Study Title:	Gastrointestinal Tract Recovery in Patients Undergoing Open Ventral Hernia Repair: A Single-Center, Randomized, Double-Blind, Trial of Alvimopan and Placebo
Date:	15-Oct-2014
Research Type:	Clinical
Study Type:	Prospective
Cubist Investigational Drug:	Alvimopan
Primary Investigator Name:	Dr. Matthew I. Goldblatt
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Additional instructions/information will be presented throughout in red text.
Please note: to create bullets within the template type "*" then hit the space bar.

1 STUDY RATIONALE/BACKGROUND

Alvimopan (Entereg) is an orally administered peripherally acting μ-opioid receptor antagonist that has been shown to decrease the duration of postoperative ileus.[2,5,8,9] Multiple double-blinded, randomized, placebo-controlled trials, have shown Alvimopan to reduce both the time to gastrointestinal recovery and the time to hospital discharge following bowel resection. This benefit was achieved without compromising pain management.[10] Alvimopan selectively and competitively inhibits the μ-opioid receptors in the GI tract, but is unable to cross the blood-brain barrier. This prevents Alvimopan from affecting the central nervous system pathway that controls analgesia, allowing it to decrease postoperative ileus time without compromising pain control.[10] In addition to accelerated gastrointestinal recovery and reduced length of hospital stay, the use of Alvimopan also significantly decreased the number of adverse events (most notably nausea and vomiting), and decreased the need for postoperative nasogastric tube reinsertion. These improved clinical outcomes had further impact by leading to lower hospital costs and increased patient satisfaction.[3,5,8,9] Alvimopan is FDA approved for patient use with the intent of accelerating upper and lower gastrointestinal recovery following bowel resections. To date, no studies have been conducted regarding the use of Alvimopan in patients undergoing ventral hernia repairs.

Conservative estimates suggest that the incidence of ventral incisional hernia after abdominal surgery via midline laparotomy is 10-20%.[1,4,7] The occurrence of a ventral incisional hernia is associated with significant patient discomfort, disability and subsequent morbidity. These factors lead most patients suffering from a ventral incisional hernia to pursue elective repair. In 2005, there were greater than 348,000 ventral hernia repairs in the United States alone.[14] If left unrepaired, these hernias can

increase in size causing pain, abdominal wall deformity, skin breakdown, intestinal obstruction and/or intestinal strangulation.[4]

One of the most common occurrences following ventral incisional hernia repair is post-operative ileus. Post-operative ileus is a source of patient discomfort and morbidity that ultimately delays discharge from the hospital and is frequently a source of patient readmission. Prolonged length of hospital stay due to post-operative ileus increases direct health care costs, as well as the indirect costs of a delay in returning to the workforce. The cause of prolonged ileus is multifactorial, but some of the main culprits include intra-operative bowel manipulation, the release of endogenous opioids, the administration of exogenous opioid analgesics during surgery and for post-operative pain control, inflammation, and fluid shifts.[3,5,8] A study by Lowe et al showed that following ventral hernia repair, 27% of their study patients had a prolonged ileus, defined as lasting more than 7 days postoperatively.[4] Likewise, the mean hospital stay for these patients was 12.5 days, due most frequently, to a delayed return of bowel function.[4]

Ventral incisional hernia repair is a common operation and post-operative ileus remains a frequent and costly post-operative occurrence for which we do not currently have an effective therapy. Alvimopan has proven to successfully decrease the duration of post-operative ileus and is FDA approved for such use in patients who have undergone bowel resection. Ultimately, decreasing the interlude between operation and return of bowel function results in shorter hospital stays, lower hospital costs, and faster rehabilitation. We propose to study the effectiveness of Alvimopan in decreasing postoperative ileus time in patients undergoing ventral hernia repair, a cohort that we feel may benefit from the use of Alvimopan but that to date has not been studied.

2 STUDY HYPOTHESIS

In patients undergoing open ventral hernia repair, we hypothesize that Alvimopan (Entereg) is associated with accelerated gastrointestinal recovery and reduced length of hospital stay compared to placebo controls.

2.1 PRELIMINARY DATA

Fitzgibbons et al, (Creighton University) employed a single-center, randomized, double-blind trial, of Alvimopan in open and laparoscopic ventral hernia repair patients. Comparisons were made between the length of time (in post-operative days) until patient flatus, bowel movement, and discharge from hospital. The treatment group (Alvimopan) showed a trend toward first flatus, bowel movement, and hospital discharge compared to the placebo group. However, this was not significant due to the small sample number within the sample population. The study results reported by Fitzgibbon et al. warrant a larger sample size to determine the outcomes achieved with Alvimopan in ventral hernia patients.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 STUDY OBJECTIVES

3.1.1 PRIMARY OBJECTIVES:

Primary Objective: To investigate the efficacy and safety of Almimopan, 12mg, administered orally 30 to 90 minutes preoperatively and twice daily postoperatively for a maximum of 7 days (15 total doses) in conjunction with a standardization postoperative care pathway for managing postoperative ileus after ventral hernia repair.

3.1.2 SECONDARY OBJECTIVES:

Secondary Objective: To investigate the post-operative gastrointestinal recovery, and treatment related morbidity after ventral hernia repair.

3.2 STUDY ENDPOINTS

3.2.1 PRIMARY ENDPOINT:

Length of time (hrs/days) to gastrointestinal tract recovery

3.2.1.1 PRIMARY ENDPOINT DEFINITION:

Time to gastrointestinal recovery will be measured by the following: Time to first flatus, time to toleration of a liquid diet, time to toleration of a solid diet, time to toleration or oral pain medications, time to first bowel movement, time to GI-2 recovery, time to GI-3 recovery, incidence of nasogastric tube insertion, episodes of emesis, use of anti-nausea medication, nausea, bloating, incidence of diet reduction or restriction, and initiation of TPN.

Time to first flatus and time to first bowel movement are patient reported endpoints that occur during the hospitalization. Patients will be asked about flatus twice daily by the physician or a qualified study or clinical staff member. Additionally, patients will be instructed to notify the nurse following first flatus and/or bowel movement so that the time can be recorded.

Toleration of a diet and toleration of oral pain medication are defined as ingestion of diet or medications that occurs without vomiting or significant nausea for four hours following ingestion.

GI-2 recovery is defined as both toleration of solid food and occurrence of first bowel movement. GI-3 recovery is defined as toleration of solid food and either occurrence of first flatus or occurrence of first bowel movement.

Patients requiring nasogastric tube insertion, requiring reduction or restriction of diet, having episodes of emesis, and/or needing initiation of TPN will be recorded. VAS

nausea, bloating and pain scores will be recorded by nursing staff at least twice each day. The number of doses of anti-nausea medication administered during the hospitalization will also be recorded.

3.2.2 SECONDARY ENDPOINT(S):

Length of hospital stay, 30-day treatment related morbidity and re-admission rates, and post-operative pain scores.

3.2.2.1 SECONDARY ENDPOINT DEFINITION(S):

Length of stay will be measured in hours from the time that surgery is completed until the hospital discharge order is written (hrs/days).

Treatment related morbidity and re-admission rates will be assessed from the time surgery is completed to 30-days post-operatively. Treatment related morbidity and re-admission rates include: POI, indigestion, and any event determined by the attending physician to be directly related to treatment.

Post-operative pain scores will be obtained from patients daily until hospital discharge, 2-weeks post-operatively, and 30-days post-operatively using the Visual Analog Pain Scale (scale, 1-10) and the Hernia-Related Quality-of-Life Survey (HerQLes).

4 STUDY DESIGN

4.1 SITES

Medical College of Wisconsin, Milwaukee, WI

4.2 INCLUSION/EXCLUSION CRITERIA

4.2.1 INCLUSION CRITERIA

1. Subjects will be informed about the study, have read, understood, and signed the Informed Consent Form
2. Subjects of either gender that are ≥18 years of age
3. Subjects who can ambulate preoperatively
4. Subjects will have a Body-Mass Index (BMI) of ≤ 40mg/m^2
5. Subjects with an ASA classification of 1, 2 or 3
6. Subjects not receiving an epidural to control perioperative pain
7. Subjects will be undergoing elective single-staged open ventral (incisional or midline) hernia repair
8. Subjects in which intra-operatively their surgical field/wound is characterized as Type 1 (Appendix II)
9. Subjects with a hernia defect ≥9 cm^2 large

4.2.2 EXCLUSION CRITERIA

1. Subjects who are not able to comprehend or comply with study requirements
2. Subjects who are pregnant
3. Subjects with BMI > 40
4. Subjects with autoimmune disorder requiring >10mg of a corticosteroid per day
5. Subjects with pre-existing systemic infections
6. Subjects with a wound-healing disorder
7. Subjects who have taken therapeutic doses of opioids for more than 7 consecutive days immediately prior to taking Alvimopan
8. Subjects who are immunocompromised such as HIV or transplant, or receiving chemo or radiation therapy
9. Subjects with a hernia defect < 9cm^2 large when measured intra-operatively
10. Subjects in which intra-operatively their surgical wound field/wound is characterized as Type 2, 3, or 4 (Appendix II)
11. Subjects in which the ventral incisional hernia repair requires more than one operation to reduce the hernia or to complete the hernia repair
12. Subjects with a hernia repair requiring an emergent procedure
13. Subjects in which untreated cancer was found intra-operatively
14. Subjects with cirrhosis or are currently being treated with dialysis
15. Subjects with severe hepatic impairment (Childs-Pugh class C)
16. Subjects with end-stage renal disease
17. Subjects scheduled for a concomitant procedure that involves the GI tract
18. Subjects with unplanned procedures that involve the GI tract
19. Subjects requiring post-operative NGT
20. Subjects participating in another prospective interventional study that involves the use of a device, drug, or surgery that would compromise the current study
21. Subjects with an epidural to control perioperative pain

4.3 SAMPLE SIZE

4.3.1 NUMBER OF CHARTS TO BE REVIEWED

Not Applicable.

4.3.2 NUMBER OF SUBJECTS TO BE ENROLLED

140: 70 Alvimopan, 70 Placebo

4.3.3 SAMPLE SIZE DETERMINATION

A total of 140 patients are expected to undergo research related treatments. The study will contain one open surgery arm. The open surgery arm will be a single-site prospective, randomized, double-blinded, placebo-controlled clinical trial with 1:1

randomization between the study drug and placebo with 70 patients in each group for a total of 140 patients in the study. An interim evaluation of efficacy will be conducted separately in the open surgery arm when half the patients have been recruited.

This study is expected to enroll up to 140 subjects from one academic medical center (Froedtert Hospital and the Medical College of Wisconsin) a site that performs state of the art hernia repairs and is a high volume hernia practices.

The study has been designed to provide at least 80% power to detect a 24-hour decrease in the time to return of bowel function in the treatment group compared to the control group at a one-sided 2.5% significance level. This corresponds to a two-sided 5% significance level, but acknowledges the one-sided nature of the study hypothesis. Based on data from studies of the experimental treatment in other contexts, as well as internal data, we expect a standard deviation of 48 hours. Adjusting for the increase in sample size to accommodate the planned interim analysis, 64 evaluable patients per group will provide the desired power. More details of the power characteristics are shown under the Interim Analysis section. We will recruit 70 patients in each arm to accommodate a 5-10% dropout rate.

4.4 SCREENING, RANDOMIZATION, BLINDING

4.4.1 SCREENING PROCEDURE

1. All subjects undergoing open ventral (incisional or midline) hernia repair will be approached by study staff prior to surgery to participate in the study.
2. Patients who meet all inclusion/exclusion criteria will be approached for voluntary informed consent.
3. Final determination on whether a subject will be included in the study will be made during surgery. If intra-operatively it is concluded that the subject does not meet the study criteria, the subject will be excluded and the reason will be documented.
4. The study team will maintain a screening log for all patient approached for consent per institutional IRB guidelines.

4.4.2 RANDOMIZATION

Patients will be randomized after written informed consent has been obtained and eligibility has been verified. Operationally, the blinded randomization will be carried out using patient-specific study numbers. Before the initiation of the study a list linking study IDs to treatment and control group will be generated following the randomization plan, and provided to Froedtert Hospitals Investigational Drug Services (IDS). The IDS will receive study drugs from Cubist Pharmaceuticals, Inc. and package and distribute study medications to each study patient. The patient will then receive medication dispensed from the bottle with the corresponding study ID.

4.4.3 BLINDING

The study will be performed in a double-blind fashion. The investigator, study staff, subjects, and monitors, will remain blinded to the treatment assignment. Alvimopan and the placebo will be visually identical and will be similarly packaged and administered.

The identity of the study drug may only be revealed if the subject experiences a medical emergency whose management would require knowledge of the blinded treatment assignment. The master randomization code list will be maintained by the IDS. Prior to unblinding, the surgeon or other care provider must contact the study principle investigator, and every attempt must be made by the treating surgeon to discuss the intended unblinding with the principle investigator (or a designee from IDS). All cases of unblinding, including justification for unblinding, must be fully documented by the principle investigator, site investigator, and IDS designee. The principle investigator may obtain the identity of the study drug dispensed to a subject through IDS.

If the subject becomes unblinded, the subject will continue to be followed for adverse events up to 30 days, or 14 days past discharge if the patient is an inpatient after 30 days, but the efficacy data from this point will be carried forward and analyzed in the intent-to-treat analysis.

4.5 REGULATORY AND ETHICS

4.5.1 INFORMED CONSENT

Voluntary written informed consent must be obtained before any study-related procedures are performed in accordance with International Conference on Harmonization (ICH) guidelines and the requirements of informed consent (Title 21 Code of Federal Regulations (CFR) Parts 50.20 and 50.25). Consent must be documented by the use of a written consent form approved by Cubist and the Institutional Review Board (IRB) in accordance with Title 21 CFR Part 50.27. In the case of non-interventional studies, a waiver of informed consent may be granted by your IRB and will need to be provided to Cubist. A technical guide is available upon request to assist you in understanding informed consent requirements.

All patients who meet inclusion criteria and voluntarily agree to participate in the study will sign an IRB approved informed consent.

4.5.2 INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE

The Medical College of Wisconsin IRB will oversee the proposed study.

4.5.3 INVESTIGATIONAL NEW DRUG (IND) FILING

As the Sponsor Investigator you are responsible for determining whether an IND is necessary in order to conduct your proposed clinical study. Cubist Pharmaceuticals does not make this determination for Sponsor-Investigator studies. We strongly encourage you to contact the Food and Drug Administration (FDA) for assistance in determining the necessity of an IND. Information on who to contact can be found by clicking the following link: IND Guidance. Section 312.2 of Title 21 of the Code of Federal Regulations details the applicability and exceptions of the IND regulations. A technical guide is available upon request to assist you in understanding when an IND may be required.

The study team submitted an IND application to the FDA to support our study.

5 STUDY PROCEDURES

5.1 TREATMENT

Consented patients in the Treatment Group will receive 12 milligrams (mg) of Alvimopan per-oral (PO) 30 minutes to 90 minutes prior to ventral hernia repair in the pre-operative area and continue 12 mg PO twice daily until hospital discharge or post-operative day (POD) 7 for a maximum of 15 in-hospital doses (Appendix II).

Patients in the Control Group will receive 12 milligrams (mg) of Placebo orally (PO) 30 minutes to 1 hour prior to VHR in the pre-operative area and continue 12 mg PO twice a day until hospital discharge or post-operative (POD) 7 for a maximum of 15 in-hospital doses.

If the maximum allowed number of doses is not achieved in a seven day period (15 doses) the remaining study medication is to be returned to FH IDS for proper disposal. Under no circumstances is study medication to be re-used or re-packaged for sale or distribution.

5.2 INTERVENTION

Not applicable.

5.3 PROCEDURES

Patients who meet all includion criteria will undergo the study related procedures stated below.

During enrollment, FH IDS will assign medication to patients in order of enrollment and according to the randomization code list. The patient will then receive medication dispensed from the bottle with the corresponding study ID.

Patient treatment will follow (section 5.1).

Following surgery, patients will be admitted to the hospital and a basic standardized treatment pathway will be initiated.

1) Following surgery patients are admitted with NPO status, PRN IV opioid pain medication, and PRN IV anti-nausea medication.

2) Epidural use is up to the discretions of the treating surgeon.

a. Non-narcotic adjuncts can be used as determined by the physician

3) Nasogastric tubes are NOT routinely left in following surgery. However, nasogastric tube use is up to the discretion of the treating surgeon. Patients who require NGT will be excluded from the study.

4) Patients remain NPO until the following criteria are met: reported flatus, absence of nausea and/or emesis and/or bloating, and absence of abdominal distention. Alternatively, clinical determination made by the physician can be utilized for diet advancement. If clinical determination outside of these parameters is used then the justification for the clinical decision making will be recorded for these patients.

5) Transition to oral pain medication will occur at or after the time of transition to clear liquids.

6) Diet advancement after clears will occur at physician discretion

7) Minimum discharge criteria include: toleration of diet beyond clears, toleration of oral pain medication, and absence of nausea/vomiting/distention.

a. Toleration of solid food is NOT required for discharge

b. Production of a bowel movement is NOT required for discharge

5.4 ADVERSE EVENT REPORTING

If your study collects patient specific safety data, provide timelines and a detailed description of procedures for collecting, assessing and reporting adverse events. A technical guide is available upon request to assist you in completing the following section.

It is the responsibility of the investigator(s) to oversee the safety of the study. The safety monitoring will include careful assessment and appropriate reporting of complications/events as noted below.

Adverse events will be reviewed for clinical relevance and cause relation and reported as the events occur.

The ACS NSQIP Variables and Definitions guidance document will be used to ensure consistency of defining and reporting the complications or events in this study.

5.4.1 DEFINITONS

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Pregnancy is not an AE; however, if a female subject becomes pregnant during the conduct of the study, the Investigator should discontinue study medication immediately. Follow up information regarding the outcome of the pregnancy and any sequelae, including fetal or neonatal abnormalities should be obtained and documented. All information obtained about the pregnancy including information on the infant after birth should be forwarded to Cubist Pharmacovigilance as soon as possible.

The identification of the presence of a non-susceptible microorganism during treatment is generally not considered an AE unless associated with other unintended consequences (e.g., worsening of the disease under treatment).

5.4.2 RELATIONSHIP TO STUDY MEDICATION

Many terms and definitions can be used to describe the causal relationship between a drug product and an AE. Examples include: definitely, probably, possibly, unlikely related, or not related. Phrases such as “plausible relationship”, “suspected causality”, or “causal relationship cannot be ruled out” have also been used to describe a positive causal attribution between the product and the AE. There is currently no standardized nomenclature.

1. Not Related: an AE with a temporal relationship to the drug administered that makes a causal relationship improbable, and/or for which other drugs or underlying or concurrent disease provide a plausible explanation
2. Unlikely Related: an AE that has a plausible temporal relationship to the drug administered, but for which other causative factor(s) more likely account for the event and where dechallenge (withdrawal of drug treatment) or dose reduction was not felt clinically indicated or improvements on dechallenge or dose reduction have not been observed
3. Possibly Related: an AE that has a plausible temporal relationship to the drug administered, but for which other causative factor(s) could account for the event and where improvements on dechallenge or dose reduction may or may not have been observed.

5.4.3 EXPECTEDNESS OF AE

An AE is considered *unexpected* if the specificity or severity is not consistent with the applicable product information. In this case, where a study is being performed prospectively outside of the current labeled use (e.g., the investigator holds their own IND), the Investigator Brochure is considered the applicable product information.

Warnings and precautions as provided in the prescribing information packet include:

1. A higher number of myocardial infarctions was reported in patients treated with alvimopan 0.5 mg twice daily compared with placebo 12 in a 12-month study in patients treated with opioids for chronic pain, although a causal relationship has not been established

2. Patients recently exposed to opioids are expected to be more sensitive to the effects of ENTEREG and therefore may experience abdominal pain, nausea and vomiting, and diarrhea.
3. Not recommended in patients with severe hepatic impairment.
4. Not recommended in patients with end stage renal disease.
5. Most common adverse reaction (incidence >1.5%) occurring with a higher frequency than placebo among ENTEREG-treated patients undergoing surgeries that included a bowel resection was dyspepsia.
6. Not recommended in patients with complete GI obstruction or in patients who have surgery for correction of complete bowel obstruction.
7. Not recommended in pancreatic or gastric anastomosis.

5.4.4 RECORDING AND REPORTING AN AE

If AEs are collected, any AE, regardless of seriousness, severity, or causal relationship to a drug, should be recorded on the case report form or SAE form. For retrospective studies, investigators should report all AEs identified during the study period defined in the protocol.

Any AE, regardless of seriousness, severity, or causal relationship to the study medication, will be recorded on the case report form or SAE form. The form contains fields that allow for complete evaluation of an AE. All AEs starting with the first intervention or dose of study medication and throughout the duration of the study (through last patient visit) will be monitored.

5.4.5 RECORDING AND REPORTING A SAE

5.4.5.1 STUDIES NOT PERFORMED UNDER AN IND

Please report all required safety data to your IRB in accordance with your IRB's directions. Healthcare professionals are encouraged to report adverse events or side effects related to the use of these products to the FDA's MedWatch Safety Information and Adverse Event Reporting Program; online reporting is available via: www.fda.gov/MedWatch/report.htm. *On the same day that you notify the FDA or your IRB, please send a copy of the AE report that you have submitted to the FDA or your IRB to Cubist's Pharmacovigilance department at pv@cubist.com. You will also be expected to cooperate with Cubist regarding any safety related inquiries related to this report.*

Not Applicable.

5.4.5.2 STUDIES PERFORMED UNDER YOUR OWN IND

You are obligated to notify the FDA in a written IND Safety Report of any adverse experience that you assess as both serious and related to the drug and are unexpected no later than 15 calendar days after your initial receipt of the information. Please refer to 21 CFR Part 312.32 for definitions and reporting timeframes and requirements.

Please report all required safety data to your IRB in accordance with your IRB's directions.

On the same day that you notify the FDA of any SAE you must send a copy of each IND Safety Report (Initial Written Report and any Follow-ups to a Written Report) to Cubist's Pharmacovigilance department at pv@cubist.com. You will also be required to cooperate with Cubist regarding any safety related inquiries.

Recording of AEs

Any AE, regardless of seriousness, severity, or causal relationship to a drug, will be recorded on the case report form or SAE form. The form contains fields that allow for complete evaluation of an AE. All AEs starting with the first intervention or dose of study medication and throughout the duration of the study (through last patient visit) will be monitored.

Reporting of SAEs

The study team will notify the FDA in a written IND Safety Report of any adverse experience that is assessed as both serious and related to the drug and is unexpected (not previously described in the package insert or Investigator's Brochure). Each notification shall be made no later than 15 calendar days after initial receipt of the information. 21 CFR Part 312.32 will be referenced for definitions and reporting timeframes and requirements.

Written notification using a MedWatch form (Form FDA 3500A) will be submitted or in narrative format. The submission will be clearly marked with the studies assigned IND number and "IND Safety Report". In each written IND Safety Report, the study team will identify all safety reports (if any) previously filed with the IND concerning similar adverse experience, and will analyze the significance of the adverse experience in light of the previous, similar reports.

The study team is obligated to notify the FDA by telephone or FAX of any unexpected fatal or life-threatening experiences assessed as related to the drug no later than 7 calendar days after initial receipt of the information. The telephone call or FAX will be made to the Regulatory Project Manager at the study teams FDA review division. The telephone/FAX notification will be followed by a written IND Safety Report within 15 days of your initial receipt.

The study team is also, obligated to promptly investigate all safety information and submit follow-up information to an initial written report (IND Safety Report—Follow-up to a Written Report) as soon as relevant information is available.

On the same day that you notify the FDA, the study team will send a copy of each IND Safety Report (Initial Written Report and Follow-up to a Written Report) to Cubist. Copies of the IND Safety Report will be sent to Cubist Pharmacovigilance via email or FAX. Email: pv@cubist.com FAX: 877-224-3324

In the cover letter to Cubist, the study team will identify ourselves as a Sponsor-Investigator, provide our assigned IND number, full contact information, protocol title, and when the report was sent to the FDA.

6 DATA COLLECTION AND ANALYSIS

6.1 DATA COLLECTION

For each subject who meets inclusion criteria, a clinical report form (CRF) must be completed and signed by the investigator to certify that the data within each CRF are complete and correct according to data collection schedule (Appendix I). Every effort

should be made to respond to all questions on each CRF page, completion of the data is required by the protocol. The header section of each CRF page should be completed to identify the Investigators/surgeon and subject identification.

Upon receipt of completed CRFs and prior to entering data into the aggregate data summary table, the site-coordinator will ensure the accuracy of data recorded by comparison to supporting source documents. Adherence to proper recording of information as well as assuring that corrections are being made will also be addressed.

One interim analysis will be conducted when the first half of patients in each group (35 treatment and 35 control) complete their 30-day follow-up visit. Specifically, the interim analysis will be blinded and conducted at a nominal 0.0031 one-sided level of significance, while the final analysis will be conducted at a nominal 0.0219 one-sided level of significance. These values were calculated using a third-degree Kim-DeMets power alpha-spending function evaluated at the halfway point. If the actual information fraction at the time of the analysis is different, or the DSMC requests additional unblinded analysis, the significance levels will be adjusted using the alpha-spending function.

Results of the interim analysis will determine if it is futile to continue patient enrollment based on statistically significant differences (24 hour decrease in the time to return of bowel function in the treatment group compared to controls at a one-sided 2.5% significance level between the treatment and control groups). In addition, the MCW IRB in collaboration with the study investigators may terminate the study at any time to maintain patient safety.

The following table shows the probability of early stopping and the overall power of the study for various hypothetical effect sizes. If the design assumptions are correct, the study will stop early for efficacy with 23% probability, but if the actual effect is 50% larger (due to larger mean difference or smaller within-group standard deviation), then the trial will stop early 60% of the time.

Relative effect size*	**Probability of concluding superiority of the intervention**		
	At interim analysis	**At final analysis**	**Overall**
0	0.31%	2.19%	2.5%
0.5	4.1%	24.6%	28.7%
1	**22.9%**	**57.1%**	**80.0%**
1.5	60.0%	38.8%	98.8%
2	89.4%	10.1%	99.9%

* The relative effect size is the ratio of the actual effect size to the design effect size of 24 hour difference with 48-hour within-group standard deviation.

6.2 DATA VALIDATION

Data validation (verification of case report forms against source data documents) is required for both prospective and retrospective studies in which data is being entered on case report forms. Validation should be completed by an independent, study monitor, internal or external to the investigator/sponsor institution, who is not involved in the conduct or oversight of the study. For database studies you will be required to attest that you have entered into a data use agreement with the database owner and that the data in the database has undergone validation/verification by that owner. A technical guide is available upon request to assist you in completing the following section.

The study team's certified clinical research professional (CCRP) will review all data fields on the data collections forms. Data validation will occur after patients complete their final assessment at 30-days. Charts will be reviewed in batches of five. A list of missing data or data fields that need to be updated will be created. All errors, if any, will be identified and corrected. When all variables are reviewed, the CCRP will review the action items with the study team. Corrected fields on the paper data collection form will be dated and initialed by the study team.

6.3 DATA / STATISTICAL ANALYSIS

All efficacy analyses will be intent to treat. The time to bowel function recovery and hospital length of stay will be compared between the two groups using Student's t-test. Due to the short-term nature of the outcome measures we expect no censoring.

7 PUBLICATION

It is intended that the results from this study will be published jointly by the investigators and members directly involved with study design and completion. The study PI will maintain ownership of all study related data. The investigators will comply with the ICMJE's Uniform Requirements for manuscripts submitted to biomedical journals.

8 TIMELINE

Upon final review of the study protocol, the signed contract shall be completed within 1-2 months. Duration of IRB/ethics approval is estimated to occur between 2-3 months after initial submission. To reach the goal of 140 patients in each study arm, at an estimated rate of 40 enrolled patients per year, the study will last at least three years. If the interim analysis indicates that 35 patients per arm is sufficient to detect a significant difference between groups, final enrollment may occur within two years after the first enrolled patient.

9 REFERENCES

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6. McGreevy J, Goodney P, et al. (2003) A prospective study comparing the complication rates between laparoscopic and open ventral hernia repairs. *Surgical Endoscopy* 17: 1778-1780.

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