Economic Analysis of Alvimopan for Prevention and Management of Post-operative Ileus

Authors

Daniel R. Touchette, Pharm.D., M.A.¹

Yoojung Yang, Pharm.D., MS¹

Funda Tiriyaki, Pharm.D., MS¹

William L. Galanter, M.D., Ph.D.^{1,2}

¹University of Illinois at Chicago, College of Pharmacy, Chicago IL

²University of Illinois at Chicago, College of Medicine, Chicago IL

Word Count:

Abstract 297

Manuscript 3379

Short Title:

Economic Analysis of Alvimopan for POI

Corresponding Author:

Daniel Touchette,
Assistant Professor
University of Illinois at Chicago
College of Pharmacy
833 S. Wood St. M/C 886
Chicago, IL 60612

Phone: 312 355 3402

email: drtouche@uic.edu

Funding:

This study was supported by the Agency for Healthcare Research and Quality grant U18HS016973 funding the UIC Center for Education and Research in Therapeutics (CERT) program.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality.

Keywords:

Gastroenterology; pharmacoeconomics; surgery; outcomes; evidence based medicine

Acknowledgements:

The authors would like to acknowledge Bruce Lambert, PhD, and Gordon Schiff, MD, for their insightful comments in developing this analysis and for the review of the study methods and manuscript. Also, we would like to thank Jay Goldstein, MD, for his review and feedback on the study manuscript.

Conflicts of interest:

Daniel Touchette, PharmD, MA, assumes responsibility as the submission's guarantor.

Dr. Touchette was involved in the conception and initiation of the analysis, and in preparation of the manuscript. Dr. Touchette has no conflicts of interest to report.

Yoojung Yang, PharmD, MS, was involved in the conception of the study, development of the analysis, and in preparation of the manuscript. Dr. Yang is currently completing a one-year Fellowship, jointly sponsored by the University of Illinois at Chicago and the Takeda Pharmaceutical Company Limited.

Funda Tiriyaki, PharmD, MS was involved in the development of the analysis and in substantially editing the manuscript. Dr. Tiriyaki has no conflicts of interest to report.

William Galanter, MD, PhD, was involved in the conception of the study, development of the analysis, and in substantially editing the manuscript. Dr. Galanter has no conflicts of interest to report.

Abstract

Objective: To determine whether alvimopan for prevention of post-operative ileus (POI) among patients undergoing small- or large-bowel resection via laparotomy is associated with lower total costs compared to standard post-operative care.

Methods: We constructed a formal decision model from the healthcare system perspective. Clinical outcomes (time to discharge order written [DCO], post-operative nasogastric tube insertion, POI-related readmission within 7 days, nausea and vomiting) were obtained from meta-analyses of published studies. Cost inputs included drugs, nursing labor, readmission, and hospitalization. Costs were assessed by determining the net cost of alvimopan use and subsequent reduction in length of stay (LOS). Sensitivity analyses and a scenario analysis were conducted.

Results: The costs for alvimopan were \$570 based on an average of 9.5 doses. Given the 18.4-hour mean reduction in DCO, the use of alvimopan reduced hospitalization costs by \$2,021. The mean difference in overall cost of care was \$1,168 (95% certainty interval: -\$437 to \$5,879), favoring the use of alvimopan. In sensitivity analyses, the association of alvimopan with lower costs was robust to several changes in key parameters including the cost and number of doses of alvimopan, DCO, readmission rates, and hospitalization cost. In scenario analyses, alvimopan use yielded a cost saving of \$897 when no difference in readmission rates was assumed and a net cost of \$278 when no difference in

DCO was assumed. In the scenario analysis using data from a study that did not enforce opioid use, alvimopan resulted in a cost-saving of \$65 per patient.

Conclusion: For the base case, alvimopan was cost-saving for prevention of POI among patients undergoing bowel resection via laparotomy, although these potential cost-savings were highly dependent on a difference in DCO. This finding is not applicable to the less-invasive laparoscopic surgical approach for which quality data on alvimopan use are lacking. Limitations of this analysis included the use of DCO as a proxy for LOS and difficulty interpreting study results due to inconsistent reporting and conduct of the clinical trials evaluating alvimopan.

Introduction

Post-operative ileus (POI) is defined as "a transient cessation of co-ordinated bowel motility after surgical intervention, which prevents effective transit of intestinal contents and/or tolerance of oral intake."¹ POI is common in surgeries in which the bowel or nearby structures are manipulated during surgery. Clinical symptoms include delayed and incomplete gastric emptying, abdominal distension, pain, nausea, and vomiting. Complications include atelectasis, pneumonia, and delayed enteral nutrition, ambulation, and wound healing.²⁻⁴ Recovery time varies from days to weeks. Recovery is complicated by the use of opioids, which can also decrease gastric motility. POI is responsible for causing considerable morbidity in some patients.

POI is a major contributor to delaying hospital discharge after abdominal surgery, increasing length of stay (LOS) by approximately two to three days.⁵ In one analysis, 3% of patients undergoing colon and rectum operations were readmitted for bowel obstruction and ileus.⁶ POI significant enough to be coded in billing records has been associated with substantial increases in length of stay and \$8,000-\$10,000 per patient in additional cost.^{7,8} Overall, POI is estimated to cost the US healthcare system an estimated \$1.46 billion annually.

Alvimopan is a peripherally acting μ -opioid antagonist that has been demonstrated to accelerate upper and lower gastrointestinal (GI) recovery following bowel surgery in patients expected to receive opioids for postoperative pain management.⁹⁻¹⁴ Specifically,

alvimopan has been shown to reduce the need for nasogastric tube reinsertion and the incidence of nausea and vomiting in patients undergoing laparotomy.⁹⁻¹⁴ Alvimopan has also been found to decrease time to discharge order written (DCO).^{9,11-13} While readmissions due to POI were not statistically significantly different in any of the clinical trials, alvimopan reduced the proportion of patients requiring hospitalization for any cause in a pooled analysis.¹⁰ However, with an estimated cost of up to \$840 per patient, using alvimopan typically results in a substantial addition to the immediate cost of therapy.^{15,16} As a result of this immediate cost, a potential for cardiovascular complications with long term use, and concerns about off-label use institutions may restrict or refuse the use of alvimopan.¹⁷

At the time of undertaking this study, we had identified only a single economic analysis of alvimopan in the literature.¹⁸ By comparing only the cost of alvimopan and the cost-offsets associated with a reduced LOS, this analysis showed that alvimopan would be expected to reduce costs. However, significant limitations existed in the methodology used in this analysis, bringing into question the validity of the report's results. Most importantly, there was a lack of clarity as to how the cost analysis was developed and the results were not explored sufficiently by sensitivity analyses.

Given the cost of alvimopan and the need for a more detailed, comprehensive cost-consequence analysis for formulary decision-makers, we developed a decision model designed to assess total costs and cost offsets associated with alvimopan use in patients

undergoing small- or large-bowel resection via laparotomy and scheduled to receive opioids.

Methods

We constructed a formal decision model to assess costs from the healthcare system perspective. We adhered to the methods recommended by the Panel on Cost-Effectiveness in Health and Medicine and guidelines from the International Society for Pharmacoeconomic and Outcomes Research.¹⁹

Comparators

In this analysis, we compared a standardized, accelerated post-operative care pathway (usual care) to usual care plus alvimopan. The standardized accelerated post-operative care pathway consisted of the removal of nasogastric tube no later than noon on post-operative day one, introduction of liquid diet and ambulation on post-operative day one, and introduction of solid food by post-operative day two. This multimodal approach to accelerate recovery is currently regarded as best practice in post-operative management of patients undergoing major bowel surgeries.²⁰⁻²³ The alvimopan comparison arm was based on the following regimen: alvimopan 12 mg administered 30 minutes to 5 hours prior to surgery, followed by subsequent maintenance dose of 12 mg given every 12 hours for a maximum of 7 days post-operatively (15 maximum total doses).

Patient Population

We performed the analysis targeting patients undergoing partial small- or large-bowel resection with primary anastomosis via laparotomy and scheduled to receive post-operative pain management with intravenous (IV) opioid-based patient-controlled analgesia. The time horizon considered for this evaluation was the duration of hospitalization.

Model Design

We used a decision tree (Figure 1) to assess the net cost of using alvimopan 12mg versus usual care. The design of both comparison arms is identical. Based on the published results of four randomized clinical trials, we identified LOS as a primary cost driver in our model.^{9,11-13} However, time to DCO was used as a proxy for LOS in all four clinical trials.^{9,11-13} We therefore had to use time to DCO in our model rather than the preferable terminal outcome, LOS. From those studies, we also identified adverse outcomes associated with a considerable cost (i.e. a cost sufficient to potentially alter the expected value of alvimopan in the decision model) and included them in the decision tree. Specifically, we included post-operative nasogastric tube insertion (NGT), POI-related readmission within 7 days, nausea, and vomiting. Other clinical outcomes of the trials such as all-cause readmission within 10 days, time to recovery of gastrointestinal (GI) function, and time to readiness for discharge were originally considered, but were determined to be irrelevant or have insufficient evidence linking them to important clinical or economic terminal outcomes. In particular, the time to GI recovery was measured as a composite endpoint defined as the later of the following events: tolerance of solid food, first bowel movement, or first flatus. We deemed that this composite

outcome served as an intermediate to LOS and did not add information beyond our existing proxy for LOS.

Model Inputs

We conducted a thorough literature review via PubMed to September 10, 2011 (no starting date specified) using the following search terms: *alvimopan, phase III trial, bowel, resection, postoperative, ileus*. First, published randomized clinical trials of alvimopan were obtained and reviewed. We then identified two meta-analyses and a pooled analysis of the trials to support our model inputs of the clinical outcomes.^{10,14,18}

Clinical inputs were selected from the Delaney meta-analysis, as this analysis likely presents the most accurate estimates available for the effectiveness of alvimopan.¹⁰ Table 1 shows the estimates and proportions reported by each of the studies for outcomes relevant to the model.^{9-13,18,24} Table 2 shows the inputs actually used in the base case of the model and the associated sources.^{8,10,16,24-26}

Alvimopan drug cost was estimated using 80% of the average wholesale price (AWP) reported in the 2010 Red Book.¹⁶ In the base-case analysis, the mean number of alvimopan doses (9.5) observed in the Delaney analysis was used.¹⁰ Costs of POI-related readmission and per-day hospitalization (used to calculate the cost-saving associated with the reduction in time to DCO) were taken from a systematic review of published studies on the economic burden of POI.^{8,26} To estimate resources utilized in NGT insertion, we solicited information regarding equipment used (BARD tube and suction canister) and nursing time required from an expert panel of four surgical nurses. The total cost of

nursing labor was determined by multiplying average salaries (as reported by the US Bureau of Labor Statistics)²⁵ by the duration of time to perform insertion obtained from surveying a panel of experts. For the purpose of our decision model, costs associated with nausea and vomiting were assumed to involve only the anti-emetic drug costs and excluded nominal costs such as emesis basins. Given the current guideline recommendations to use an anti-emetic agent from a different pharmacologic class in patients with post-operative nausea and vomiting who fail on the first drug,²⁷ we assumed ondansetron and prochlorperazine, both generically available, as the anti-emetic agents used in nausea and vomiting, respectively, and estimated these generic drug prices based on 50% of the AWP.¹⁶ All cost data was inflation adjusted to the end of 2010 using the consumer price index for medical care or hospital and related services.²⁵

Sensitivity Analyses

We performed various sensitivity analyses to account for uncertainty in the model assumptions and to address the variability of published data. We did several one-way and multi-way sensitivity analyses over low and high estimates of select variables (see Table 2). Each variable was subjected to a one-way sensitivity analysis. The range over which each variable was varied was chosen based on the 95% confidence interval as reported in the studies that provided the base-case estimates. Where confidence intervals were not available (i.e. doses of alvimopan), we chose the triangular distribution and inputted the range from the Delaney trial for the extreme values (i.e. 1-15 doses).¹⁰ Specifically, we used the following distributions: beta for event probabilities, log-normal for hospital costs including readmission and nursing time, triangular for number of doses

of alvimopan, and normal for the difference in time to DCO between the alvimopan and usual care arms. Monte Carlo simulation was then used to evaluate the overall uncertainty of the model result in the base case. All analyses were performed using TreeAge Pro[®] 2009.

In addition, several scenario analyses were conducted to address shortcomings identified in the literature supporting alvimopan use. A European study assessing alvimopan use in post-operative ileus observed a much lower efficacy of alvimopan than did the other three international studies.²⁴ Due to potential heterogeneity in the results, specifically a lower utilization of opioids and differences in the European healthcare system (demonstrated by a longer time to discharge), all European study subjects were omitted from subsequent meta-analyses.^{9-14,18,24} We therefore conducted two scenario analyses using estimates from one European study to populate the model. In the first scenario analysis, only the base case estimates for number of alvimopan doses, DCO, and the probabilities of nausea and vomiting were replaced with those from the European study. Since NGT reinsertion and readmission for post-op ileus were not evaluated in the European Phase III trial, the probabilities of the outcomes were set equal to the base-case alvimopan values, using estimates from the Delaney meta-analysis.^{10,24} In the second scenario analysis, we assumed that alvimopan produced no benefit with respect to reducing the need for NGT reinsertion or post-op ileus-related readmission and the model inputs were set equal to the usual care. These two scenarios represent the two possible extremes for the effectiveness of alvimopan.

Results

Base Case

In the base-case model, the added drug costs for alvimopan were estimated at \$570 per person and there was an estimated cost offset of \$2,021 resulting from reduced LOS (as proxied by DCO) with alvimopan use. Additional cost offsets were realized by reductions in the need for gastric tube reinsertion, nausea, vomiting, and post-operative ileus related readmissions. Overall, the use of alvimopan resulted in a total cost of \$11,084. In comparison, usual care resulted in a total cost of \$12,271. Hence in the base-case, alvimopan use was associated with an average savings of \$1,187 per person.

Sensitivity Analyses on the Base Case

The stability of the base-case depended primarily on two variables: cost of a hospital day, and mean time to discharge. The mean cost of a hospital day created the most variability in the model. Usual care became the preferred option (i.e. total cost less than alvimopan) when the cost of a hospital day was reduced below a threshold of \$362 per day. Similarly, when the difference in DCO between alvimopan and usual care was reduced to 3.5 hours, usual care became the less costly preferred option. Other variables - the cost and probability of POI-related readmission, and the number of doses and cost of alvimopan - but were not able to change the base case results when varied in a univariate manner.

The Monte Carlo simulation conducted on the base-case resulted in a mean and median difference in costs of \$1,168 and \$630, respectively. The 95% certainty interval (i.e. the interval containing 95% of the observations, removing 2.5% of the observations from

each tail of the distribution) was -\$437 to \$5,879. The 80% certainty interval ranged from -\$194 to \$3,008 and 19.6% of all observations fell below \$0. Given our distribution inputs for the Monte Carlo simulation, it was not certain that alvimopan would be truly cost-saving.

Scenario Analysis

When model inputs for number of alvimopan doses, DCO, probability of experiencing nausea, and probability of vomiting were set to values observed in the European phase III trial,²⁴ the use of alvimopan resulted in a total cost of \$18,084 compared with the usual care cost of \$18,149 (difference = \$65). When the other model inputs of NGT reinsertion and probability of readmission were set equal to the base-case values for usual care (i.e. no difference observed), the use of alvimopan resulted in a total cost of \$18,375, more costly than usual care by \$226.

Discussion

Our analysis provides a much more detailed and comprehensive breakdown of the overall costs associated with alvimopan than the previously published analyses.^{18,28} In our base-case analysis, alvimopan was likely cost-saving as was the case in two previously published cost analyses.^{18,28} Alvimopan achieves a net cost-saving in our model, provided time to discharge is reduced by an average of at least 3.5 hours. However, in the Monte Carlo simulations, the 80% certainty interval included \$0, indicating a potential that alvimopan may not be cost-saving given uncertainty in the underlying parameters of the

model. Furthermore, when looking at our scenario analysis including the results of the European phase III study,²⁴ it appeared that alvimopan could potentially increase the total cost of care. This has important policy implications for institutions that do not uniformly enforce opioid PCA for post-operative pain management, as described below.

Our analysis is primarily limited by the strength of the data available in existing publications. The meta-analysis conducted by Delaney et al. well described statistical methods, including an analysis of the between-treatment effects among the three included clinical trials.¹⁰ The second pooled analysis included an additional study,¹¹ but did not sufficiently describe the methods used for pooling data or whether any validity analyses were conducted.¹⁸ However, both pooled analyses excluded a large European phase III study in which alvimopan outcomes were not as favorable as in North American studies.²⁴ Inclusion of this study's findings would have reduced the differences seen between alvimopan and usual care in LOS considerably, possibly but not likely impacting the statistical significance of the findings.

Furthermore, inconsistencies in the numbers of included subjects between the two pooled analyses bring into question the validity of these results. Specifically, the number of subjects and reasons for exclusion in the pooled analysis by Delaney et al. appear well documented (see Table 1).¹⁰ The pooled results and economic analysis by Bell et al. includes an additional study by Ludwig et al. when compared with Delaney et al., but the total number of subjects analyzed is greater than that of both the Delaney pooled analysis and Ludwig trials combined.^{11,18} In addition, the reported rates of nausea and vomiting do

not appear consistent between the pooled analyses, even with the addition of the Ludwig data. Because of these limitations in the Bell manuscript, we chose to use the results of the Delaney pooled analysis as the base-case inputs for our model.

As stated in previous reports,^{10,18} clinical practice differed between the United States (US) and European hospitals in these clinical trials, with a differing utilization of opioids and a longer hospital length of stay in the European study subjects.²⁹⁻³¹ Clinical practice and hospital length of stay has likewise been shown to differ substantially between Canadian and US hospitals.³¹⁻³³ Despite these differences, Canadian study subjects remained in the pooled analyses while those in the European study were excluded. Furthermore, there are significant issues with using randomized clinical trials in economic analyses that have not been addressed in sensitivity analyses by Bell.³¹ Clinical trials notoriously attempt to standardize care in ways that are different from usual clinical practice to reduce heterogeneity and improve the effect size. The North American studies mandated use of opioid patient-controlled analgesia (PCA) as well as placing restrictions on non-opioid analgesics, while promoting discharge following achievement of the gastrointestinal recovery outcomes. Further, acute pain services promoting and monitoring PCA are widely present in many larger urban European hospitals.^{34,35} Given this, differences observed in the European study may have had more to do with the study design that allowed more freedom for variability in pain management than with regional discrepancies in clinical practice. Given the uncertainty raised by this possibility, we chose to conduct an additional scenario analysis using data from the European study to

provide formulary decision-makers with additional information on which to base their decision.²⁴

Alvimopan was compared with the standard of care for managing POI in clinical trials, namely nasogastric tube insertion, early administration of intravenous fluids and solid food, and encouraging early ambulation. In recent studies, chewing gum has been shown to improve time to first bowel movement, and reduce hospital length of stay following appendectomy,³⁶ radical cystectomy for bladder cancer,³⁷ and abdominal surgery.³⁸ Results of a meta-analysis suggest that given its safety profile and beneficial effects, chewing gum should be offered to select patients after assessment of mental status and aspiration risk.³⁸ Studies are needed to assess if alvimopan is superior to chewing gum or if the addition of alvimopan to chewing gum results in further LOS reductions or other benefits.

The use of laparoscopy, a less invasive surgical procedure, has also been shown to reduce postoperative surgical complications including GI recovery time, vomiting, and hospital length of stay.^{15,39,40} Decreased manipulation of the bowels and less pain and subsequent opioid use are likely factors in these findings. In the phase III clinical trials evaluating alvimopan, only subjects who underwent laparotomy were enrolled. One retrospective analysis evaluating the use of alvimopan in subjects undergoing either open or laparoscopic bowel resection suggested that similar benefits may be observed in subjects undergoing laparoscopic surgery.²⁸ However, this study utilized an open label design with a retrospective analysis with insufficient sample size (given the results observed in

prospective clinical trials) and had substantial and important differences in baseline subject characteristics. Non-opioid use was higher in the alvimopan group, and total exposure to opioids (i.e. total dose given) was not controlled for in the analyses. Given these serious limitations, it remains unclear whether alvimopan results in improvements in POI-related outcomes in subjects undergoing laparoscopic surgery.

Limitations

There are several important limitations to our pharmacoeconomic analysis. As mentioned above, inconsistent reporting of clinical and economic outcomes in meta-analyses, differences in the conduct of clinical trials, and difficulty interpreting these results were a major concern. In an effort to overcome these limitations, we made a written request for data from the manufacturers of alvimopan (Entereg[®]), but received no response.[personal communication, June 1, 2010] Without access to primary data from the clinical trials, we attempted to address these issues using sensitivity analyses to provide formulary administrators with the most information possible on which to base their decisions.

We were unable to quantify benefits of alvimopan in terms of an effectiveness or utility measure such as quality-adjusted life-years gained, due to relatively minor impact of the drug on outcomes that affect these measures. There may be willingness by some to pay an additional amount for a medication that decreases vomiting and improves patient satisfaction by reducing the need for NGT, rehospitalization, and decreased LOS.

However, due to the small potential gains associated in these outcomes by alvimopan, these benefits were not included in our analysis.

We did not consider the potential increased risk of bowel perforation or other adverse events in our analysis.⁴¹ Most documented adverse events associated with alvimopan use appeared to be either minor or no different from control subjects. In the case of bowel perforation, this rare event is unlikely to significantly affect the economic analysis, but should be considered carefully by clinicians as it changes the risk-benefit ratio of alvimopan. More research is needed to determine the incidence, severity, and consequences of this potentially serious complication.

Finally, a factor limiting the accuracy of these findings pertained to the use of time to discharge order (DCO) instead of the actual time to discharge. This was necessary due to the use of this surrogate marker in the primary sources of data. Although it is not clear that this difference biases the results in any way, using the actual time to discharge would have been a more appropriate way to determine changes in the LOS.

Conclusion

Alvimopan is a potentially useful medication in the treatment of patients undergoing bowel resection surgery via laparotomy. The medication is likely to reduce hospital length of stay and total cost of care in this population, although limitations exist in published reports that raise questions regarding the certainty of these findings. Research

is needed to determine the effects of alvimopan when chewing gum is used as part of the post-surgical regimen or when surgery is performed using laparoscopic procedures.

References

1. Zeinali F, Stulberg JJ, Delaney CP. Pharmacological management of postoperative ileus. *Can J Surg* 2009;52:153-7.
2. Baig MK, Wexner SD. Postoperative ileus: a review. *Dis Colon Rectum* 2004;47:516-26.
3. Behm B, Stollman N. Postoperative ileus: etiologies and interventions. *Clin Gastroenterol Hepatol* 2003;1:71-80.
4. Senagore AJ. Pathogenesis and clinical and economic consequences of postoperative ileus. *Am J Health Syst Pharm* 2007;64:S3-7.
5. Chang SS, Baumgartner RG, Wells N, Cookson MS, Smith JA, Jr. Causes of increased hospital stay after radical cystectomy in a clinical pathway setting. *J Urol* 2002;167:208-11.
6. Kiran RP, Delaney CP, Senagore AJ, Steel M, Garafalo T, Fazio VW. Outcomes and prediction of hospital readmission after intestinal surgery. *J Am Coll Surg* 2004;198:877-83.
7. Asgeirsson T, El-Badawi KI, Mahmood A, Barletta J, Luchtefeld M, Senagore AJ. Postoperative ileus: it costs more than you expect. *J Am Coll Surg* 2010;210:228-31.
8. Goldstein J, Matuszewski K, Delaney C, et al. Inpatient economic burden of postoperative ileus associated with abdominal surgery in the United States. *P&T* 2007;32:82-90.
9. 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;48:1114-29.
10. Delaney CP, Wolff BG, Viscusi ER, et al. Alvimopan, for postoperative ileus following bowel resection: a pooled analysis of phase III studies. *Annals of Surgery* 2007;245:355-63.
11. Ludwig K, Enker WE, Delaney CP, et al. Gastrointestinal tract recovery in patients undergoing bowel resection: results of a randomized trial of alvimopan and placebo with a standardized accelerated postoperative care pathway. *Arch Surg* 2008;143:1098-105.
12. Viscusi E, Goldstein S, Witkowski T, et al. Alvimopan, a peripherally acting mu-opioid receptor antagonist, compared with placebo in postoperative ileus after major abdominal surgery. *Surgical Endoscopy* 2006;20:64-70.
13. Wolff BG, Michelassi F, Gerkin TM, et al. Alvimopan Postoperative Ileus Study Group. Alvimopan, a novel, peripherally acting [mu] opioid antagonist: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial of major abdominal surgery and postoperative ileus. *Ann Surg* 2004;240:728-35.
14. Wolff BG, Weese JL, Ludwig KA, et al. Postoperative ileus-related morbidity profile in patients treated with alvimopan after bowel resection. *Journal of the American College of Surgeons* 2007;204:609-16.
15. Delaney CP, Marcello PW, Sonoda T, Wise P, Bauer J, Techner L. Gastrointestinal recovery after laparoscopic colectomy: results of a prospective, observational, multicenter study. *Surg Endosc* 2010;24:653-61.
16. Red Book 2010: Pharmacy's Fundamental Reference. 113th ed. Montvale, NJ: Thomson Reuters; 2010.

17. Becker G, Blum HE. Novel opioid antagonists for opioid-induced bowel dysfunction and postoperative ileus. *Lancet* 2009;373:1198-206.
18. Bell TJ, Poston SA, Kraft MD, Senagore AJ, Delaney CP, Techner L. Economic analysis of alvimopan in North American Phase III efficacy trials. *American Journal of Health-System Pharmacy* 2009;66:1362-8.
19. Siegel J, Weinstein M, Russell L, Gold M. Recommendations for reporting cost-effectiveness analyses. *JAMA* 1996;276:1339-41.
20. Basse L, Hjort Jakobsen D, Billesbolle P, Werner M, Kehlet H. A clinical pathway to accelerate recovery after colonic resection. *Ann Surg* 2000;232:51-7.
21. Delaney CP, Fazio VW, Senagore AJ, Robinson B, Halverson AL, Remzi FH. 'Fast track' postoperative management protocol for patients with high co-morbidity undergoing complex abdominal and pelvic colorectal surgery. *Br J Surg* 2001;88:1533-8.
22. Delaney CP, Zutshi M, Senagore AJ, Remzi FH, Hammel J, Fazio VW. Prospective, randomized, controlled trial between a pathway of controlled rehabilitation with early ambulation and diet and traditional postoperative care after laparotomy and intestinal resection. *Dis Colon Rectum* 2003;46:851-9.
23. Kariv Y, Delaney C, Senagore A, et al. Clinical outcomes and cost analysis of a "fast track" postoperative care pathway for ileal pouch-anal anastomosis. a case control study. *Dis Colon Rectum* 2007;50:137-46.
24. Buchler MW, Seiler CM, Monson JR, et al. Clinical trial: alvimopan for the management of post-operative ileus after abdominal surgery: results of an international randomized, double-blind, multicentre, placebo-controlled clinical study. *Aliment Pharmacol Ther* 2008;28:312-25.
25. U.S. Department of Labor, Bureau of Labor Statistics. (Accessed September 10, 2011, at www.bls.gov.)
26. Iyer S, Saunders W, Stemkowski S. Economic burden of postoperative ileus associated with colectomy in the United States. *J Manag Care Pharm* 2009;15:485-94.
27. Ignoffo RJ. Current research on PONV/PDNI: practical implications for today's pharmacist. *Am J Health Syst Pharm* 2009;66:S19-24.
28. Absher RK, Gerkin TM, Banares LW. Alvimopan use in laparoscopic and open bowel resections: clinical results in a large community hospital system. *Ann Pharmacother* 2010.
29. Westert GP, Lagoe RJ, Keskimaki I, Leyland A, Murphy M. An international study of hospital readmissions and related utilization in Europe and the USA. *Health Policy* 2002;61:269-78.
30. Wunsch H, Angus DC, Harrison DA, et al. Variation in critical care services across North America and Western Europe. *Crit Care Med* 2008;36:2787-93, e1-9.
31. Marshall DA, Hux M. Design and analysis issues for economic analysis alongside clinical trials. *Med Care* 2009;47:S14-20.
32. Fu Y, Chang WC, Mark D, et al. Canadian-American differences in the management of acute coronary syndromes in the GUSTO IIb trial: one-year follow-up of patients without ST-segment elevation. Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) II Investigators. *Circulation* 2000;102:1375-81.
33. Glick HA, Polsky D, Willke RJ, Alves WM, Kassell N, Schulman K. Comparison of the use of medical resources and outcomes in the treatment of aneurysmal subarachnoid hemorrhage between Canada and the United States. *Stroke* 1998;29:351-8.

34. Stamer UM, Mpasios N, Stuber F, Maier C. A survey of acute pain services in Germany and a discussion of international survey data. *Reg Anesth Pain Med* 2002;27:125-31.
35. Werner MU, Soholm L, Rotboll-Nielsen P, Kehlet H. Does an acute pain service improve postoperative outcome? *Anesth Analg* 2002;95:1361-72, table of contents.
36. Ngowe MN, Eyenga VC, Kengne BH, Bahebeck J, Sosso AM. Chewing gum reduces postoperative ileus after open appendectomy. *Acta Chir Belg* 2010;110:195-9.
37. Choi H, Kang SH, Yoon DK, et al. Chewing gum has a stimulatory effect on bowel motility in patients after open or robotic radical cystectomy for bladder cancer: a prospective randomized comparative study. *Urology* 2010.
38. Hocevar BJ, Robinson B, Gray M. Does chewing gum shorten the duration of postoperative ileus in patients undergoing abdominal surgery and creation of a stoma? *J Wound Ostomy Continence Nurs* 2010;37:140-6.
39. Chen HH, Iroatulam AJ, Alabaz O, et al. Laparoscopic colectomy is superior to laparotomy for reduction of disability in patients with colorectal adenoma. *Changgeng Yi Xue Za Zhi* 1999;22:586-92.
40. Chen HHMD, Wexner SDMD, Iroatulam AJNMD, et al. Laparoscopic colectomy compares favorably with colectomy by laparotomy for reduction of postoperative ileus. *Diseases of the Colon & Rectum* 2000;43:61-5.
41. US Food and Drug Administration. Potential signals of serious risks/new safety information identified from the adverse event reporting system (AERS) between July - September 2009.
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm199544.htm>. Accessed: December 10, 2010. In; 2009.

Table 1. Outcomes reported in phase III clinical studies of alvimopan and pooled analyses results

	Delaney ⁹	Ludwig ¹¹	Viscusi ¹²	Wolff ^{d4}	Buchler ²⁴	Pooled Bell ^{18,a}	Pooled Delaney ^{10,b}
UC n	145	303	224	149	292	695	383
A12 n	138	307	222	165	297	714	397
Doses A12						8.9	9.5
Time to DCO written UC (h)	122	138	126.2 ^c	146	220.7	142.9	146.8
Time to DCO written A12 (h)	115	120	126.2 ^c	126	214.8	124.9	128.4
Difference in DCO Written (h)	7	18	15.2	20	5.9	18.0	18.4
Nausea UC (%)	68	66.2	54.0	64.2	8	65	60.2
Nausea A12 (%)	58.9	57.8	50.2	54.5	10	56	51.1
Vomiting UC (%)	32	24.6	25.0	25.5	8	27	26.1
Vomiting A12 (%)	15	14.0	20.8	19.9	5	19	19.6
Readmission for POI UC (%)	NR	1.9	11.2 ^d	~8	NR	NR	11.7 ^d
Readmission for POI A12 (%)	NR	0.9	8.6 ^d	~4	NR	NR	7.7 ^d
NGT reinsertion UC (%)	6.9	10.3	8.2	14.8	NR	NR	12.2
NGT reinsertion A12 (%)	7.2	6.0	5.5	4.8	NR	NR	6.8

^aMethods for pooling data not given. Includes only bowel surgery subjects. Includes Delaney, Ludwig, Viscusi, and Wolff studies.

^bExcludes subjects undergoing total abdominal hysterectomy. Includes Delaney, Viscusi, and Wolff studies.

^cTime to DCO written not provided for each treatment group. Mean study time to DCO presented, along with difference. Mean value provided for reference.

^dPOI-specific readmission rates not reported. Values are total readmission rates.

Abbreviations:

UC = usual care

A12 = alvimopan 12 mg two hours before surgery and then twice daily

DCO = discharge order written

POI = post-operative ileus

NGT = nasogastric tube

NR = not reported

Table 2. Inputs used for base-case and sensitivity analyses

Variable	Base	Low	High	Scenario	References
<i>Clinical Inputs</i>					
Time to DCO (h)					Base Case: Delaney ¹⁰ ; Scenario: Buchler ²⁴
A12	128.4	53.0	265.0	214.8	
UC	146.8	67.0	280.0	220.7	
Nausea (%)					Base Case: Delaney ¹⁰ ; Scenario: Buchler ²⁴
A12	51.1	46.0	56.0	10.0	
UC	60.2	55.0	65.0	8.0	
Vomiting (%)					Base Case: Delaney ¹⁰ ; Scenario: Buchler ²⁴
A12	19.6	15.8	23.4	5.0	
UC	26.1	21.8	30.4	8.0	
NGT reinsertion (%)					Base Case: Delaney ¹⁰ ; Scenario: Buchler ²⁴
A12	6.6	4.8	8.4	6.6	
UC	11.5	9.1	13.9	11.5	
Readmission (%)					Base Case: Delaney ¹⁰ ; Scenario: Buchler ²⁴
A12	1.00	0.26	1.70	1.00	
UC	2.00	0.97	3.05	2.00	
<i>Cost inputs</i>					
Alvimopan 12 mg					
Cost per dose (\$)	60.00	37.50	75.00	60.00	2010 Red Book ¹⁶
Number of doses	9.5	5.0	14.0	11.6	Base case: Delaney ¹⁰ ; Scenario: Buchler ²⁴
NGT reinsertion					
Nursing wage (\$ per hour)	31.31	25.00	50.00	31.31	Bureau of Labor Statistics ²⁵
Nursing time (h)	0.26	0.18	0.34	0.26	Expert opinion
NGT (\$) ^a	12.59	7.78	20.73	12.59	
Nausea treatment					
Ondansetron (\$ per dose) ^b	0.56	0.56	1.20	0.56	2010 Red Book ¹⁶
Vomiting treatment					
Prochlorperazine (\$ per dose) ^b	1.5	1.50	1.80	1.50	2010 Red Book ¹⁶
Post-op hospitalization cost (\$ per day)	1,910	192	7,755	1,910	Goldstein ⁸ ; Iyer ²⁶

Readmission cost (\$) ^c	29,094	6,365	109,187	29,094	Goldstein ⁸ , Iyer ²⁶
------------------------------------	--------	-------	---------	--------	---

^aIncludes BARD tube and suction canister

^bCosts of nausea and vomiting were assumed to only consider anti-emetic agents

^cPOI-related readmission within 7 days

Abbreviations:

UC = usual care

A12 = alvimopan 12 mg two hours before surgery and then twice daily

DCO = discharge order written

POI = post-operative ileus

NGT = nasogastric tube

NR = not reported

Figure 1. Decision analysis model