HHS Public Access

Author manuscript

J Am Coll Surg. Author manuscript; available in PMC 2017 May 01.

Published in final edited form as:

J Am Coll Surg. 2016 May ; 222(5): 870–877. doi:10.1016/j.jamcollsurg.2016.01.051.

Alvimopan Use, Outcomes, and Costs: A Report from the Surgical Care and Outcomes Assessment Program-Comparative Effectiveness Research Translation Network Collaborative

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Abstract

Background—Randomized trials show that alvimopan hastens return of bowel function and reduces length of stay by one day among patients undergoing colorectal surgery. However, its effectiveness in routine clinical practice and impact on hospital costs remains uncertain.

Study Design—We performed a retrospective cohort study of patients undergoing elective colorectal surgery in Washington State (2009–2013) using data from a clinical registry (Surgical Care and Outcomes Assessment Program) linked to a statewide hospital discharge database (Comprehensive Hospital Abstract Reporting System). We used generalized estimating equations to evaluate the relationship between alvimopan and outcomes while adjusting for patient, operative, and management characteristics. Hospital charges were converted to costs using hospital-specific charge-to-cost ratios, and were adjusted for inflation to 2013 dollars.

Results—Among 14,781 patients undergoing elective colorectal surgery at 51 hospitals, 1,615 (11%) received alvimopan. Patients who received alvimopan had a LOS that was 1.8 days shorter ($p<0.01$) and costs that were $2,017 lower ($p<0.01$) compared to those who did not receive alvimopan. After adjustment, LOS was 0.9 days shorter ($p<0.01$), and hospital costs were $636 lower ($p=0.02$) among those receiving alvimopan compared to those who did not.

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Disclosure Information: All other authors have nothing to disclose.

Presented at the American College of Surgeons 101st Annual Clinical Congress, Chicago, IL, October 2015.

Conclusions—When used in routine clinical practice, alvimopan was associated with a shorter LOS and limited but significant hospital cost savings. Both efficacy and effectiveness data support the use of alvimopan in routine clinical practice, and its use could be measured as a marker of higher quality care.

Keywords

alvimopan; colorectal surgery; ileus; enhanced recovery after surgery

Introduction

More than 330,000 colorectal operations are performed annually in the United States (US), (1) and approximately 17% of patients will develop a post-operative ileus (POI). (2) POI is estimated to cost the US healthcare system over $1.5 billion per year, (3) which does not include the burden placed on patients and their families. While POI has many potential causes, opioid use is believed to be a key determinant. (4) Alvimopan (Entereg®, Merck) is a pharmaceutical—approved by the Food and Drug Administration (FDA) in 2008—that prevents opioid-induced POI in the setting of colorectal and pelvic surgery. Alvimopan blocks peripheral μ-opioid receptors in the gastrointestinal tract, but has limited systemic absorption and ability to cross the blood brain barrier, and therefore still permits opioid-mediated central pain control. (5) Multiple randomized controlled trials (RCT) have shown that alvimopan decreased time to return of bowel function by 5–28 hours depending on the dose. (6–10) In the one RCT that evaluated LOS, alvimopan reduced LOS by 24 hours. (9)

There remains considerable interest in determining whether alvimopan is effective in routine clinical practice. Many processes that were standardized and carefully monitored in RCTs in order to demonstrate efficacy (such as dose and frequency of drug administration and implementation of enhanced recovery after surgery [ERAS]-type programs) may not occur in routine practice, and thus the drug may appear to be more or less effective than what was initially reported. Concerns over the effectiveness of alvimopan persist as several well-done observational studies have reported LOS savings greater than one day. (11–13) Additionally, some believe that the cost of the drug is excessive and unwarranted even though it is estimated to be approximately $67.50 per pill or $937.50 for a full course of seven days of treatment (14) and few patients actually receive the full course. Both of these factors may prevent adoption of alvimopan in routine clinical care.

To address these questions, we sought to evaluate the relationship between alvimopan use, LOS, and hospital costs among patients undergoing elective colorectal surgery in Washington State (WA). We hypothesized that alvimopan use would be associated with a LOS reduction no greater than one day, and that alvimopan use would not be associated with higher hospital costs.

Methods

We performed a retrospective cohort study of all adult patients undergoing elective colorectal surgery from January 1, 2009 to December 31, 2013 at hospitals participating in the Surgical Care and Outcomes Assessment Program (SCOAP). Patients treated prior to

2009 were excluded as alvimopan was not approved by the FDA until May 2008. SCOAP is a quality improvement and benchmarking collaborative based in WA for which the Comparative Effectiveness Research Translation Network (CERTAIN) provides research and analytic support. (15, 16) This clinical registry collects information about patient demographics, disease characteristics, management, and outcomes. SCOAP data is collected directly from the medical record by trained, audited abstractors using standardized definitions that are available via a secure page at www.SCOAP.org. To obtain hospital cost data, SCOAP cases were linked to the WA Comprehensive Hospital Abstract Reporting System (CHARS), a hospital discharge database that includes data from all public and private hospitals in WA, excluding Veterans Affairs and military hospitals. The use of de-identified data does not require review by the University of Washington Human Subjects Division, and the linkage to CHARS was approved by the WA Department of Social and Health Services Institutional Review Board.

Of patients who had elective colorectal surgery between 2009 and 2013 (n=15,565), the following sequential exclusion criteria were applied: patients who were missing information about alvimopan receipt ($n_{excluded}$=31); patients younger than 18 ($n_{excluded}$ =4); individuals who had colorectal surgery listed as a secondary operation ($n_{excluded}$ =226) or who were designated as having an additional or staged procedure during the same admission ($n_{excluded}$ =67); those who had undergone a colon resection within the previous 30 days ($n_{excluded}$ =70); patient with ASA class V ($n_{excluded}$ =13) or who were intubated ($n_{excluded}$ =3); and those with ASA class listed as “emergent” ($n_{excluded}$ =264) or “not applicable” ($n_{excluded}$ =106) as we could not confirm that these were elective cases.

Potential confounding variables were recorded in SCOAP and included sociodemographic characteristics (age, sex, insurance type, categorized body mass index [BMI]), comorbidities, and management details. A Charlson comorbidity index was calculated for each patient based on comorbidities reported in the medical record at the time of their operation. (17) Other indicators of baseline patient health included the use of home oxygen and mobility devices such as a walker or wheelchair. The primary indication for each operation was classified as diverticulitis, neoplasm (colon cancer, rectal cancer, colon mass, or polyps), inflammatory disease (Crohn’s disease or ulcerative colitis), or other. The operation performed was defined by anatomic site (left versus right colon, rectum) and extent of operation (partial versus total colectomy, low anterior resection, abdominoperineal resection, ostomy takedown). Surgical approach was categorized as either open or minimally invasive (including laparoscopic, laparoscopic converted to open, laparoscopic/hand-assisted, robotic or robotic converted to open). Operative time was based on the interval from incision to final wound closure. Patients with operative time less than the 1st percentile, or 40 minutes, were recoded as missing (n=137) as were individuals with operative time greater than 24 hours (n=5). Process-of-care measures included the use of an epidural, patient-controlled analgesia (PCA), and presence a nasogastric tube (NGT) at the conclusion of surgery.

The exposure variable in this study was a binary indicator of alvimopan receipt at any time during the hospital stay. The outcome variables were LOS and total hospital costs. SCOAP records were used to obtain LOS, defined as the total days in hospital from the date of

surgery to the date of discharge. No patient was missing LOS data, but 5% of patients (n=760) of patients had a LOS 2 days or shorter and were recoded as missing to prevent the inclusion of potentially erroneous data. Clinical expertise was used to make this judgment. Total charges for the index hospitalization were recorded in CHARS. Payer-perspective costs, adjusted for inflation to 2013 dollars, were derived from hospital charges using publicly available hospital specific Medicaid charge-to-cost ratios. (18, 19) A subset of individuals (n=1,722) was missing charge data if they were treated at a US military hospital (SCOAP collects data from military hospitals even though CHARS does not), a non-WA hospital (SCOAP collects data from one hospital in Oregon as part of a regional quality improvement collaborative), or linkage was not possible.

Patient characteristics were summarized using frequency distributions for categorical variables, and means and medians for continuous variables. Categorical variables were compared using the Pearson chi-square statistic. Continuous variables were compared using the two-tailed Student t-test when normally distributed, and non-parametric equality of medians test when not normally distributed. Multivariable regression using generalized estimating equations (GEE) was used for the primary analysis evaluating the relationship between alvimopan, LOS, and costs after adjusting for potential confounding variables, clustered at the hospital level. We specified a gamma distribution to account for non-normally distributed LOS and costs.(20) A planned, post-hoc analysis included any in-hospital complication as an additional potential confounding variable in the model.

A planned sensitivity analysis was performed used propensity score matching. The probability of receiving alvimopan was estimated using a logistic regression model inclusive of all measured patient and management variables, as well as hospital, listed as potential confounders in the primary analysis. Patients were matched 1:1 using the nearest neighbor method based on propensity score, and LOS and costs were compared between the matched groups, again using GEE to account for correlated data at the hospital level.

Analyses were conducted using STATA, version 12 (STATA Corp, College Station, TX).

Results

From 2009 to 2013, 14,781 patients underwent a colorectal procedure across 51 hospitals. Overall, 1,615 patients (11%) received alvimopan at 26 hospitals that administered the drug at least once. Use among patients increased from 6% in 2009 to 17% in 2013, and the proportion of hospitals where the drug was administered at least once increased from 66% to 82% over the study period. Patients who received alvimopan were more likely to have characteristics typically associated with shorter LOS and lower costs. On average, they were younger; more often had commercial insurance; more frequently had no comorbid conditions and an ASA Class I or II; more frequently had a normal BMI; less frequently used home oxygen or a home mobility device; were less likely to smoke; were more likely to have a neoplasm as an indication for surgery; had higher rates of low anterior resection and laparoscopic surgery; longer median operation time; less frequently had an epidural or NGT at the end of the operation; and more frequently had a PCA. Patients who received

alvimopan were significantly less likely to have an inhospital complication (8% versus 18%, p<0.01). There were no differences with regards to patient sex. (Table 1)

Unadjusted analyses showed that patients who received alvimopan had a mean LOS that was 1.8 days shorter (7.0 versus 5.2 days, p<0.01) and mean hospital costs that were $2,017 less ($10,667 versus $12,684, p<0.01) compared to patients who did not receive alvimopan. The differences in patient and management characteristics between patients who did and did not receive the drug were anticipated to have biased the unadjusted outcomes in favor of the alvimopan group. Adjustment for the potential confounding effects of these variables demonstrated a statistically significant association between alvimopan use and shorter LOS of 0.9 days (95% CI −1.1 days, −0.7 days) as well as lower costs (−$636, 95% CI −$1,168, −$105). (Table 2)

In the planned post-hoc analysis, which accounted for in-hospital complications, alvimopan receipt remained associated with a significantly shorter LOS (−0.7 days, 95% CI −0.9 days, −0.5 days) but not lower overall hospital costs (−$383, 95% CI −$867, +$101). The planned sensitivity analysis using a propensity score match resulted in a subgroup of 1,668 patients (834 in each cohort), all of whom were treated at a hospital where alvimopan was administered at least once during the study period. After matching, patients who received alvimopan less frequently had an epidural (13% versus 19%, p<0.01), but were otherwise well balanced with regard to patient, operative, and process-of-care characteristics. (Table 3) In the propensity score match, LOS was approximately 33 hours shorter (−1.4 days, 95% CI: −1.7 days, −1.0 days) and hospital costs were $1,720 lower (95% CI: −$2,456, −$984) in patients who received alvimopan. (Table 4)

Discussion

We sought to describe the effect of alvimopan on LOS and costs among patients undergoing elective colorectal surgery in WA. Knowing that alvimopan decreased LOS by one day in the carefully controlled setting of an RCT, (9) we hypothesized that the LOS savings associated with alvimopan use would be less than one day. In fact, we found this to be the case: patients who received alvimopan had shorter LOS of 0.9 days. Additionally, we found that alvimopan use was associated with limited but significant cost savings of $636. These findings persisted even after several approaches at adjustment for measured potential bias. These findings suggest that, as demonstrated in RCTs, alvimopan use has a modest impact on LOS when used in typical practice. It is important to note the fact that patients who received alvimopan, on average, were lower risk patients compared to those who did not. While the reason for this is unclear, it may be related to use of pre-surgical optimization programs in the pre- that can be implemented along with enhanced recovery protocols.

Previous randomized studies demonstrated that alvimopan leads to reduced incidence of ileus and shorter LOS, (6–10) and observational studies have shown an association between alvimopan use and improved outcomes. (11–13) While these studies consistently showed that alvimopan is associated with either faster return of bowel function or shorter LOS, the magnitude of effect varied between studies. While this variation is expected given differences between RCTs and non-randomized effectiveness evaluations, (21, 22) it

complicates the determination of the effectiveness of the drug. Furthermore, the measured outcomes are not consistent across studies (e.g. return of bowel function versus clinical ileus versus LOS) which can make comparisons difficult. We used LOS as a surrogate measure, and previous work has shown that the incidence of POI is associated with longer LOS. (23) Our estimates demonstrated an associated LOS savings of 0.9 days, which is plausible given results from RCTs. (9) While no observational study can definitively prove causality, our findings support the effectiveness of alvimopan in the real-world setting. Despite the fact that these findings were confirmed in the planned sensitivity analysis, the propensity score adjustment resulted in an exaggerated estimate of the association between alvimopan use and LOS. Previous work has demonstrated that propensity score analyses in some cases can inflate rather than mitigate bias due to the presence of unmeasured confounding that cannot be included in the propensity score. (24)

Previous observational studies and modeled analyses of pooled data from RCTs reported cost savings of $731–$1,329 in patients who received alvimopan. (13, 14, 25–27) In our study, use of alvimopan was associated with a cost savings of $636. Due to the fact that charges (and subsequently costs) are not itemized in CHARS, the mechanism of this cost savings is not known. While a $636 dollar cost savings may seem inconsequential for an individual patient, from a healthcare systems perspective it is important. If alvimopan had been given to the 13,166 patients in our study who did not receive it, more than $8 million dollars may have been saved over the five year study period. This is important given the concern that alvimopan might increase the cost of care for patients. A full seven day course of the drug costs nearly $1000 (14) and it must be given to a patient before surgery. Such an intervention is expensive because, like other prophylactic medications given for relatively common events, every patient must be given the drug in order to realize the effects. In the planned sensitivity analysis that included complications, we found that costs were not significantly different between those who did and did not receive alvimopan despite the LOS savings. This may be due to the fact that we included all in-hospital complications, covering a range of events from urinary tract infection to re-operation, introducing significant variability in the associated costs of events. Regardless, alvimopan was not associated with higher costs in this setting further supporting our hypothesis that the drug does not lead to higher costs overall.

Even though we accounted for all measurable sources of bias in this study, we may have overestimated the effect of alvimopan because of an inability to measure all potentially confounding variables. Examples of unmeasured bias may include individual surgeon effects and operative technique (e.g. bowel handling during surgery), which are not captured in clinical databases; optimization of fluids and electrolytes in the peri-operative period; participation in enhanced recovery or fast-track protocols; carbohydrate loading prior to surgery; narcotic minimization strategies; and early resumption of oral intake post-operatively. While omission of these factors may overestimate the impact of alvimopan, there are other factors that may have led us to underestimate the effects of alvimopan. For example, administration of alvimopan was recorded as a binary variable, indicating that the patient received it at least once during their hospital stay. We suspect that in routine clinical practice compliance is lower than what was achieved in the RCTs, something that commonly occurs in the real world setting. (21, 22) The impact of this noncompliance is that patients

may not have received the drug as it was designed and therefore the effectiveness of the drug would be less than if it had been correctly administered.

A final consideration is that for patients with LOS of two days or less we recoded them as missing. We made this decision *a priori* based on the empirical data. Anecdotally, it is not unusual for patients in well-established enhanced recovery programs to be discharged on post-operative day two. We found that many of the patients who were discharged on post-operative day two or sooner (meaning within 48 hours of surgery) had undergone extensive procedures such as abdominoperineal resection. Given this finding, we were concerned about the integrity of this data. Post-operative day two was empirically selected as it represented the lowest 5% of the patient population. We did perform a sensitivity analysis to determine the effect of using 24 hours (post-operative day one) as the criteria for "missing data" (as this was the first percentile of data) and found a similar LOS savings associated with alvimopan.

One criticism of alvimopan is that it may simply be a marker for the existence of ERAS programs. While we could not measure the presence or absence of ERAS programs at each hospital, we attempted to account for them by measuring factors that are often included in ERAS pathways such as avoidance of NGT use after surgery and use of directed post-operative pain management strategies intended to avoid ileus.(28) Additionally, a recent observational study of patients undergoing colorectal surgery within the context of an established ERAS program showed that alvimopan use was associated with significantly shorter LOS and lower total costs,(29) supporting the hypothesis that alvimopan is effective outside of the practices associated with ERAS programs. Given this evidence along with the finding that alvimopan has been shown to be associated with lower rates of ileus, (6–10) future studies could explore the association between patient reported outcomes and alvimopan. It remains to be determined if lower rates of ileus would lead to higher patient satisfaction overall. Patient reported outcomes are increasingly identified as an important research target, and such a study may further inform our assessment of the overall value of alvimopan.

Conclusion

This study found that use of alvimopan in WA was associated with shorter LOS and a limited but significant cost savings in patients undergoing elective colorectal surgery, even after accounting for measurable sources of bias. Effectiveness evaluations are important in determining the value of drugs and devices prior to routine adoption and the available data support the use of alvimopan as a quality improvement initiative.

Acknowledgments

Support: Dr Ehlers was supported by a training grant from the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under Award Number T32DK070555. Dr Farjah received support as a Cancer Research Network Scholar (CRN4: Cancer Research Resources & Collaboration in Integrated Health Care Systems, grant number U24 CA171524).

Dr Bastawrous receives compensation for being on the advisory board of Cubist. Dr Thirlby receives a salary for being the Medical Director of SCOAP.

Disclosures Outside the scope of this work: Dr Bastawrous is a paid consultant for Intuitive Surgical; Dr Billingham is paid for expert testimony in case unrelated to topics in this work, and receives royalties for co-editing a book.

Disclaimer: SCOAP is a program of the Foundation for HealthCare Quality. The Comparative Effectiveness Research Translation Network (CERTAIN) is a program of the University of Washington that provided research and analytic support for this publication and was supported by funding from the Agency for Healthcare Research and Quality under award number R01HS020025. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, the Cancer Research Network, the Foundation for HealthCare Quality, or the Agency for Healthcare Research and Quality.

Abbreviations

CERTAIN	Comparative Effectiveness Research Translation Network
CHARS	Comprehensive Hospital Abstract Reporting System
FDA	Food and Drug Administration
GEE	generalized estimating equations
LOS	length of stay
POI	post-operative ileus
RCT	randomized controlled trial
SCOAP	Surgical Care and Outcomes Assessment Program
WA	Washington State

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Table 1

Patient, Operative, and Process-of-Care Variables Associated with Receipt of Alvimopan

	Alvimopan				All		p Value
	No		Yes				
	n	%	n	%	n	%	
Patient characteristic							
n	13,166		1,615		14,781		
Median age, y (range	62 (18–102)		61 (18–96)		62 (18–102)		0.02*
Female	7,239	55	869	54	8,108	55	0.37†
Private insurance	6,019	46	856	53	6,875	47	<0.01
Charlson Score‡							<0.01
0	9,260	70	1,216	75	10,476	71	
1	2,993	23	332	21	3,325	23	
2	731	6	54	3	785	5	
3	182	1	13	1	195	1	
ASA Class							<0.01
I	616	5	126	8	742	5	
II	7,229	55	978	61	8,207	56	
III	4,954	38	492	31	5,446	37	
IV	355	3	17	1	372	3	
BMI 18.5–25 kg/m^2	4,201	32	574	36	4,775	32	<0.01
Home oxygen	179	1	7	<1	186	1	<0.01
Mobility device§	684	5	29	2	703	5	<0.01
Current smoker	2,665	20	248	15	2,913	20	<0.01
Operative characteristic							
Laparoscopic‖	5,663	43	1,030	64	6,693	45	<0.01
Median Operating Time[range]	144[40–795]		150[41–688]		144[40–795]		<0.01
Indication							
Neoplasm	5,854	45	825	51	6,679	45	<0.01

	Alvimopan				All		p Value
	No		Yes				
	n	%	n	%	n	%	
Diverticulitis	3,049	23	379	24	3,428	23	
Inflammatory	1,118	9	133	8	1,251	9	
Other	3,145	24	278	17	3,423	23	
Operation type							
LAR	4,345	33	729	46	5,074	34	<0.01
Right	4,297	33	364	23	4,661	32	
Left	2,006	15	229	14	2,235	15	
TAC	611	5	88	6	699	5	
APR	549	4	103	6	652	4	
Proctectomy	549	4	37	2	586	4	
Stoma takedown	715	6	57	4	772	5	
In hospital complication	2,387	18	131	8	2,518	17	<0.01
Process-of-care							
Epidural	2,505	19	237	15	2,742	19	<0.01
Nasogastric tube[#]	1,192	9	59	4	1,251	9	<0.01
PCA	10,056	76	1,260	78	11,316	77	<0.01

Due to rounding, some column percentages may not sum to precisely 100.

[*]Comparison using test for the median for continuous variables that were not normally distributed.

[†]Comparison of patients who did and did not receive alvimopan using χ^2 tests for heterogeneity unless otherwise indicated.

[‡]Calculated based on reported comorbid conditions and lab values.

[§]Use of any home mobility device including walker, wheelchair, scooter, or cane.

[//]Includes laparoscopic, laparoscopic converted to open, laparoscopic/hand-assisted, robotic, and robotic converted to open

[#]Nasogastric tube in place when the patient left the operating room.

LAR, low anterior resection; Right, right hemicolectomy; Left, left hemicolectomy; TAC, total abdominal colectomy; APR, abdominoperineal resection PCA, patient-controlled analgesia.

Table 2

Unadjusted and Adjusted Outcomes for Length of Stay and Hospital Costs

	Alvimopan		Unadjusted differences*	Adjusted differences†
	No	Yes		
Length of stay, d [95% CI] ‡	7.0	5.2	−1.8 [−1.5, −2.1]	−0.9 [−1.1, −0.7]
Costs, USD [95% CI]§	$12,684	$10,667	−$2,017 [−$957, −$3,077]	−$636 [−$105, −$1,168]

*Comparison of patients who did and did not receive alvimopan using 2 sample t test.

†Adjusted for patient sociodemographic characteristics, clinical comorbidities, operative details, and process-of-care metrics described in Table 1 using generalized estimating equation models.

‡Length of stay defined as time from surgery to discharge.

§Hospital costs from the payer perspective.

Table 3

Characteristics of Propensity Score Matched Subgroups for Planned Sensitivity Analysis

	Alvimopan				p Value
	No		Yes		
	n	%	n	%	
Patient characteristic	834	50.0	834	50.0	
Median age, y (range)	60 (18–97)		62 (18–96)		0.07*
Female	467	56	474	57	0.73†
Private insurance	435	52	433	52	0.75
Charlson Score‡					0.74
0	611	73	618	74	
1	179	22	176	21	
2	34	4	27	3	
3	10	1	13	2	
ASA Class					
1	48	5.8	58	7	0.618
2	507	60.8	489	58.6	
3	271	32.5	276	33.1	
4	8	1	11	1.3	
BMI 18.5–25 kg/m^2	291	35	284	34	0.95
Home oxygen	2	<1	6	1	0.16
Mobility device§	15	2	13	2	0.70
Current smoker	138	17	142	17	0.79
Operative characteristic					
Laparoscopic‖	432	52	397	48	0.09
Median operating time, min (range)	151 (41–769)		142 (45–688		0.04
Indication					0.16
Neoplasm	377	45	360	43	
Diverticulitis	200	23	199	24	

	Alvimopan				p Value
	No		Yes		
	n	%	n	%	
Inflammatory	101	12	85	10	
Other	156	19	190	23	
Operation extent					
LAR	353	42	334	40	0.17
Right	197	24	214	26	
Left	131	16	121	15	
TAC	65	8	56	7	
APR	61	7	65	8	
Proctectomy	9	1	24	3	
Stoma takedown	19	2	20	2	
Processes-of-care					
Epidural	155	19	104	13	<0.01
Nasogastric tube[#]	43	5	44	5	0.91
PCA	627	75	644	77	0.33

[*] Comparison using test for the median for continuous variables that were not normally distributed. Comparison of patients who did and did not receive alvimopan using χ^2 tests for heterogeneity unless otherwise indicated.

[≠] Calculated based on reported comorbid conditions and lab values.

[§] Use of any home mobility device including walker, wheelchair, scooter, or cane.

[//] Includes laparoscopic, laparoscopic converted to open, laparoscopic/hand-assisted, robotic, and robotic converted to open

[#] Nasogastric tube in place when the patient left the operating room.

PCA, patient-controlled analgesia; LAR, low anterior resection; Right, right hemicolectomy; Left, left hemicolectomy; TAC, total abdominal colectomy; APR, abdominoperineal resection.

Table 4

Unadjusted and Adjusted Outcomes for Length of Stay and Hospital Costs in the Propensity Score Matched Group

	Alvimopan		Unadjusted differences*	Adjusted differences†
	No	Yes		
Length of stay, d [95% CI]‡	6.9	5.5	−1.4 [−0.9, −1.8]	−1.4 [−1.7, −1.0]
Costs, USD [95% CI]§	$12,228	$11,258	−$969 [−$2,253, +$314]	−$1,720 [−$2,456, −$984]

*Comparison of patients who did and did not receive alvimopan using 2 sample t test.

†Adjusted using the generalized estimating equations model to account for correlated data at the hospital level.

‡Length of stay defined as time from surgery to discharge.

§Hospital costs from the payer perspective.