National PBM Drug Monograph

Alvimopan (Entereg®)

10 April 2009

VHA Pharmacy Benefits Management Services and the Medical Advisory Panel

The purpose of VACO PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary [1,2,3,4,5,6,7,8]

- The FDA-approved indication for alvimopan (Entereg; 12-mg oral capsule) is to accelerate the time to gastrointestinal recovery following partial large or small bowel resection in patients at least 18 years of age.
- Alvimopan is a μ-opioid receptor antagonist that prevents the peripheral GI effects of opioids on motility and secretion without reversing the central analgesia provided. It is the second peripheral opioid antagonist to be approved by the FDA and the only drug approved for improving time to post-operative GI recovery.
- Alvimopan is available only through the Entereg Access Support and Education (E.A.S.E) program, a restricted access program. Any hospital that would like to use alvimopan must first register with this program and provide educational materials on the proper administration of the medication to the clinical staff.
- Alvimopan 12-mg is to be used for a maximum of 15 doses. The first dose must be administered 30 minutes to 5 hours before surgery. Following surgery, alvimopan is dosed twice daily until hospital discharge or maximum of 7 days.
- Alvimopan was studied in four placebo-controlled randomized controlled trials and found to moderately decrease time to upper and lower GI recovery with decreases in time to GI recovery ranging from 7.5-22 hours. Alvimopan was also shown to decrease time to hospital discharge order written by approximately 1 day when compared to placebo.
- Alvimopan demonstrated a statistically significant reduction in the incidence of postoperative ileus in two phase three trials with numbers needed to treat (NNT) of 10.5 and 25 respectively. In addition, alvimopan was shown to reduce readmission within 10 days for any reason with an NNT of 29 and to prevent prolonged hospital length of stay due to complications of postoperative ileus (POI) with a NNT of 20. However, alvimopan did not show a statistically significantly reduction in readmission within 7 days due to POI.
- Phase III trials demonstrated that alvimopan was safe and well-tolerated. The most common side effects reported with alvimopan which were reported in ≥ 3% of patients treated with alvimopan and for which the rate of events was at least 1% higher when compared to placebo included anemia, constipation, dyspepsia, flatulence, hypokalemia, back pain, and urinary retention.
- In studies for opioid-induced bowel dysfunction (a nonapproved indication), the alvimopan treatment group (0.5mg twice daily for 12 months) had a higher number of myocardial infarctions (7 with alvimopan, 0 with placebo). However, a causal relationship has not been established, and this effect was not noted in studies using larger doses (12-mg) for shorter periods (15 days) for post-operative GI recovery.
- Based on Federal Supply Schedule (FSS) pricing, a treatment course of alvimopan would cost approximately $700 per patient.
- **Conclusions:** Alvimopan is currently the only pharmacologic treatment option available for acceleration of time to GI recovery following bowel resection. Alvimopan is first line pharmacologic therapy for acceleration of GI recovery following bowel resection. When used, alvimopan should be used as an adjunct to any current non-pharmacologic treatment options for accelerating GI recovery time, including encouraged mobility, removal of the NGT within one day of surgery, and early re-introduction of liquids and solid foods. Alvimopan is available only through the restricted access program, Entereg Access Support and Education (E.A.S.E).

- **Recommendations:** Alvimopan is to be administered for a maximum of 7 days only to patients undergoing bowel resection and who are scheduled for IV opioid analgesia. Its use should be restricted to general and GI surgery. In addition, a prior approval process should be in place to verify appropriate use of this medication based upon the developed criteria for use and those outlined through the E.A.S.E. program. Hospitals desiring to use alvimopan must register with this program and provide educational material on the proper usage of alvimopan to the clinical staff.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant for possible addition of alvimopan to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics[1]

Alvimopan is a selective antagonist of the μ-opioid receptor with a Ki of 0.4nM which due to its high affinity for this receptor demonstrates slower disassociation when compared to other opioid ligands. Ki is representative of the affinity of the molecule to the target receptor with the strength increasing as Ki decreases. The Ki of naloxone is 3.5 - 4nM, and will, therefore, not displace alvimopan from the GI tract μ-opioid receptors. Through competitive binding to the gastrointestinal μ receptor; alvimopan antagonizes the peripheral effects of opioids on GI motility and secretion without reversing the central analgesic effects of the opioid. Alvimopan also has an active metabolite that has less affinity for the μ-opioid receptor than the parent compound. It is an amide hydrolysis compound that is exclusively a product of intestinal flora metabolism.

Absorption:

- Peak concentration is noted approximately 2 hours following oral administration.
- The absolute bioavailability is approximately 6%.
- No significant accumulation was noted after twice daily dosing.
- Concentrations of alvimopan and its metabolite are higher (1.9 fold and 1.4 fold respectively) in post-operative ileus patients than healthy individuals.
- High fat meals decreased the extent and rate of absorption.
    - C_{max} and AUC were decreased by 38% and 21% respectively.
    - T_{max} was prolonged by approximately 1 hour.

Metabolism and Excretion:

- Average plasma clearance is 402 (± 89) mL/min.
- Renal clearance accounts for ~35% of total clearance.
- Biliary secretion is the primary pathway for elimination.
    - Unchanged and unabsorbed alvimopan following biliary excretion was then hydrolyzed to its metabolite by gut micro flora.
- The mean terminal phase half-life for alvimopan following multiple doses was 10-17 hours.
- The mean terminal phase half-life for its metabolite ranged from 10-18 hours.

Special Populations:

- Age, race, gender, Crohn's disease, and renal impairment were found to have no clinically significant impact on pharmacokinetics of alvimopan.
- In patients with mild hepatic impairment (Child-Pugh Class A and B), exposure to alvimopan was higher than healthy comparators; however, there were no consistent effects on C_{max} or half-life.
    - The pharmacokinetics did appear to be more variable in these patients.
- In patients with severe hepatic impairment (Child-Pugh Class C), an approximate 10-fold increase in C_{max} was found.

FDA Approved Indication(s) and Off-label Uses [1,2,3]

Alvimopan is FDA approved "to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis" in patients

greater than 18 years of age.[1] It is currently being studied for use in opioid-induced constipation at a much lower dose than is currently marketed for bowel resection recovery. At present, any off-label use of alvimopan is prohibited through the Entereg Access Support and Education (E.A.S.E) program.

Current VA National Formulary Alternatives

There are currently no alternative medications approved by the FDA for the prevention of post-operative ileus. While there is no gold standard treatment for post operative bowel recovery, typical interventions are non-pharmacologic including: encouraged mobility, removal of the NGT within one day of surgery, and early re-introduction of liquids and solid foods.

Dosage and Administration[1]

Alvimopan is available in capsule formation and is dosed at 12-mg 30 minutes to 5 hours prior to surgery followed by 12-mg twice daily for up to 7 days or until discharge following partial large or small bowel resection. A maximum of 15 doses is allowed for this medication due to safety concerns found in a 12-month study evaluating the use of alvimopan 0.5mg twice daily for the treatment of opioid-induced constipation. An increased rate of myocardial infarctions, bone fractures, and neoplasms was noted in the alvimopan treatment group, but no causal relationship has been established, and these results were not found in short term use following bowel resection surgery.

No dosage adjustment is necessary with patients with mild-to-moderate hepatic disorder (Child-Pugh Class A or B). Alvimopan is not recommended for use in patients with severe hepatic disorder (Child-Pugh Class C) as it can result in a 10-fold increase of plasma levels of alvimopan.

No adjustment is necessary for patients with mild-to-severe renal disease; however, these patients should be monitored closely for adverse events. No studies have been conducted in patients with end-stage renal disease; therefore, use of alvimopan is not recommended.

Efficacy [4,5,6,7,8]

Efficacy Endpoints:

- GI-3 was the time to recovery of GI function defined as the later of the following:
  - Time to first toleration of solid food
  - Time to first bowel movement or first passed flatus
- GI-2 was the time to recovery of GI function defined as the later of the following:
  - Time to first toleration of solid food
  - Time to first bowel movement
- Time to hospital discharge order written

Summary of Efficacy Results:

- Two randomized controlled trials and a meta-analysis found a statistically significant acceleration in time to GI-3 recovery following bowel resection, ranging from 9.9 to 22 hours.
- The third randomized controlled trial found a 7.5 hour improvement in time to GI-3 recovery, but it was not statistically significant.
- Two phase III trials and a meta-analysis found a statistically significant improvement in time to hospital discharge order written, up to approximately 1 day earlier than patients on placebo.
- The third phase III trial showed an improvement of approximately 7 hours for time to hospital discharge order written in the alvimopan treatment group.
- Improvements in efficacy measures were noted with both the 12-mg and 6-mg alvimopan treatment groups; however, the FDA felt that data was more consistent with the

12-mg results leading to the marketing of only the 12-mg strength since safety was felt to be similar among both active treatment strengths.

For further details on the efficacy results of the clinical trials, refer to *Appendix: Clinical Trials* (page 9).

Adverse Events (Safety Data) [1,3]

Serious Adverse Events:

In a 12-month study of alvimopan 0.5mg twice daily for opioid-induced constipation, a higher number of myocardial infarctions was noted in the active group when compared to placebo (7 with alvimopan, 0 with placebo). However, a causal relationship has not been established. The increase in MI was not observed in postoperative ileus patients receiving short-term alvimopan.

In the same 12-month study, a statistically significant difference was noted with benign, malignant, and unspecified neoplasms [p=0.027, 1 placebo patient (<1%), 14 alvimopan patients (3%)]. Also noted in this study was a higher rate of bone fractures in the alvimopan treatment group. The incidence was 1.1% with placebo (3 patients) and 3.7% (20 patients) with alvimopan. However, a causal relationship has not been established between these effects and alvimopan, and the increases in incidence of these events were not noted in post-operative ileus patients being treated short-term.

Common Adverse Events:[1]

Table 1: Treatment-Emergent Adverse Reactions* Reported in ≥ 3% of patients treated with alvimopan and for which the rate of events was at least 1% higher when compared to placebo

	Bowel Resection Patients		All Surgical Patients	
	Placebo % (n=986)	Alvimopan % (n=999)	Placebo % (n=1365)	Alvimopan % (n=1650)
Anemia	4.2	5.2	5.4	5.4
Constipation	3.9	4.0	7.6	9.7
Dyspepsia	4.6	7.0	4.8	5.9
Flatulence	4.5	3.1	7.7	8.7
Hypokalemia	8.5	9.5	7.5	6.9
Back Pain	1.7	3.3	2.6	3.4
Urinary Retention	2.1	3.2	2.3	3.5

*Defined as an event occurring after the first dose of study and within 7 days of the last dose or events present at baseline, but worsening in severity after the start of the study medication

For further details on the safety results of the clinical trials, refer to *Appendix: Clinical Trials* (page 9).

Precautions/Contraindications[1]

Precautions:

- Patients recently exposed to opioids may be more sensitive to the effects of this medication and may experience gastrointestinal side effects (e.g., abdominal pain, diarrhea, nausea, and vomiting).
    - Caution should be used in patients who have had more than 3 doses of opioids within a week of surgery as these patients were not studied.
- Use in patients undergoing correction of complete bowel obstruction is not recommended.
- As no adequate studies have been completed in pregnancy or lactation, alvimopan should be used cautiously in these patients and only when clearly indicated.

Contraindications:

- Use of alvimopan is contraindicated in patients who have taken therapeutic doses of opioids for 7 consecutive days prior to administration of this medication.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for generic name a*lvimopan:* Innopran XL 120mg tablet, Aristospan 20mg injection, Eletriptan 20mg tablet, Alprazolam 0.25mg tablet, Almotriptan 12.5 mg tablet, Alphagan P eye drops

LA/SA for trade name *Entereg:* Inderal* 40mg tablet, Entocort EC 3mg capsule, Entecavir 0.5mg tablet, Coreg CR 10mg capsule

* high alert drug per ISMP

Drug Interactions[1]

Drug-Drug Interactions:

- Alvimopan has not been shown to affect the pharmacokinetics of other drugs, nor do other medications affect the pharmacokinetics of alvimopan.

Drug-Food Interactions:

- High-fat meals immediately prior to administration have been shown to decrease the oral absorption of alvimopan.
    - However, as most patients will be NPO while on this medication, this has little to no clinical impact on dosing.

Acquisition Costs

Table 2: Cost

Drug	Cost/capsule	Maximum total treatment cost
Alvimopan 12-mg	$46.46	$696.83

Pharmacoeconomic Analysis [4,5,6,9,10,11]

There are currently no published pharmacoeconomic analyses for alvimopan. However, there is published literature on the economic burden of postoperative ileus and the increased length of stay associated with this complication. The studies found that the economic impact of this surgical complication totals $1.46 billion annually for the United States. In addition, alvimopan has published outcomes data showing decreased occurrence of postoperative ileus, decreased complications of POI resulting in increased length of stay, and lower readmission rates.

Table 3: Costs to Prevent One Outcome

	Incidence in Placebo group	Incidence in Alvimopan 12mg group	Absolute Risk Reduction	Relative Risk Reduction	Number Needed to Treat	Total Treatment Cost to Prevent One Outcome
Complications of POI resulting in increased length of stay[9]	**7.0%**	**2.0%**	**5.0%**	**71.4%**	**20**	$13,936.60
Readmission within 7 days due to complications of POI[9]*	**--**	**--**	**--**	**--**	**--**	--
Readmission within 10 days for any cause[9]	**8.3%**	**4.9%**	**3.4%**	**41%**	**29**	$20,208.07
Postoperative Ileus						$7,316.72 -

Wolff, *et al* [6]	**15.8%**	**6.3%**	**9.5%**	**60.1%**	**10.5**	$17,420.75
Viscusi, *et al* [5]	**10.3%**	**6.3%**	**4%**	**38.8%**	**25**	
Delaney, *et al* [4]*	--	--	--	--	--	

* Findings not statistically significant

There is currently no consistent data that provides the costs associated with the outcomes listed above. The Wolff, *et al*[9] did not report an actual decrease in LOS with alvimopan vs. placebo, and it's unclear whether readmission for any cause can be attributed to alvimopan since its use did not show a statistically significant decrease in readmission due to POI complications. Therefore, it is difficult to accurately assess the pharmacoeconomic value of alvimopan 12-mg in terms of preventing the above outcomes. However, in the phase III trials, alvimopan was associated with a hospital discharge order written approximately one day earlier than the placebo treatment group.

According to national VA data, approximately 5000 patients undergo bowel resection surgery annually. Of these patients, it is estimated that 10%-20% would be eligible to receive alvimopan based upon the developed criteria for use and those outlined through the E.A.S.E. program.

Conclusions

Alvimopan is currently the only pharmacologic treatment option available for acceleration of time to GI recovery following bowel resection. Alvimopan is first line pharmacologic therapy for acceleration of GI recovery following bowel resection. When used, alvimopan should be used as an adjunct to any current non-pharmacologic treatment options for accelerating GI recovery time, including encouraged mobility, removal of the NGT within one day of surgery, and early re-introduction of liquids and solid foods. Alvimopan is available only through the restricted access program, Entereg Access Support and Education (E.A.S.E).

Recommendations

Alvimopan is to be administered for a maximum of 7 days only to patients undergoing bowel resection and who are scheduled for IV opioid analgesia. Its use should be restricted to general and GI surgery. In addition, a prior approval process should be in place to verify appropriate use of this medication based upon the developed criteria for use and those outlined through the E.A.S.E. program. Hospitals desiring to use alvimopan must register with this program and provide educational material on the proper usage of alvimopan to the clinical staff.

References:

1. Product Package Insert for alvimopan (Entereg). May 2008.
2. Alvimopan (Entereg) website. http://www.entereg.com
3. Information on File. Alodor Corporation.
4. Delaney CP, Weese JL, Hyman NH, *et al.* Phase III trial of alvimopan, a novel, peripherally acting, mu opioid antagonist, for postoperative ileus after major abdominal surgery. Dis Colon Rectum 2005; 48: 1114-1129.
5. Viscusi ER, Goldstein S, Witkowski T, *et al.* Alvimopan, a peripherally acting mu-opioid receptor antagonist, compared with placebo in postoperative ileus after major abdominal surgery: results of a randomized, double-blind, controlled study. Surg Endosc 2006; 20: 64-70.
6. Wolff BG, Michelassi F, Gerkin TM, *et al.* Alvimopan, a novel, peripherally acting mu opioid antagonist: results of a multi-center, randomized, double-blind, placebo-controlled, phase III trial of major abdominal surgery and postoperative ileus. Ann Surg 2004; 240(4): 728-735.

7. Herzog TJ, Coleman RL, Guerrieri JP, *et al.* A double-blind, randomized, placebo-controlled phase III study of the safety of alvimopan in patients who undergo simple total abdominal hysterectomy. Am J Obstet Gynecol 2006; 195: 445-53.

8. Tan EK, Cornish J, Darzi AW, *et al.* Meta-analysis: alvimopan vs. placebo in the treatment of post-operative ileus. Aliment Pharmacol Ther 2006; 25: 47-57.

9. Wolff BG, Weese JL, Ludwig KA, Delaney CP, Stamos MJ, Michelassi F, *et al.* Postoperative Ileus-Related Morbidity Profile in Patients Treated with Alvimopan after Bowel Resection. J Am Coll Surg 2007; 204(4): 609-16.

10. Senagor AJ. Pathogenesis and clinical and economic consequences of postoperative ileus. Am J Health-Syst Pharm 2007; 64: S3-S7.

11. Goldstein JL, Matuszewski KA, Delaney CP, *et al.* Inpatient economic burden of postoperative ileus associated with abdominal surgery in the United States. P&T 2007; 32(2): 82-90.

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Appendix: Clinical Trials

A literature search was performed on PubMed/Medline (1966 to September 2008) using the search terms alvimopan and Entereg. The search was limited to studies performed in humans and published in English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Randomized, Controlled Phase III trials

Citation	Delaney CP, Weese JL, Hyman NH, *et al.* Phase III trial of alvimopan, a novel, peripherally acting, mu opioid antagonist, for postoperative ileus after major abdominal surgery. Dis Colon Rectum 2005; 48: 1114-1129.
Study Goals	This study was designed to evaluate the safety and efficacy of alvimopan in the management of postoperative ileus for patients undergoing major abdominal surgery.
Methods	**Study Design** Study participants were randomized in 1:1:1 fashion to placebo and alvimopan 6-mg and 12-mg. Patients received 1 dose of medication at least 2 hours prior to surgery and then were dosed twice daily for 7 days postoperatively or until discharged from hospital. The study's primary endpoint was defined as time to GI-3 and the secondary endpoint was defined as time to GI-2. Additional secondary endpoints for the study were time to first BM, toleration of solid food, need for reinsertion of NG tube**,** and written hospital discharge order. Also assessed were the visual analog pain scores. Endpoints were assessed until hospital discharge or up to 10 days postoperatively if patient remained in the hospital. Treatment emergent adverse events were those that onset or worsened following the first administration of the study medication and up to seven days following the last dose of the medication. **Data Analysis** Efficacy analysis was based on a modified intent to treat population (patients who had at least 1 on-treatment evaluation of endpoints). The time to event effects were analyzed using Cox proportional hazard models and the mean time to event was estimated using Kaplan-Meier cumulative curves. P-values were calculated for comparisons using the Wald chi-squared test. The safety assessments and need for re-insertion of NGT were analyzed using Fisher's exact test.
Criteria	**Inclusion criteria** Adults between the ages of 18 and 80 who were scheduled to undergo laparotomy, partial colectomy with primary anastomosis, or total abdominal hysterectomy were included. Study participants were also scheduled to receive postoperative intravenous patient-controlled opioid analgesia, and to have the intraoperative NGT tubes removed at the end of surgery or the morning of postoperative day 1. **Exclusion criteria** - Use of opioid analgesics within 4 weeks of surgery - Current severe cardiovascular, pulmonary, renal, hepatic, hematologic, or systemic disease - Pregnancy - Clinically significant laboratory abnormalities in screening - Complete bowel obstruction or inflammatory bowel disease - Total colectomy, colostomy, or ileostomy - Expectation to receive epidural opioids, local anesthetics, or NSAIDs for postoperative pain management
Results	**Demographics:**

	Placebo n=153	Alvimopan 6-mg n=150	Alvimopan 12-mg n=146
Mean Age in years (Range)	58.6 (30-88)	58.2 (29-87)	57.1 (30-93)
Number of White Patients (%)	131 (86)	123 (82)	118 (81)
Number of Female Patients (%)	108 (71)	97 (65)	96 (66)
Mean BMI, kg/m^2 (Range)	28.4 (17.3-56.6)	28.2 (16.9-50.9)	28.4 (18.4-47.5)

Efficacy:

Endpoint	Difference from Placebo to Alvimopan 6-mg Mean Time to Event (h)	HR for Alvimopan 6-mg (95% CI)	p-Value	Difference from Placebo to Alvimopan 12-mg Mean Time to Event (h)	HR for Alvimopan 12-mg	p-value
GI-3	14.1	1.45 (1.13-1.85)	0.003	7.5	1.28 (0.99-1.64)	0.059
GI-2	15.2	1.46 (1.11-1.93)	0.007	10.5	1.31 (0.99-1.73)	0.057
First BM	17	1.55 (1.18-2.03)	0.002	15	1.47 (1.12-1.94)	0.006
First Solid Food	10	1.30 (1.02-1.66)	0.033	2.3	1.12 (0.88-1.43)	0.37
Hospital Discharge Order Written	14	1.50 (1.18-1.9)	<0.001	7.2	1.18 (0.93-1.5)	0.17

– For all efficacy points, 145 patients were in the placebo group, 141 patients were in the alvimopan 6-mg treatment group, and 138 patients were in the alvimopan 12-mg treatment group.

- The proportions of patients requiring reinsertion of NGT were 6.9% for placebo, 2.1% for

alvimopan 6-mg, and 7.2% for alvimopan 12-mg. The differences were not statistically significant.

- In addition, no change was noted in pain scores between patients on placebo or active treatment.

Treatment Emergent Adverse Events –reported in ≥ 10% of patients in any treatment group

	Placebo (%) n=153	Alvimopan 6-mg (%) n=150	Alvimopan 12-mg (%) n=146
Nausea	68	64	58.9
Vomiting NOS	32	25.3	15.1*
Abdominal Distention	15.7	11.3	16.4
Headache NOS	11.8	16	11.6
Hypotension NOS	15	12	11.6
Pruritis NOS	9.8	13.3	11.6
Pyrexia	12.4	12	10.3
Hypertension NOS	9.2	12.7	12.3
Insomnia	15	8.7	10.3
Tachycardia NOS	9.8	11.3	9.6
Constipation	14.4	8	6.8
Flatulence	11.1	8	8.9
Dyspepsia	10.5	5.3	10.3
Postoperative Ileus	7.2	10	7.5
Diarrhea NOS	10.5	8	5.5

*P<0.04

- Overall, discontinuations were similar between the placebo and alvimopan 12-mg groups (26.7% and 20.9% respectively); however, only 15.8% of patients discontinued in the alvimopan 6-mg treatment group.
- The number of patients that discontinued treatment due to adverse effects was similar between placebo and alvimopan 12-mg (15% and 16.4% respectively), but was considerably lower in the alvimopan 6-mg group (6.7%).

Conclusions

The authors concluded that alvimopan 6-mg accelerated time to GI recovery and was safe and well tolerated. They found a positive trend with alvimopan 12-mg.

Critique

Jadad Score=3 out of 5

This is a well designed trial that did not provide statistically sound evidence on the use of alvimopan 12-mg. While statistically significant results were found with the 6-mg dosage, the same results were not noted with the 12-mg dosage. One of the largest concerns with this trial in regards to the 12-mg dosage is that often the HR ratio confidence interval crossed 1 which means that an association cannot be determined. In addition, the 12-mg dosage was not tolerated as well as the 6-mg dosage.

This trial would be applicable to our population as it had representation from both genders and included patients that ranged in age from 30-88. However, it is not known if the results were altered based upon the age of the patient. In addition, the majority of patients in the trial were undergoing bowel resection which is the approved indication.

Randomized, Controlled Phase III trials

Citation	Viscusi ER, Goldstein S, Witkowski T, *et al.* Alvimopan, a peripherally acting mu-opioid receptor antagonist, compared with placebo in postoperative ileus after major abdominal surgery: results of a randomized, double-blind, controlled study. Surg Endosc 2006; 20: 64-70.
Study Goals	This study was designed to evaluate the safety and efficacy of alvimopan in the management of postoperative ileus for patients undergoing major abdominal surgery.
Methods	**Study Design** Study participants were randomized in 1:1:1 fashion to placebo and alvimopan 6-mg and 12-mg. Patients received 1 dose of medication at least 2 hours prior to surgery and then were dosed twice daily until hospital discharge or for a maximum of 7 days postoperatively. All patients received a multi-modal management protocol with scheduled removal of NGT no later than noon on postoperative day 1, offering of liquids and encouraging ambulation on day 1, offering of solid food on day 2. The study's primary endpoint was defined as time to GI-3 and the secondary endpoint was defined as time to GI-2. Additional secondary endpoints for the study were time to first BM, first flatus, toleration of solid food, readiness for discharge based on recovery of GI function alone and written hospital discharge order. Also assessed were the visual analog pain scores. Endpoints were assessed until hospital discharge or up to 10 days postoperatively if patient remained in the hospital. Treatment emergent adverse events were those that onset or worsened following the first administration of the study medication and up to seven days following the last dose of the medication. **Data Analysis** Efficacy analysis was based on a modified intent to treat population (patients who had at least 1 on-treatment evaluation of endpoints). The time to event effects were analyzed using Cox proportional hazard models and the mean time to event was estimated using Kaplan-Meier cumulative curves. P-values were calculated for comparisons using the Wald chi-squared test.
Criteria	**Inclusion criteria** Adults ≥ 18 years of age undergoing laparotomy for partial small or large bowel resection with primary anastomosis, or total abdominal hysterectomy and who were scheduled for postoperative opioid-based patient controlled analgesia. **Exclusion criteria** - Acute course of opioids less than 1 week before the study or chronic course less than 2 weeks prior to the study - Pregnancy - Complete bowel obstruction - Total colectomy, colostomy, or ileostomy - Presence of any condition known or suspected to be associated with an increased risk of postoperative morbidity.
Results	**Demographics:**

	Placebo n=224	Alvimopan 6-mg n=220	Alvimopan 12-mg n=221
Mean Age in years (Range)	57 (20-93)	56 (21-91)	58 (23-90)
Number of White Patients (%)	169 (75.4)	167 (75.9)	175 (79.2)
Number of Male Patients (%)	80 (35.7)	86 (39.1)	80 (36.2)
Mean BMI, kg/m^2 (Range)	29.0 (16.8-67)	27.9 (16.5-46.8)	28.4 (17.9-70.8)

Efficacy:

Endpoint	Difference from Placebo to Alvimopan 6-mg Mean Time to Event (h)	HR for Alvimopan 6-mg (95% CI)	P-Value	Difference from Placebo to Alvimopan 12-mg Mean Time to Event (h)	HR for Alvimopan 12-mg	P-value
GI-3						
Unadjusted	7.5	1.20 (0.98-1.47)	0.080	9.9	1.24 (1.01-1.52)	0.038
Adjusted for CVs*	Not reported	1.24 (1.01-1.53)	0.037	Not reported	1.26 (1.03-1.54)	0.028
GI-2						
Unadjusted	16.4	1.37 (1.09-1.74)	0.008	13.7	1.33 (1.05-1.68)	0.018
Adjusted for CVs*	Not reported	1.40 (1.11-1.76)	0.005	Not reported	1.36 (1.07-1.72)	0.012
First BM						
Unadjusted	18.7	1.52 (1.20-1.91)	<0.001	16.2	1.48 (1.18-1.87)	<0.001
Adjusted for CVs*	Not reported	1.54 (1.23-1.94)	<0.001	Not reported	1.52 (1.20-1.91)	<0.001
First solid food						
Unadjusted	6.2	1.15 (0.94-1.41)	0.174	7.7	1.19 (0.97-1.46)	0.095
Adjusted for CVs*	Not reported	1.19 (0.97-1.46)	0.090	Not reported	1.20 (0.98-1.47)	0.077
Hospital Discharge Order Written						

Unadjusted	14.2	1.31 (1.07-1.59)	0.008	15.2	1.28 (1.05-1.56)	0.015
Adjusted for CVs*	Not reported	1.36 (1.12-1.66)	0.002	Not reported	1.30 (1.07-1.59)	0.010

*CV= significant covariates included were gender and surgery duration

- In addition, no difference was detected between the placebo and active groups in regards to the pain scores (placebo 61.1, alvimopan 6-mg 62.0, and alvimopan 12-mg 60.4).

Treatment Emergent Adverse Events –reported in ≥ 5% of patients in any treatment group

	Placebo (%) n=224	Alvimopan 6-mg (%) n=220	Alvimopan 12-mg (%) n=221
Nausea	54	47.7	50.2
Vomiting	25	20	20.8
Pruritis	14.3	10.5	12.2
Pyrexia	13.4	11.4	12.2
Flatulence	12.5	11.8	10.9
Abdominal Distension	12.9	11.8	10.0
Hypotension	10.3	11.8	9.5
Insomnia	8.5	13.2	8.6
Oliguria	12.1	7.3	7.7
Hypertension	10.3	8.2	7.7
Diarrhea	7.6	8.6	7.7
Headache	8.0	9.1	6.8
Hypokalemia	6.7	8.6	6.3
Postoperative Ileus	10.3	5.5	6.3
Body Temperature Increased	8.9	7.3	5.0
Constipation	7.6	4.5	7.2
Postoperative wound infection	7.1	2.7	5.4
Tachycardia	6.7	4.1	3.6
Hypomagnesemia	5.4	5.5	3.2
Dizziness	5.8	3.2	4.1

*p-values not provided

- Overall, discontinuations were lower in both the alvimopan 6-mg and alvimopan 12-mg groups (15% and 17.1% respectively) with 21.4% discontinuing in the placebo group.
- The number of patients that discontinued treatment due to adverse effects was higher with placebo (12.9%) than either treatment group (alvimopan 6-mg =7.7%, alvimopan 12-mg=7.7%).

Conclusions

The authors concluded that alvimopan accelerated the time to GI recovery and was safe and well tolerated.

Critique

Jadad Score=3 out of 5

This is a well designed trial that showed a statistically significant difference in the primary and secondary endpoints when comparing placebo and the 12-mg dosage while adjusting for possible confounding factors including gender and length of surgery. In addition, analgesia was not affected by the use of alvimopan. In this trial, the confidence intervals did not cross 1 when discussing the 12-mg treatment group allowing for greater confidence in the results.

This trial is applicable to our population as it had representation from both genders and included patients that ranged in age from 20-93. It also included subjects from most races. However, it is not known if the results were altered based upon the age of the patient as this was not a covariate for which the results were adjusted. The majority of patients in the trial were undergoing bowel resection which is the approved indication.

Randomized, Controlled Phase III trials

Citation	Wolff BG, Michelassi F, Gerkin TM, *et al.* Alvimopan, a novel, peripherally acting mu opioid antagonist: results of a multi-center, randomized, double-blind, placebo-controlled, phase III trial of major abdominal surgery and postoperative ileus. Ann Surg 2004; 240(4): 728-735.
Study Goals	This study was designed to evaluate the safety and efficacy of alvimopan in the management of postoperative ileus for patients undergoing major abdominal surgery.
Methods	**Study Design** Study participants were randomized to placebo and alvimopan 6-mg and 12-mg. Patients received 1 dose of medication at least 2 hours prior to surgery and then were dosed twice daily for 7 days postoperatively or until hospital discharge. All patients received a multi-modal management protocol which included offering of liquids and encouraging ambulation on day 1, offering of solid food on day 2. The study's primary endpoint was defined as time to GI-3 and the secondary endpoint was defined as time to GI-2. Additional secondary endpoints for the study were time to first BM, toleration of solid food, readiness for hospital discharge based on GI recovery**,** and written hospital discharge order. Pain scores and reinsertion of NGT were also assessed. Endpoints were assessed until hospital discharge or up to 10 days postoperatively if patient remained in the hospital. Treatment emergent adverse events were those that onset or worsened following the first administration of the study medication and up to seven days following the last dose of the medication. **Data Analysis** Efficacy analysis was based on a modified intent to treat population (patients who had at least 1 on-treatment evaluation of endpoints). The time to event effects were analyzed using Cox proportional hazard models and the mean time to event was estimated using Kaplan-Meier cumulative curves. P-values were calculated for comparisons using the Wald chi-squared test. The safety assessments and NGT reinsertion were analyzed using Fisher's exact test.
Criteria	**Inclusion criteria** Adults between the ages of 18 and 80 who were scheduled to undergo small or large bowel resection with primary anastomosis, or radical total abdominal hysterectomy. Eligible participants were also scheduled to receive postoperative intravenous patient-controlled opioid analgesia, and to have the intraoperative NGT tubes removed at the end of surgery or the morning of postoperative day 1. **Exclusion criteria** - Not mentioned
Results	**Demographics:**

	Placebo n=149	Alvimopan 6-mg n=155	Alvimopan 12-mg n=165
Mean Age in years (Range)	60.9 (20-87)	59.3 (19-88)	61.3 (20-89)
Number of White Patients (%)	131 (88)	134 (86)	145 (88)
Number of Female Patients (%)	79 (53)	68 (44)	88 (53)
Mean BMI, kg/m^2 (Range)	28.7 (16.7-49.6)	27.8 (16.8-44.2)	27.1 (13.7-45.9)

Efficacy:

Endpoint	Difference from Placebo to Alvimopan 6-mg Mean Time to Event (h)	HR for Alvimopan 6-mg (95% CI)	p-Value	Difference from Placebo to Alvimopan 12-mg Mean Time to Event (h)	HR for Alvimopan 12-mg	p-value
GI-3	15	1.28 (1.00-1.64)	<0.05	22	1.54 (1.21-1.96)	<0.001
GI-2	20	1.38 (1.07-1.79)	0.013	28	1.67 (1.30-2.15)	<0.001
Hospital Discharge Order Written	13	1.25 (0.98-1.58)	0.070	20	1.42 (1.12-1.79)	0.003

- For all efficacy points, 149 patients were in the placebo group, 155 patients were in the alvimopan 6-mg treatment group, and 165 patients were in the alvimopan 12-mg treatment group.
- The incidence of NGT reinsertion was significantly lower in the 12-mg treatment group when compared to placebo (4.8% vs. 14.8%, p=0.004).
- The incidence of NGT reinsertion was also lower in the 6-mg treatment group (8.4%) but this result was not statistically significant.
- Daily and maximum postoperative pain scores were comparable among the treatment groups.

Common Treatment Emergent Adverse Events

	Placebo (%) n=165	Alvimopan 6-mg (%) n=169	Alvimopan 12-mg (%) n=176

Nausea	64.2	60.9	54.5
Vomiting	25.5	24.3	19.9
Hypotension	13.9	13.6	13.6
Oliguria	15.2	11.8	13.1
Hypertension	10.9	11.8	12.5
Pyrexia	13.9	14.2	10.8
Abdominal Distension	15.2	11.8	10.8
Tachycardia	13.9	13.0	10.8
Hypokalemia	17.0	10.7	9.7
Pruritis	15.8	10.7	7.4
Postoperative Ileus	15.8	8.3	6.3

*****p-values not provided

- Overall, discontinuations were lower in both the alvimopan 6-mg and alvimopan 12-mg groups (26 and 24 patients respectively) with 34 patients discontinuing in the placebo group.
- The number of patients that discontinued treatment due to adverse effects was higher with placebo (26 patient) than either treatment group (alvimopan 6-mg =18 patients, alvimopan 12-mg=14 patients).

Conclusions

The authors concluded that alvimopan 6-mg and 12-mg accelerated GI recovery when compared to placebo without affecting postoperative pain scores. In addition, the 12-mg dose shortened time to discharge order written by approximately 1 day.

Critique

Jadad Score= 3 out of 5

This is a well designed trial that provided statistically useful evidence on the effectiveness of alvimopan 12-mg. In this trial, the HR confidence intervals for the 12-mg dosage did not cross 1 providing statistically significant evidence. However, the authors did not include results for all efficacy measure nor did they calculate statistical significance for adverse events. In addition, exclusion criteria were not mentioned so impact of certain patient populations cannot be assessed from these results.

This trial would be applicable to our population as it had representation from both genders and included patients that ranged in age from 19-89. However, it is not known if the results were altered based upon the age of the patient. The majority of patients in the trial were undergoing bowel resection which is the approved indication.

Randomized, Controlled Phase III trials

Citation	Herzog TJ, Coleman RL, Guerrieri JP, *et al.* A double-blind, randomized, placebo-controlled phase III study of the safety of alvimopan in patients who undergo simple total abdominal hysterectomy. Am J Obstet Gynecol 2006; 195: 445-53.
Study Goals	The study was designed to investigate the safety and efficacy of alvimopan in patients undergoing simple total abdominal hysterectomies (TAH).
Methods	**Study Design** Study participants were randomized into a 4:1 ratio with 106 patients receiving placebo and 413 patients receiving alvimopan 12-mg. Patients received 1 dose of medication at least 2 hours prior to surgery and then were dosed twice daily for 7 days postoperatively. Patients who were discharged < 7 days postoperatively completed seven days of treatment at home. The primary endpoint was proportion of responders (GI-3 recovery of ≤ 60 hours). The study's secondary endpoints were defined as GI-3 and GI-2. Other secondary endpoints for the study were time to first flatus, time to first BM, toleration of solid food, and written hospital discharge order. Treatment emergent adverse events were those that onset or worsened following the first administration of the study medication and up to seven days following the last dose of the medication. **Data Analysis** To meet 95% power for detection of a 20% increase in proportion of responders if 50% responded to placebo, a sample size of 101 placebo patients and 404 alvimopan patients was required. Efficacy analysis was based on a modified intent to treat population (patients who had at least 1 on-treatment evaluation of endpoints). The time to event effects were analyzed using Cox proportional hazard models and the mean time to event was estimated using Kaplan-Meier cumulative curves. The safety assessments were analyzed using Fisher's exact test.
Criteria	**Inclusion criteria** Women ≥ 18 year of age who underwent a simple total hysterectomy and who were scheduled for patient controlled opioid analgesia. **Exclusion criteria** Patients with opioid exposure within 2 weeks of the surgery, complete bowel obstruction, previous or planned colectomy, colostomy, ileostomy, or the prescence of any condition associated with increased postoperative morbidity.
Results	**Demographics:**

	Placebo n=106	Alvimopan n=413
Mean Age in years (Range)	43.1 (24-77)	44.1 (24-74)
Number of White Patients (%)	83 (78.3)	318 (77)
Mean BMI, kg/m^2 (Range)	30.3 (19.6-51.0)	29.2 (15.3-52.7)

Efficacy

- Proportions of responders with alvimopan was not statistically significant when compared to placebo (75% vs. 71.6 percent)

Endpoint	Placebo Mean Time to Event (h) N=102	Alvimopan Mean time to Event (h) N=408	Difference (h)—(95% CI)	P-value
GI-3	55.4	53.5	-1.9 (-5.1,1.3)	0.18
GI-2	92.0	71.8	-20.2 (-26.5, -13.9)	<0.001
First flatus	46.7	42.4	-4.3 (-7.8, -0.8)	0.039
First BM	91.6	69.4	-22.2 (-28.7, -15.8)	<0.001
First Solid Food	51.5	49.9	-1.6 (-4.8,1.6)	0.46
Hospital Discharge Order Written	*68.6*	*66.3*	*-2.3 (-6.5, 1.9)*	0.27

Treatment Emergent Adverse Events –reported in ≥ 5% of study population

	Placebo (%) N=106	Alvimopan 12-mg (%)	Absolute Risk Increase	Number Needed to Harm

			N=413		
	Dyspepsia	4.7	4.8	0.1%	1000
	Dizziness	7.5	8.5	1%	100
	Hypertension	5.7	6.8	1.1%	91
	Headache	11.3	13.3	2%	50
	Diarrhea	3.8	6.1	2.3%	43
	Tachycardia	2.8	5.1	2.3%	43
	Urinary tract infection	7.5	9.9	2.4%	42
	Vomiting	25.5	31.2	5.5%	18
	Nausea	63.2	72.2	9%	11
	Constipation	31.1	22.8		
	Flatulence	18.9	18.4		
	Pruritis	15.1	13.3		
	Pyrexia	11.3	9.9		
	Insomnia	10.4	9.7		
	Abdominal distension	10.4	8.2		
	Anemia	7.5	5.3		
	Hypotension	5.7	4.6		
	Back Pain	6.6	3.9		

****** p-values were not reported for safety data

- Total discontinuations were lower with the alvimopan treatment group than the placebo (8% vs. 11.3%).
- The number of patients that discontinued treatment due to adverse effects was also higher with placebo (4.7%) than the treatment group (3.9%).

Conclusions	The authors concluded that alvimopan had a similar safety profile to placebo and significantly decreased time to lower gastrointestinal recovery following total abdominal hysterectomy.
Critique	**Jadad Score=3 out of 5** This trial was a well designed trial that met power for its primary endpoint. However, it did not show a statistically significant difference in the primary endpoint. In addition, many of the confidence intervals for the secondary endpoints crossed zero lowering the statistical value of the results. This trial will also not apply to the cases for which alvimopan will be used in the VA as it is based on TAH, an indication for which alvimopan is not approved and cannot be used for under the restrictions of the E.A.S.E. program. Also, TAH are not as common at the VA as bowel resections so it has a lesser impact upon our population.

Pooled Analyses from Phase III trials

<table>
<tr><td>Citation</td><td>Wolff BG, Weese JL, Ludwig KA, Delaney CP, Stamos MJ, Michelassi F, et al. Postoperative Ileus-Related Morbidity Profile in Patients Treated with Alvimopan after Bowel Resection. J Am Coll Surg 2007; 204(4): 609-16.</td></tr>
<tr><td>Study Goals</td><td>The goal of the study was to compare the incidence of POI related postoperative morbidity of alvimopan 12-mg to placebo.</td></tr>
<tr><td>Methods</td><td>Study Design
This study was a pooled analysis from four phase III clinical trials. A total of 1409 patients who had been randomized to receive either alvimopan 12-mg or placebo were included in the analysis. Patients received one dose of either placebo or the study medication at least 30 minutes prior to surgery and twice daily postoperatively for either 7 days or discharge from the hospital.
The study evaluated the incidence of POI-related postoperative morbidity which included the insertion of NG tube postoperatively or POI-related prolonged hospital stay or readmission.
Data Analysis
The comparison of proportions was conducted using Fisher's exact test with p-values.</td></tr>
<tr><td>Criteria</td><td>Inclusion criteria
Patients 18 years of age or older undergoing bowel resection with primary anastomosis and who were scheduled for postoperative pain management with IV opioid-based PCA.
Exclusion criteria
Patients with chronic opioid use within 1 week of surgery</td></tr>
<tr><td>Results</td><td>Demographics:
<table>
<tr><td></td><td>Placebo
n=695</td><td>Alvimopan 12-mg
n=714</td></tr>
<tr><td>Mean Age in years (Range)</td><td>60.4</td><td>60.7</td></tr>
<tr><td>Number of Patients ≥ 65yrs (%)</td><td>291 (41.9)</td><td>308 (43.1)</td></tr>
<tr><td>Number of White Patients (%)</td><td>589 (84.7)</td><td>599 (83.9)</td></tr>
<tr><td>Number of Female Patients (%)</td><td>362 (52.1)</td><td>358 (50.1)</td></tr>
<tr><td>Mean BMI, kg/m^2 ± SD</td><td>28.5 ± 6.2</td><td>27.7 ± 6.0</td></tr>
</table>
<table>
<tr><th>Endpoint</th><th>Alvimopan 12-mg</th><th>Placebo</th><th>p-value</th><th>RRR</th><th>ARR</th><th>NNT</th></tr>
<tr><td>Overall Postoperative morbidity</td><td>7.6</td><td>15.8</td><td><0.001</td><td>51.8%</td><td>8.2%</td><td>12</td></tr>
<tr><td>Post-operative NG –tube insertion</td><td>6.6</td><td>11.5</td><td>0.001</td><td>42.6%</td><td>4.9%</td><td>20</td></tr>
<tr><td>Re-admission for any reason within 10 days of discharge</td><td>4.9</td><td>8.3</td><td><0.01</td><td>40.9%</td><td>3.4%</td><td>29</td></tr>
<tr><td>Complications of POI resulting in prolonged stay</td><td>2.1</td><td>6.8</td><td><0.001</td><td>69.1%</td><td>4.7%</td><td>21</td></tr>
<tr><td>Complications of POI resulting in re-admission</td><td>1</td><td>2</td><td>0.126</td><td>50%</td><td>1</td><td>100</td></tr>
</table></td></tr>
<tr><td>Conclusions</td><td>The authors concluded that alvimopan 12-mg improves markers of postoperative morbidity and can improve patient outcomes beyond the current best-practice.</td></tr>
<tr><td>Critique</td><td>The mean age of patients included was 61 years of age with greater than 40% of the study population being over the age of 65. In addition, approximately 49% were male which makes this study applicable to the VA population. The analysis included a relatively large study sample at 1409 and showed clinically and statistically significant differences. However, the data utilized was from 4 trials which were not powered individually to show differences in these outcomes.</td></tr>
</table>

Pooled Analyses from Phase III trials

Citation	Delaney CP, Wolff BG, Viscusi ER, Senagore AJ, Fort JG, Wei D, *et al.* Alvimopan, for Postoperative Ileus following Bowel Resection: A Pooled Analysis of Phase III Studies. Ann Surg 2007; 245(3): 355-63.
Study Goals	The study was designed to examine the safety and efficacy of alvimopan in patients undergoing bowel resection.
Methods	**Study Design** This study was a pooled analysis from four phase III clinical trials. A total of 1212 patients who had been randomized to receive alvimopan 6-mg, 12-mg or placebo were included in the analysis. Patients received one dose of either placebo or the study medication at least 30 minutes prior to surgery and twice daily postoperatively for either 7 days or discharge from the hospital. The study's primary endpoints were defined as GI-3. Secondary endpoints for the study were GI-2 readiness for hospital discharge and hospital discharge order. Efficacy assessments were performed in the hospital up to 10 days postoperatively. Safety assessments included adverse events, laboratory tests, vital signs, and electrocardiograms. Serious AE's were defined as events that were immediately life-threatening, required intervention to prevent permanent disability, or resulted in prolonged hospital stay or readmission, persistent or significant impairment, or inability to carry out normal life functions. **Data Analysis** For the efficacy endpoints, treatment effect was assessed for each time-to-event endpoint using Cox proportional hazards model. Hazard ratios and respective p-values were calculated using the chi-squared test. For safety analyses, p-values were calculated using 2-sided Fisher exact test.
Criteria	**Inclusion criteria** Patients at least 18 years of age undergoing partial bowel resection and scheduled for postoperative patient controlled opioid based pain management were included. **Exclusion criteria** Patients who had taken opioids within 4 weeks of surgery or who were expected to receive epidural opioids, local anesthetics, or NSAIDs (ketorolac) were excluded. Additionally, patients who had severe cardiovascular, renal, pulmonary, hepatic, hematologic, or other systemic diseases were excluded. Patients with complete bowel obstruction, inflammatory bowel disease, prior treatment with vinca alkaloids, or a history of substance abuse were also excluded.
Results	**Demographics:**

	Placebo n=153	Alvimopan 6-mg n=150	Alvimopan 12-mg n=146
Mean Age in years (Range)	58.6 (30-88)	58.2 (29-87)	57.1 (30-93)
Number of White Patients (%)	131 (86)	123 (82)	118 (81)
Number of Female Patients (%)	108 (71)	97 (65)	96 (66)
Mean BMI, kg/m^2 (Range)	28.4 (17.3-56.6)	28.2 (16.9-50.9)	28.4 (18.4-47.5)

Efficacy

Endpoint	Placebo: Time to Event ± SEM (hr)	Difference from placebo to Alvimopan 6-mg (hr) (± 95% CI)	Difference from placebo to Alvimopan 12-mg (hr) (± 95% CI)
GI-3	118.8 ± 2.9	-12.4 (-19.7, -5.2)	-14.8 (-22.1, -7.6)
GI-2	128.1 ± 3.09	-15.0 (-22.6, -7.3)	-18.3 (-26.0, -10.7)
Ready for discharge	126.3 ± 2.87	-14.2 (-21.3,-7.1)	-17.6 (-24.7, -10.6)
Discharge Orders Written	146.8 ± 2.82	-16.0 (-23.1, -8.8)	-18.4 (-25.6, -11.3)

Safety –includes all serious adverse events and statistically significant non-serious adverse events

	Placebo (%) n= 402	Alvimopan 6-mg (%) n=397	Alvimopan 12-mg (%) n=413
Nausea	60.2	54.4	51.1*
Vomiting	26.1	22.4	19.6*
Pruritis	13.9	11.1	9.4*
POI	13.9	7.6*	8.0*
POI**	6.7	1.8*	1.9*
Postoperative GI disorder NOS**	3.2	2.8	1.9
Postoperative wound infection**	1.7	0.8	1.5
Postoperative abscess**	0.7	1.3	0.5

*p<0.05 when compared to placebo

** Serious adverse event defined as those immediately life-threatening, requiring intervention to prevent permanent impairment, or resulting in prolong hospitalization or re-admission, persistent or significant disability, or disruption in ability to carry out normal life functions.

	- Overall, discontinuations were lower in both the alvimopan 6-mg and alvimopan 12-mg groups (13.8 % and 16.9% respectively) with 20.6% discontinuing in the placebo group. - The number of patients that discontinued treatment due to adverse effects was also higher with placebo (17.0%) than either treatment group (alvimopan 6-mg =9.6%, alvimopan 12-mg=12.1%).
Conclusions	The authors concluded that alvimopan was safe and effective in accelerating GI recovery time following partial bowel resection.
Critique	The mean age of patients included was 61 years of age with greater than 40% of the study population being over the age of 65. In addition, approximately 49% were male which makes this study applicable to the VA population. The analysis included a relatively large study sample at 1212 patients and showed clinically and statistically significant differences.

Pooled Analyses from Phase III trials

Citation	Senagore AJ, Bauer JJ, Wei D, *et al.* Alvimopan accelerates gastrointestinal recovery after bowel resection regardless of age, gender, race, or concomitant medication use. Surgery 2007; 142(4): 478-86.
Study Goals	The study was designed to determine if covariates affect the GI recovery time in alvimopan studies.
Methods	**Study Design** This study was a pooled analysis from five phase III clinical trials. A total of 1877 patients who had been randomized to receive either alvimopan 12-mg or placebo were included in the analysis. Patients received one dose of either placebo or the study medication at least 30 minutes prior to surgery and twice daily postoperatively for either 7 days or discharge from the hospital. Trial endpoints were defined as GI-2 and GI-3. Covariates taken into account in this study included, age (<65, ≥65, and ≥75), gender, race (white or non-white), and perioperative use/non-use of GI-targeted antibiotics, mechanical bowel preparation, H_2-receptor antagonists, and/or proton pump inhibitors. **Data Analysis** For all analyses, the time to event data was analyzed using Cox proportional hazard models. Each was assessed independently and p-values were based on a chi-squared test. Magnitudes of treatment effects were noted by Kaplan-Meier means.
Criteria	**Inclusion criteria** Patients 18 years of age or older undergoing bowel resection with primary anastomosis and who were scheduled for postoperative pain management with IV opioid-based PCA were included. **Exclusion criteria** Patients with chronic opioid use within 1 week of surgery were excluded. Patients who received epidural anesthesia were discontinued from the study.
Results	

	GI-2		
	Placebo, hrs (95% CI) n=924	Alvimopan, hrs (95% CI) n=953	p-value
Overall	117.9 (114.2-121.5)	100.9 (98.0-103.7)	<0.001
<65	116.6 (111.6-121.6)	99.1 (95.4-102.9)	≤0.014
≥65	119.6 (114.2-124.9)	102.9 (98.6-107.2)	≤0.014
≥75	125.1 (115.6-134.7)	104.7 (98.2-111.2)	≤0.014
Male	120.8 (115.5-126.0)	102.1 (98.2-106.1)	≤0.014
Female	114.8 (109.8-119.9)	99.5 (95.5-103.6)	≤0.014
White	117.1 (113.4-120.9)	100.7 (97.7-103.7)	≤0.014
Non-White	121.8 (109.7-133.9)	101.9 (93.9-109.9)	≤0.014

	GI-3		
	Placebo, hrs (95% CI) n=924	Alvimopan, hrs, (95% CI) n=953	p-value
Overall	105.2 (101.8-108.6)	92.5 (89.8-95.2)	<0.001
<65	102.3 (97.8-106.8)	90.1 (86.6-93.5)	≤0.036
≥65	108.8 (103.5-114.0)	95.4 (91.2-99.6)	≤0.036
≥75	115.7 (106.8-124.6)	97.8 (91.1-104.6)	≤0.036
Male	111.0 (105.9-116.0)	94.1 (90.3-98.0)	≤0.036
Female	99.5 (95.0-103.9)	90.7 (87.0-94.5)	≤0.036
White	104.2 (100.7-107.7)	92.1 (89.2-94.9)	≤0.036
Non-White	111-8 (99.8-123.8)	95.5 (87.5-103.5)	≤0.036

- For concomitant medication usage, no time frames were provided but it was stated that alvimopan significantly reduced time to GI-2 and GI-3 (p<0.001) when compared to placebo.

Conclusions	The authors concluded that alvimopan significantly reduced GI-recovery time following bowel resection independently of confounding factors.
Critique	The mean age of patients included was 61 years of age with greater than 40% of the study population being over the age of 65. In addition, approximately 49% were male which makes this study applicable to the VA population. The analysis included a relatively large study sample at 1877 patients and showed clinically and statistically significant differences. However, the authors did not provide times to recovery for concomitant medications used, so no validity may be assessed for that endpoint.

Meta Analysis

Citation	Tan EK, Cornish J, Darzi AW, *et al.* Meta-analysis: alvimopan vs. placebo in the treatment of post-operative ileus. Aliment Pharmacol Ther 2006; 25: 47-57.

<table>
<tr><td>Study Goals</td><td>The meta-analysis was designed to compare alvimopan with placebo after bowel resection or total abdominal hysterectomy.</td></tr>
<tr><td>Methods</td><td>Study Design
Five trials met criteria to be included in this meta-analysis. The outcomes looked at were recovery of gastrointestinal tract function (GI-3 and GI-2), and treatment emergent adverse events. This analysis also looked at the post operative pain scores assessed by the visual analog scale between 0 and 100.
Data Analysis
For the efficacy measures, hazard ratios were reported with 95% confidence intervals. A hazard ratio of >1 favored the alvimopan group. For the safety measures, odds ratios were calculated and an OR >1 showed higher incidence anticipated in the alvimopan group. Study quality was assessed using the Jadad Score based on patient selection, comparability of study groups, and assessment of the outcomes. All 5 trials received 5 out of 5 stars.</td></tr>
<tr><td>Criteria</td><td>Inclusion criteria
Studies included in this meta analysis had to compare alvimopan to placebo, report on at least one of the outcome measures, clearly document the drugs administered and dosages and clearly distinguish the operation as bowel resection or total abdominal hysterectomy.
Exclusion criteria
Studies were excluded if outcomes were not clearly reported or if it was impossible to calculate or extract data from the published results.</td></tr>
<tr><td>Results</td><td>Efficacy
<table>
<tr><th>Endpoint</th><th>HR for Alvimopan 6-mg (95% CI)</th><th>P-Value</th><th>HR for Alvimopan 12-mg</th><th>P-value</th></tr>
<tr><td>GI-3</td><td>1.50 (1.14-1.96)</td><td>0.003</td><td>1.30 (1.16-1.45)</td><td><0.001</td></tr>
<tr><td>GI-2</td><td>1.58 (1.22-2.04)</td><td><0.001</td><td>1.61 (1.26-2.05)</td><td><0.001</td></tr>
<tr><td>First BM</td><td>1.60 (1.32-1.93)</td><td><0.001</td><td>1.74 (1.29-2.35)</td><td><0.001</td></tr>
<tr><td>First Solid Food</td><td>1.58 (1.04-2.38)</td><td>0.03</td><td>1.14 (1.01-1.30)</td><td>0.04</td></tr>
<tr><td>Ready For Discharge</td><td>1.40 (1.19-1.63)</td><td><0.001</td><td>1.26 (1.13-1.40)</td><td><0.001</td></tr>
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Treatment Emergent Events
<table>
<tr><th>Event</th><th>OR for Alvimopan 6-mg (95% CI)</th><th>P-Value</th><th>OR for Alvimopan 12-mg</th><th>P-value</th></tr>
<tr><td>Postoperative Ileus</td><td>0.68 (0.35-1.33)</td><td>0.26</td><td>0.58 (0.33-1.04)</td><td>0.07</td></tr>
<tr><td>Nausea</td><td>0.82 (0.64-1.05)</td><td>0.11</td><td>0.90 (0.60-1.35)</td><td>0.60</td></tr>
<tr><td>Vomiting</td><td>0.79 (0.60-1.05)</td><td>0.10</td><td>0.73 (0.47-1.14)</td><td>0.17</td></tr>
<tr><td>Abdominal distension</td><td>0.79 (0.55-1.12)</td><td>0.19</td><td>0.79 (0.57-1.09)</td><td>0.15</td></tr>
<tr><td>Constipation</td><td>0.55 (0.32-0.94)</td><td>0.03</td><td>0.76 (0.46-1.27)</td><td>0.30</td></tr>
<tr><td>Flatulence</td><td>0.84 (0.53-1.34)</td><td>0.47</td><td>0.83 (0.58-1.19)</td><td>0.30</td></tr>
<tr><td>Pruritis</td><td>0.83 (0.52-1.32)</td><td>0.44</td><td>0.79 (0.53-1.16)</td><td>0.23</td></tr>
<tr><td>Hypotension</td><td>0.97 (0.66-1.43)</td><td>0.89</td><td>0.86 (0.58-1.27)</td><td>0.45</td></tr>
<tr><td>Hypertension</td><td>1.03 (0.68-1.57)</td><td>0.88</td><td>1.01 (0.66-1.54)</td><td>0.98</td></tr>
<tr><td>Pyrexia</td><td>0.90 (0.62-1.32)</td><td>0.60</td><td>0.80 (0.57-1.13)</td><td>0.21</td></tr>
<tr><td>Tachycardia</td><td>0.88 (0.56-1.39)</td><td>0.60</td><td>0.74 (0.46-1.18)</td><td>0.20</td></tr>
<tr><td>Insomnia</td><td>0.95 (0.32-2.85)</td><td>0.93</td><td>0.84 (0.56-1.28)</td><td>0.42</td></tr>
<tr><td>Headache</td><td>1.28 (0.80-2.04)</td><td>0.30</td><td>1.01 (0.66-1.54)</td><td>0.97</td></tr>
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- In addition, the fives studies showed no statistically significant difference in the postoperative pain scores.</td></tr>
<tr><td>Conclusions</td><td>The authors concluded that alvimopan was a well tolerated effective medication that appeared to be efficacious at 6-mg with little added benefit from the 12-mg dosage.</td></tr>
<tr><td>Critique</td><td>This was a well designed meta-analysis that included results on strengths of studies, heterogeneity of the study results, and a funnel graph to illustrate the improbability of publication bias. In addition, this meta-analysis is consistent with the previously reported trials suggesting that alvimopan is safe and well tolerated. The patients included in the trials are representative of our population. However, this does include data from total abdominal hysterectomies which is not an approved indication and may lead to some alteration of the results in practice as these patients will not be treated with this medication.</td></tr>
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