomosis or radical TAH to placebo or alvimopan 6 or 12 mg in a 1:1:1 manner. The protocol was changed during the trial to enroll no additional radical TAH patients because American trials did not show benefit in this subset of patients,31–33 and the 106 radical TAH patients were excluded from the analysis and results. The study drug was administered 2 hours before surgery and then twice daily beginning on postoperative day 1 and continuing until discharge or for a maximum of seven days after surgery. Ambulation was encouraged on postoperative day 1, and diets were advanced as tolerated. Epidural analgesics were prohibited, as they were in the North American trials. However, the use of nonsteroidal antiinflammatory drugs and other nonopioid analgesics was allowed (used in 69% of subjects versus 4% of North American patients in the first 48 hours after surgery), and postoperative opioid pain management consisted of either PCA or staff-administered i.v. and intramuscular administration.

The primary endpoint was GI-3, which was shortened significantly, by 8.4 hours, in the alvimopan 6-mg group but not in the alvimopan 12-mg group compared with placebo. GI-2, the secondary endpoint, was significantly shortened for both the alvimopan 6- and 12-mg groups by 14.3 and 10.7 hours, respectively. Interestingly, the time to written discharge orders was nearly twice as long in this study compared with the North American trial,31–34 perhaps due to cultural differences. Opioid consumption and pain scores did not differ among groups.

In a post hoc analysis of patients who received PCA versus those who did not, alvimopan was shown to speed GI recovery in the PCA group but not in patients without PCA.
This finding was likely due to the fact that the PCA group received approximately twice the amount of opioids compared with patients without PCA. In the PCA subgroup, alvimopan yielded comparable findings to those in the North American trials. These findings support the ideas that postoperative ileus is multimodal and that alvimopan offsets the increased duration of postoperative ileus attributable to opioid-induced constipation.

**Post hoc analyses.** In a post hoc analysis of four of the above trials, morbidity associated with postoperative ileus was examined in the 1409 patients who underwent bowel resection (92% underwent large-bowel resection) and received alvimopan 12 mg or placebo. Postoperative nasogastric tube insertion occurred in 11.5% of the placebo group and 6.6% of the alvimopan group (p = 0.001), and postoperative ileus complications resulted in a prolonged hospital stay in 6.8% of the placebo group versus 2.1% of the alvimopan group (p < 0.001). The proportion of patients with postoperative ileus complications resulting in readmission within seven days of hospital discharge was comparable between groups.

Another post hoc analysis of five randomized, double-blind, placebo-controlled, parallel-group, multicenter, Phase III trials consisting of three published reports and two abstracts (one now published as a full report) assessed time to recovery of GI function in patients who underwent bowel resection. In all the trials, alvimopan 6 or 12 mg or placebo was administered orally 30 minutes to five hours before surgery and then twice daily until discharge or up to seven days. A total of 1877 patients who underwent bowel resection and received alvimopan 12 mg or placebo were included in the analysis. Times to GI-2 (100.9 hours versus 117.9 hours) and GI-3 (92.5 hours versus 105.2 hours) were significantly shortened with alvimopan versus placebo. Nausea and vomiting occurred less frequently with alvimopan than with placebo.

**TAH.** Alvimopan was previously found not to shorten the time to GI recovery in simple TAH. In that study and others with small subsets of patients with simple TAH, the study drug was not administered after hospital discharge. The lack of benefit with alvimopan may also be attributed to the natural history of bowel recovery after TAH compared with that after bowel resection. A pooled analysis of placebo-treated patients in four Phase III trials found that the mean time to GI-3 recovery was 109.4 and 69.5 hours for bowel resection and TAH, respectively. In addition, many of the TAH patients in these trials were discharged before the first postoperative bowel movement; if GI recovery did not occur within 10 days after surgery or before discharge, censored times for events were used in the analyses.

Hence, a different trial protocol was developed to examine the role of alvimopan in simple TAH. In this randomized, double-blind, parallel-group, Phase III trial, 519 women age 18 years or older who underwent simple TAH received alvimopan 12 mg or placebo in a 4:1 ratio at least two hours before surgery and then twice daily for seven days, beginning on postoperative day 1. Women discharged before seven days received study medication to take at home. Similar to the other Phase III trials, patients were encouraged to walk on postoperative day 1 and their diets were advanced as tolerated. The primary endpoint was the safety and tolerability of alvimopan; secondary endpoints, including GI-3 and GI-2, were assessed for the seven days of treatment. Nausea and vomiting were more common with alvimopan than with placebo (72.2% versus 63.2% for nausea and 31.2% versus 25.5% for vomiting, p values not specified). Constipation and postoperative ileus occurred less frequently with alvimopan than with placebo (22.8% versus 31.1% for constipation and 0.7% versus 2.8% for postoperative ileus, p values not specified). Of all the patients in the trial, postoperative nasogastric tube insertion occurred in one placebo-treated patient. Opioid consumption and pain scores did not differ significantly between the groups. Results of the secondary efficacy endpoints are detailed in Table 2. Although alvimopan shortened the time to GI-2 and the first bowel movement, it did not reduce the time to written discharge orders.

**Clinical efficacy: Opioid-induced bowel dysfunction**

Schmidt described two Phase II trials of alvimopan in opioid-induced bowel dysfunction (OIBD) in 67 patients receiving opioids for chronic pain and 34 receiving methadone for treatment of opioid addiction. All patients were experiencing constipation on stable opioid doses and had been receiving opioids for one week to 10 years. The patients were divided into two groups. In the first parallel-group study (n = 75), patients received single doses of placebo or alvimopan 0.5, 1.5, or 3 mg. Dose-related increases in the occurrence of bowel movements and stool weight were apparent within 12 hours of administration of a single dose. Differences related to all dosages of alvimopan were significant, compared with placebo. Maximal response was seen 4 hours after the 3-mg dose and 7 hours after the 0.5-mg dose. No patients experienced reversal of analgesia.

The second study group (n = 26) received placebo or increasing alvimopan doses (0.5, 1.5, 3, or 4.5 mg on days 1–4, respectively). Stool weight increased daily through day 3 but did not increase further on the fourth day, possibly reflecting an initial evacuation of retained feces and subsequent return to normal bowel function on day 4.
In a randomized, double-blind, placebo-controlled, multicenter trial by Paulson et al., placebo or alvimopan 0.5 or 1 mg orally once daily was studied in chronic opioid users (148 with nonmalignant pain and 20 with opioid dependence) with OIBD. Patients were assigned to a study drug in a 1:1:1 manner. The study period consisted of a 14-day baseline assessment period, a 21-day treatment period, and a 14-day follow-up observation period. Patients were instructed to continue all of their prestudy medications, including opioids and noncathartic laxative bowel regimens, throughout the study period. Those using milk of magnesia, magnesium citrate, castor oil, and Epsom salts were excluded from the study; use of lactulose, polyethylene glycol, bisacodyl, senna, fiber, and docusate was allowed if part of the patient’s prestudy bowel regimen. The primary outcome was the percentage of patients with at least one bowel movement within eight hours of study drug administration on each day during the 21-day treatment period.

The primary efficacy outcome occurred in 29%, 43%, and 54% of patients in the placebo, alvimopan 0.5-mg, and alvimopan 1-mg groups, respectively ($p < 0.001$ for both alvimopan groups versus placebo). The median time to the first bowel movement after study drug administration was 21, 7, and 3 hours for the respective groups ($p < 0.001$ for alvimopan 1 mg versus placebo). Laxatives were excluded from the study; use of lactulose, polyethylene glycol, bisacodyl, senna, fiber, and docusate was allowed if part of the patient’s prestudy bowel regimen. The primary outcome was the percentage of patients with at least one bowel movement within eight hours of study drug administration on each day during the 21-day treatment period.

The primary efficacy outcome occurred in 29%, 43%, and 54% of patients in the placebo, alvimopan 0.5-mg, and alvimopan 1-mg groups, respectively ($p < 0.001$ for both alvimopan groups versus placebo). The median time to the first bowel movement after study drug administration was 21, 7, and 3 hours for the respective groups ($p < 0.001$ for alvimopan 1 mg versus placebo). Laxatives were excluded from the study; use of lactulose, polyethylene glycol, bisacodyl, senna, fiber, and docusate was allowed if part of the patient’s prestudy bowel regimen. The primary outcome was the percentage of patients with at least one bowel movement within eight hours of study drug administration on each day during the 21-day treatment period.

Adverse effects

The most common adverse effects of alvimopan are GI related. Nausea, vomiting, and nasogastric tube reinsertion occur more frequently with placebo than with alvimopan in patients with postoperative ileus. In 3015 patients receiving alvimopan ($n = 1650$) or placebo ($n = 1365$) in nine placebo-controlled trials, the following adverse effects occurred $\geq 1\%$ more often with alvimopan than placebo: constipation (9.7% versus 7.6%), dyspepsia (5.9% versus 4.8%), flatulence (8.7% versus 7.7%), back pain (3.4% versus 2.6%), and urinary retention (3.5% versus 2.3%). Although hypokalemia was more common in the subset of bowel resection patients ($n = 1985$) receiving alvimopan (9.5%) compared with placebo (8.5%), hypokalemia was actually less frequent with alvimopan than placebo. Although hypokalemia was more common in the subset of bowel resection patients ($n = 1985$) receiving alvimopan (9.5%) compared with placebo (8.5%), hypokalemia was actually less frequent with alvimopan than placebo. Although hypokalemia was more common in the subset of bowel resection patients ($n = 1985$) receiving alvimopan (9.5%) compared with placebo (8.5%), hypokalemia was actually less frequent with alvimopan than placebo. Although hypokalemia was more common in the subset of bowel resection patients ($n = 1985$) receiving alvimopan (9.5%) compared with placebo (8.5%), hypokalemia was actually less frequent with alvimopan than placebo.

Perhaps the most concerning adverse effects of alvimopan became apparent in long-term studies. When FDA issued an approvable letter for alvimopan for the treatment of postoperative ileus, it required additional safety data and a risk management plan as a result of preliminary findings from a Phase III, blinded, placebo-controlled, 12-month safety evaluation of alvimopan 0.5 mg twice daily in patients with chronic noncancer pain and OIBD (study 014). A 6-month interim analysis revealed an increased rate of serious cardiovascular events in the alvimopan-treated group. The affected patients were considered at high risk for developing cardiovascular complications, and the onset of events did not appear correlated to the duration of alvimopan exposure.

The full study results were reported in a press release in early 2007. A total of 805 patients had been enrolled and randomized in a 2:1 ratio of alvimopan:placebo. A “numerical imbalance” was noted between the alvimopan ($n = 538$) and placebo ($n = 267$) groups in terms of cardiovascular events and neoplasms. Myocardial infarction occurred in 1.3% and 0% of the alvimopan and placebo groups, respectively, and all cardiovascular adverse effects occurred in 2.6% and 1.1% of the respective groups.

Drug interactions

Although antibiotics and acid suppressants have been shown to affect gut microflora and decrease conversion of alvimopan to its active metabolite, this does not appear to be a clinically relevant interaction, likely due to the equipotent activity of alvimopan and its metabolite and the local action of the drug in the gut. Alvimopan is not a CYP substrate according to in vitro studies. Alvimopan and its metabolite do not inhibit CYP 1A2, 2C9, 2C19, 3A4, 2D6, and 2E1 or induce CYP 1A2, 2B6, 2C9, 2C19, and 3A4. Alvimopan and its metabolite are substrates for but not inhibitors of P-glycoprotein. Based on these in vitro data, alvimopan is unlikely to alter the pharmacokinetics of concurrent drugs through induction or inhibition of CYP isoenzymes or P-glycoprotein inhibition.
Dosage and administration
Alvimopan is supplied as a 12-mg capsule. The recommended adult dosage of alvimopan for prevention of postoperative ileus is 12 mg administered with a sip of water 30 minutes to five hours before surgery, followed by 12 mg twice daily beginning the day after surgery for a maximum of seven days or until discharge. Patients should not receive more than 15 total doses of alvimopan. Alvimopan is indicated only for short-term hospital use.42,43 Hospitals must register and meet requirements of the Entereg Access Support and Education (E.A.S.E.) program. This program requires that hospital staff who prescribe, dispense, or administer alvimopan receive educational materials regarding alvimopan’s short-term use, acknowledge the limit of 15 total doses, and provide assurances that hospital staff will not dispense the medication to patients at discharge or sell it to nonparticipating hospitals.

Pharmacoeconomics
Of the 22 million inpatient surgical procedures performed annually in the United States, an estimated 2.7 million lead to postoperative ileus lasting at least 1 day.44 Estimating the precise number of cases of postoperative ileus is virtually impossible, since the vast majority are undocumented and postoperative ileus is considered unavoidable after abdominal surgery. Patient discharge is typically delayed until the postoperative ileus resolves to avoid rehospitalization for intractable nausea and vomiting, dehydration, and pain crises when oral analgesics cannot be used effectively.

A significant cost-savings could be achieved with quicker patient discharge. For example, approximately $1.75 billion is spent annually on 1.8 million hospital days for 161,000 Medicare recipients undergoing major intestinal or rectal resection.45 One study examined 83 patients after TAHs or colectomies; patients with postoperative ileus averaged an extra 4.5 hospital days and an additional $4000 more in costs compared with patients who did not have postoperative ileus.46 Other researchers have reported increases in length of stay by 2.4–3 days and in hospital costs by $4118–$8785 ($p < 0.001 for both).12

At the time of writing, the cost of alvimopan was $62.50 per tablet, or $937.50 for a 15-dose course (McKay LW, GlaxoSmithKline, personal communication, 2008 Jul 2), substantially less than one day of hospital costs—assuming real-world patients are discharged 15–20 hours sooner with alvimopan treatment as were those in clinical trials (Table 2). A manufacturer-funded pharmacoeconomic analysis from the health-system perspective was recently published.47 On the basis of length of stay in the four North American Phase III clinical trials31-34 and Premier Database and U.S. Census Bureau data for hospital costs, alvimopan-treated patients, on average, would account for approximately $900 less (range, $879–$977) in hospital costs than placebo-treated patients, owing to swifter discharges (and despite the $558 acquisition cost of the mean of 8.9 alvimopan 12-mg doses used in the trials).

Notably, this pharmacoeconomic analysis did not use the actual length of hospital stay in its calculations but, rather, the time to a discharge order being written, which was 18 hours sooner with alvimopan compared with placebo. Assuming that discharges were delayed equally between the randomized placebo and alvimopan groups, results should not have been affected, though actual length of stay may have been underestimated in the analysis. Costs associated with nausea, vomiting, and other morbidities were not assessed, which, if considered, may have increased alvimopan’s cost-effectiveness.

Place in therapy
At this time, alvimopan may be considered for prevention and treatment of postoperative ileus in surgical patients undergoing partial large- or small-bowel resection with primary anastomosis. It has not been studied in conjunction with epidural opioid analgesia, a procedure known to increase the duration of postoperative ileus and a common practice in many institutions after bowel resection, or extensively with nonopioid adjunctive pain medications, which could reduce postoperative opioid requirements. Alvimopan’s efficacy in such settings is unknown. Therapy may be discontinued after the return of bowel function (the GI-2 endpoint of clinical trials) or after a maximum of 15 doses. There is no role for alvimopan in surgeries other than the aforementioned, specifically TAH, and OIBD.

Conclusion
Alvimopan, a peripherally acting μ-opioid receptor antagonist, is a novel agent for the treatment of postoperative ileus. It appears to decrease the duration of postoperative ileus and hence hospitalization by approximately one day, theoretically offsetting its acquisition costs. However, unresolved long-term safety issues, a limited indication, and its restricted-access program are likely to hinder its widespread use in the surgical population.

References
6. Kalff JC, Schraut WH, Billiar TR et al. Role of inducible nitric oxide synthase in