UC San Diego
MOORES CANCER CENTER

# The ILEUS Study: A Phase 2 Randomized Controlled Trial **I**nvestigating A**L**vimopan for **E**nhanced Gastrointestinal Recovery after Cytored**U**ctive **S**urgery and Hyperthermic Intraperitoneal Chemotherapy


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**Signature Page**

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

**PI (Print Name): Joel Baumgartner, MD**

**PI Signature:** _____

**Date:** 6/25/19

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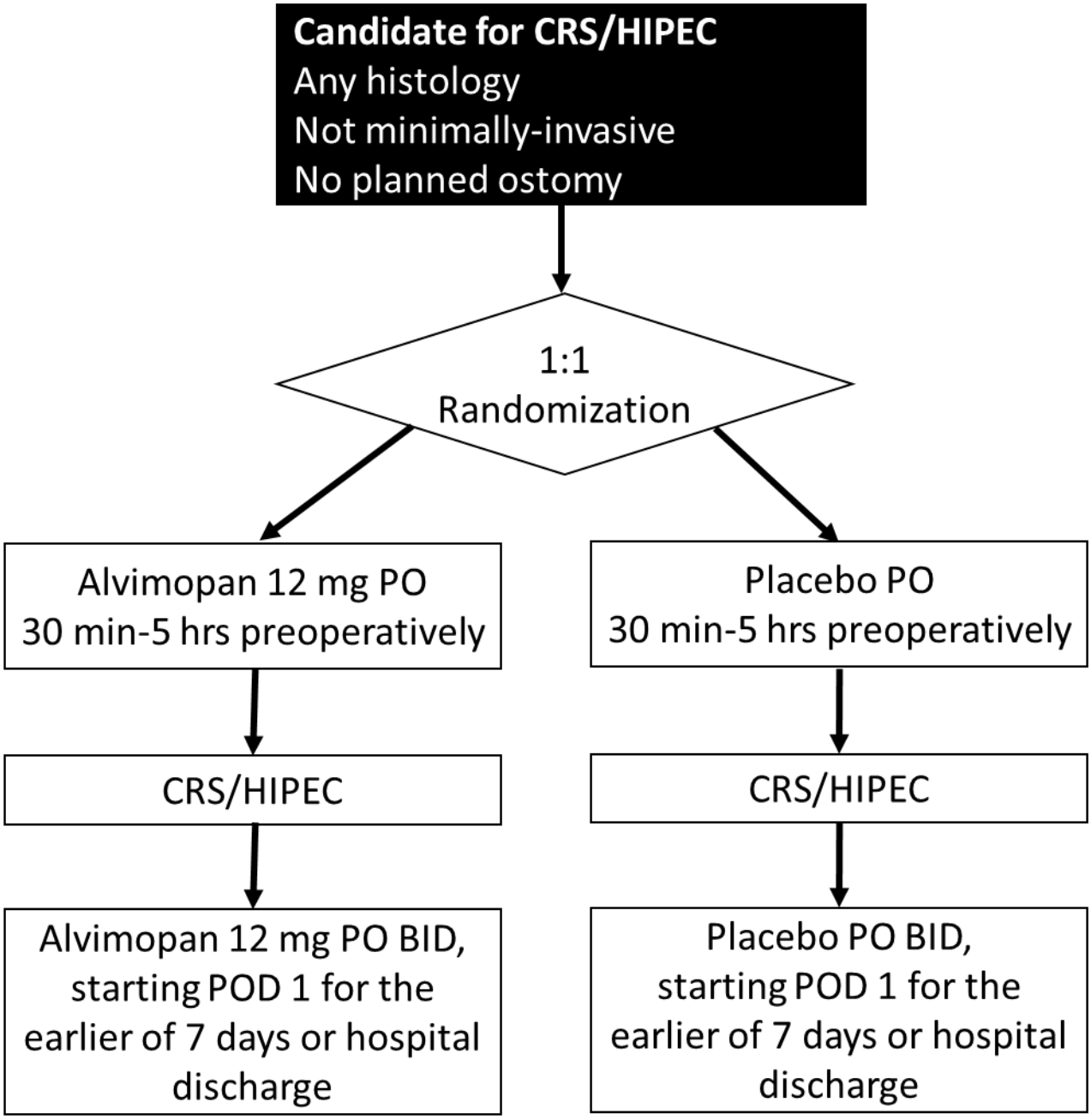
**LIST OF ABBREVIATIONS**

| | |
|---|---|
| AE | Adverse Event |
| BM | Bowel Movement |
| CBC | Complete Blood Count |
| CEA | Carcinoembryonic Antigen |
| CRS | Cytoreductive Surgery |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DSMB | Data and Safety Monitoring Board |
| ECOG | Eastern Cooperative Oncology Group |
| GI | Gastrointestinal |
| HIPEC | Hyperthermic Intraperitoneal Chemotherapy |
| HRPP | Human Research Protections Program |
| IRB | Institutional Review Board |
| LN | Lymph Node |
| NCI | National Cancer Institute |
| OS | Overall Survival |
| PC | Peritoneal Carcinomatosis |
| PD | Progressive Disease |
| PFS | Progression Free Survival |
| PO | Per Os (By Mouth) |
| POD | Postoperative Day |
| RCT | Randomized Controlled Trial |
| SAE | Serious Adverse Event |
| UPR | Unanticipated Problems involving Risk to subjects or others |

**STUDY SCHEMA**




**NOTE: Randomized Patients who do not undergo CRS/HIPEC will be considered screen failures after randomization.**

## STUDY SUMMARY

| | |
|---|---|
| Title | The ILEUS Study: A Phase 2 Randomized Controlled Trial Investigating Alvimopan for Enhanced Gastrointestinal Recovery after Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy |
| Short Title | Phase 2 Randomized Controlled Trial of Alvimopan after CRS/HIPEC |
| Phase | II |
| Methodology | Double-blind, randomized, placebo-controlled trial |
| Study Duration | 2 years |
| Study Center(s) | Single-center (UCSD) |
| Objectives | Primary Endpoint<br>• Time to recovery of upper and lower GI function (GI-2), as measured by the later of the following 2 events: time that the patient first tolerates solid food and time that the patient first passes bowel movement<br>Secondary Endpoints<br>• Proportion of prolonged ileus (> 7 days)<br>• Time to return of bowel function components: time to first flatus, time to first bowel movement, time to tolerance of solid food<br>• Time to hospital discharge order written<br>• Adverse events<br>• Subgroup analyses: number of anastomoses, number of visceral resections, epidural/no epidural, etc. |
| Number of Subjects | 128 |
| Diagnosis and Main Inclusion Criteria | Eligible participants are those who undergo open cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) |
| Study Product(s), Dose, Route, Regimen | Alvimopan 12 mg, by mouth, 30 minutes to 5 hours preoperatively, then POD 1 by mouth twice for the earlier of 7 days or hospital discharge (maximum 15 doses) |
| Duration of administration | 8 days (maximum) |
| Reference therapy | Placebo |
| Statistical Methodology | Based upon a sample size of n=64 patients per group (128 total), this study has 82% power to detect a HR of 1.59 which approximately corresponds to an improvement in the median primary endpoint (GI-2) from 9 days to 5.7 days, with a single-sided alpha of 0.05, and 5% withdrawal rate. |

## 1.0 BACKGROUND AND RATIONALE

### 1.1 Disease Background

The peritoneum is a common site of metastasis, with approximately 55,000 new cases of peritoneal metastases occurring annually in the US.[1] Tumors that commonly metastasize to the peritoneum include gastrointestinal (colorectal, small intestine, appendix, gastric, pancreatic, gallbladder, liver), gynecologic (ovarian), and primary peritoneal (peritoneal mesothelioma, primary peritoneal serous carcinoma) malignancies. Tumor histology and extent of disease are the primary determinants of long-term outcome, but patients with peritoneal metastases typically have a poor prognosis – 16 months medial survival from colorectal cancer.[2] Treatment options for peritoneal metastases are limited as systemic chemotherapy has poor penetration of the peritoneum and many peritoneal tumors are hypovascular and can be surrounded by a viscous layer of mucin.[3] The fact that the peritoneal cavity may represent the only site of metastatic disease in selected patients has prompted the utilization of aggressive surgical resection (cytoreduction) and hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of peritoneal metastases.[4] HIPEC is a method of delivering high doses of cytotoxic chemotherapy directly the peritoneal cavity with limited systemic toxicity, and is typically performed concurrently with surgical resection of visible intraperitoneal disease (cytoreductive surgery, CRS).[5] The combined procedure (CRS/HIPEC) generally is performed through a large midline incision and includes extensive lysis of adhesions, resection of all visible peritoneal metastases, often with multivisceral resections including bowel resections and possibly multiple anastomoses, and requires a mean of eight hours of operative time. Large case series have estimated CRS/HIPEC doubles the median survival verses systemic chemotherapy alone in certain settings (colorectal cancer, appendiceal cancer and peritoneal mesothelioma).[6-8] Perioperative complications of this extensive surgery are considerable, with a 1-2% risk of mortality and 16% risk of severe morbidity.[9] This procedure remains highly specialized and is mostly performed in a limited number of high-volume centers in the US, which include UCSD. Approximately 60-70 CRS/HIPEC procedures are performed annually at UCSD.

The median length of stay after CRS/HIPEC is 10 days at our institution. A majority of the hospital stay is comprised of awaiting return of bowel function. The first flatus or bowel movement does not typically occur until postoperative day 4-5, and in 13% of patients it takes longer than 7 days.[9] This is despite the fact that all patients undergo enhanced recovery pathways; including early mobilization, foley catheter removal as soon as feasible, and early advancement to liquid diet. Although attempts are made to minimize narcotic use after CRS/HIPEC - including use of epidural catheters and opioid-sparing medications (such as ketorolac and lidocaine patch) – all patients still require postoperative narcotics, which likely contributes to the prolonged ileus.

### 1.2 Study Agent

Alvimopan is an oral peripherally-acting mu opioid receptor antagonist, with limited ability to cross the blood-brain barrier. There have been eight randomized-controlled trials published in English language journals documenting the safety and efficacy of alvimopan for postoperative ileus.

From a safety standpoint, a meta-analysis of all randomized controlled trials found the

most common adverse events with alvimopan included nausea, vomiting, constipation, flatulence, distension, headache, and pruritis (all greater than 10% in incidence).[10] Rates of all common AEs from this meta-analysis is listed in the table below.

| **Adverse Event** | **Rate (%)[1]** |
|---|---|
| Nausea | 56.1 |
| Vomiting | 18.3 |
| Constipation | 15.4 |
| Flatulance | 14.5 |
| Distension | 12.2 |
| Headache | 11.2 |
| Hypotension | 8.5 |
| Hypertension | 9.4 |
| Pyrexia | 9.9 |
| Pruritis | 11.7 |
| Tachycardia | 7.1 |
| [1]Among patients receiving 12 mg alvimopan dose | |

It is worth noting that most of the GI-related adverse events are also symptoms of postoperative ileus, making attribution to alvimopan imprecise. Furthermore, many AEs were significantly lower in the alvimopan groups than the placebo groups (nausea, vomiting, constipation, and pyrexia). The remaining common AEs were no different in the alvimopan and placebo groups.

Serious adverse events were reported in 3-25.7% of participants in RCTs, and included infection, anastomotic leak, dehiscence, pain, postoperative ileus, dehydration and small bowel obstruction.[11-16] In all trials reporting SAEs, the rate in the alvimopan group was equal to or less than in the placebo group, and no trials reported deaths attributed to alvimopan.

One study investigating 0.5 mg twice daily alvimopan for 12 months for the treatment of opioid-induced bowel dysfunction found a higher incidence of myocardial infarction in the alvimopan group.[17] The events occurred 1-4 months after the start of treatment, and the increased risk of MI has not been observed in other studies with shorter duration (7 days) of alvimopan in postoperative patients.[13] A large matched-cohort study using a national inpatient database including 7050 patients found a *lower* risk of cardiovascular morbidity in the alvimopan cohort than in the control cohort (19.4% vs. 24.0%, $p = 0.0001$).[18]

Alvimopan has been found to decrease the time to return of bowel function and time to discharge in multiple randomized controlled trials, as seen in the table below.

| Study | Year | Procedures | Intervention | N | Endpoint(s)[1] |
|---|---|---|---|---|---|
| Taguchi *et al.*[19] | 2001 | 15 LBR<br>63 TAH | Alv. 1 mg | 26 | Time to flatus: RR 1.2 (p=0.59)<br>Time to BM: RR 1.2 (p=0.69)<br>Time to D/C: RR 1.2 (p=0.48) |
| | | | Alv. 6 mg | 26 | Time to flatus: **RR 2.5 (p=0.004)**<br>Time to BM: **RR 2.9 (p=0.01)**<br>Time to D/C: **RR 2.4 (p=0.003)** |
| | | | Placebo | 26 | |
| Wolff *et al.*[16] | 2004 | 395 LBR<br>56 SBR<br>18 TAH | Alv. 6 mg | 155 | Time to GI-3: **HR 1.28 (p<0.05)**<br>Time to GI-2: **HR 1.38 (p=0.013)**<br>Time to D/C: **HR 1.25 (p=0.070)** |
| | | | Alv. 12 mg | 165 | Time to GI-3: **HR 1.54 (p<0.001)**<br>Time to GI-2: **HR 1.67 (p<0.001)**<br>Time to D/C: **HR 1.42 (p=0.003)** |
| | | | Placebo | 149 | |
| Delaney *et al.*[20] | 2005 | 303 LBR<br>129 TAH | Alv. 6 mg | 150 | Time to GI-3: **HR 1.45 (p=0.003)**<br>Time to GI-2: **HR 1.46 (p=0.007)**<br>Time to D/C: **HR 1.50 (p<0.001)** |
| | | | Alv. 12 mg | 146 | Time to GI-3: HR 1.28 (p=0.059)<br>Time to GI-2: HR 1.31 (p=0.057)<br>Time to D/C: HR 1.18 (p=0.17) |
| | | | Placebo | 153 | |
| Herzog *et al.*[12] | 2006 | 519 TAH | Alv. 12 mg | 413 | Time to GI-3: HR 1.16 (p=0.176)<br>Time to GI-2: **HR 2.23 (p<0.001)**<br>Time to D/C: HR 1.13 (p=0.268) |
| | | | Placebo | 106 | |
| Viscusi *et al.*[15] | 2006 | 437 LBR/SBR<br>200 TAH | Alv. 6 mg | 220 | Time to GI-3: **HR 1.24 (p=0.037)**[2]<br>Time to GI-2: **HR 1.40 (p=0.005)**[2]<br>Time to D/C: **HR 1.36 (p=0.002)**[2] |
| | | | Alv. 12 mg | 221 | Time to GI-3: **HR 1.26 (p=0.028)**[2]<br>Time to GI-2: **HR 1.36 (p=0.012)**[2]<br>Time to D/C: **HR 1.30 (p=0.010)**[2] |
| | | | Placebo | 224 | |
| Buchler *et al.*[11] | 2008 | 705 LBR/SBR | Alv. 6 mg | 237 | Time to GI-3: 84.2 hrs (p=0.042)<br>Time to GI-2: **95.2 hrs (p<0.001)**<br>Time to D/C: HR 1.08 (p=0.13) |
| | | | Alv. 12 mg | 239 | Time to GI-3: 87.8 hrs (p=0.20)<br>Time to GI-2: **98.8 hrs (p=0.008)**<br>Time to D/C: HR 1.07 (p=0.49) |
| | | | Placebo | 229 | Time to GI-3: 92.6 hrs<br>Time to GI-2: 109.5 hrs |
| Ludwig *et al.*[14] | 2008 | 654 LBR/SBR | Alv. 12 mg | 329 | Time to GI-3: **HR 1.5 (p<0.001)**<br>Time to GI-2: **HR 1.5 (p<0.001)**<br>Time to D/C: **HR 1.4 (p<0.001)** |
| | | | Placebo | 325 | |
| Lee *et al.*[13] | 2014 | 280 RC | Alv. 12 mg | 143 | Time to GI-2: **HR 1.8 (p<0.0001)**<br>Time to D/C: **HR 1.7 (p=0.0002)** |
| | | | Placebo | 137 | |

LBR, large bowel resection (colectomy); SBR, small bowel resection; TAH, total abdominal hysterectomy; Alv., alvimopan; GI-3, solid food + BM/flatus; GI-2, solid food + BM; RR, relative risk; BM, bowel movement; D/C, discharge; HR, hazard ratio; RC, radical cystectomy

[1]Versus Placebo
[2]adjusted for sex and surgical duration

A meta-analysis incorporating the studies listed above has been completed.[10] The pooled

analysis revealed a significant reduction in time to GI-2 bowel function (6 mg, HR = 1.5, p<0.00001; 12 mg, HR = 1.59, p<0.00001), BM (6 mg, HR = 1.54, p<0.00001; 12 mg, HR 1.74, p=0.0002), and time to discharge order written (6 mg, HR = 1.37, p< 0.00001; 12 mg, HR = 1.34, p<0.00001) versus placebo.

From a pharmacokinetic standpoint, alvimopan is metabolized by the intestinal flora and is primarily excreted in the bile, secondarily in the feces, and 35% in the urine. Its half-life is 10-17 hours, although this is longer in patients with mild-moderate hepatic impairment (Child's Pugh Class A and B) and severe renal impairment. P450 drug-interactions…

Alvimopan is FDA-approved for short-term, in-hospital use in patients at risk for postoperative ileus, particularly those following bowel resection with primary anastomosis. However, due to potential increased cardiovascular risks with long-term use, distribution of the drug is restricted to short-term use (maximum 15 doses) under a Risk Evaluation and Mitigation Strategy (REMS), which includes only institutions enrolled in the ENTEREG Access Support and Education (E.A.S.E.) Program, of which UCSD is one. The current FDA-approved dose is 12 mg orally 30 minutes to 5 hours prior to surgery, followed by 12 mg orally twice daily beginning the day after surgery for up to seven days or until hospital discharge, with a maximum of 15 doses.[17]

### 1.3 Rationale

In an analysis of 50 consecutive CRS/HIPEC procedures performed at UCSD the median time to return of bowel function, as defined in prior phase III clinical trials with alvimopan (later of time to first bowel movement or tolerance of solid diet, GI-2), was 9 days. No studies have been published investigating the use of alvimopan after CRS/HIPEC. The current proposal is being performed to investigate the efficacy of alvimopan on the time to return of bowel function in patients undergoing CRS/HIPEC.

## 2.0 STUDY OBJECTIVES

### 2.1 Primary Objective

To determine the efficacy of alvimopan to reduce postoperative ileus in patients undergoing CRS/HIPEC, as measured by the composite of time to recovery of upper and lower GI function, as defined by the later of the following two events (GI-2):

- Time that the patient first tolerates solid food
- Time that the patient first passes a bowel movement

### 2.2 Secondary Objectives

1. To determine the proportion of prolonged ileus (> 7 days) in each group
2. To determine the time to return of bowel function components in each group: time to first flatus, time to first bowel movement, time to tolerance of solid food
3. To determine the time to hospital discharge order written in each group
4. To measure the adverse event rate in each group
5. To perform subgroup analyses on each group: 0 vs. 1 or greater anastomoses, 0 vs. 1 or greater visceral resection, high vs. low amount of postoperative narcotic use (above or below the median total postoperative morphine equivalent dose of narcotics), epidural vs. no epidural

## 2.3 Endpoints

**Primary Endpoint:**

The time to return of upper and lower GI function (GI-2) will be measured as follows:

- Time measured in hours from the time leaving the operating room to the later of the following two events:
    i. Time that the patient first tolerates solid food
    ii. Time that the patient first passes a bowel movement
- If upper and lower GI function have not occurred by the time of discharge, the patient will be censored.

**Secondary Endpoints:**

1. Prolonged ileus will be measured by the proportion of patients who do not pass flatus or bowel movement greater than 7 days from the time of surgery
2. The time to return of bowel function components will be measured in hours from the time leaving the operating room until:
    - The time to first flatus
    - The time to first bowel movement
    - The time to tolerance of solid food
3. The time to hospital discharge order written will be measured in hours from the time leaving the operating room
4. Adverse events will be measured using CTCAEv3 criteria.
5. Primary and secondary endpoints will be measured in each subgroup

# 3.0 PATIENT ELIGIBILITY

## 3.1 Inclusion Criteria

Subjects must meet all of the inclusion criteria to participate in this study.

1. Ability to understand and the willingness to sign a written informed consent.

2. Scheduled to undergo open (non-minimally invasive) CRS/HIPEC.

3. Scheduled to receive postoperative pain management with intravenous opioids.

4. Age $\geq$ 18 years.

5. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 2.

6. Women of child-bearing potential with negative pregnancy test prior to initiating study drug dosing.

## 3.2 Exclusion Criteria

Subjects meeting any of the exclusion criteria at baseline will be excluded from study participation.

1. Greater than 7 days of consecutive opioid use immediately prior to scheduled surgery.

2. Child-Pugh Class C hepatic impairment.

3. End-stage renal disease (GFR < 15 mL/min/1.73 $m^2$ and/or on peritoneal dialysis or hemodialysis).

4. Complete mechanical bowel obstruction.

5. Contraindication or inability to tolerate oral medication postoperatively.

6. Presence of gastrointestinal ostomy after CRS/HIPEC.

7. Pancreatic or gastric anastomosis performed during CRS/HIPEC.

8. History of allergic reactions or hypersensitivity attributed to compounds of similar chemical or biologic composition as alvimopan at the treating investigators discretion.

9. Severe or uncontrolled medical disorder that would, in the investigator's opinion, impair ability to receive study treatment (i.e. uncontrolled diabetes, chronic renal disease, chronic pulmonary disease or active, uncontrolled infection, psychiatric illness/social situations that would limit compliance with study requirements).

10. History of myocardial infarction in the 12 months prior to scheduled surgery.

11. Pregnant or nursing.

## 4.0 TREATMENT PLAN

### 4.1 Treatment Dosage and Administration

Participants will receive alvimopan (or placebo) preoperatively, then every day after surgery until hospital discharge or for a maximum of 7 days.

Twelve (12) mg of alvimopan (or placebo) will be given by mouth in the preoperative holding area 30 minutes to 5 hours prior to surgery. The treatment with continue at a dose of 12 mg BID by mouth starting on postoperative day (POD) 1 for the earlier of seven days or hospital discharge, as defined by GI-2 (later of time of tolerance of solid diet or bowel movement), for a maximum of 15 total doses. In patients with a gastrostomy tube in place, this will be clamped for 1 hour after administration of the study drug per standard of care for oral medication administration in a patient with a gastrostomy tube. Documentation of gastrostomy tube clamping after study drug administration will be made in the medical record by nurses according to the standard of care nursing policies and usual practices of each nursing unit. The study drug (alvimopan or placebo) will be administered in the hospital by the patient's nurse.

| Agent | Dose | Route | Schedule |
|---|---|---|---|
| Alvimopan | 12 mg | PO | 30 minutes – 5 hours prior to surgery, then twice daily (BID) starting POD 1 for a maximum of 7 days or until hospital discharge |
| Placebo | NA | PO | 30 minutes – 5 hours prior to surgery, then twice daily (BID) starting POD 1 for a maximum of 7 days or until hospital discharge |

### 4.2 Permitted concomitant therapy

Medications used to treat typical postoperative symptoms are permitted, as clinically indicated. This includes, but is not limited to, analgesics (local, regional and systemic; narcotics, non-steroidals, and local anesthetics), antiemetics, and anti-pruritics. These are all given per standard of care, and at the discretion of the treating clinicians.

### 4.3 Prohibited concomitant therapy

Participants with greater than seven days of consecutive opioid use immediately prior to the date of surgery (CRS/HIPEC) are ineligible for the study. Any other use of preoperative opioids may be used with caution, at the investigator's discretion.

### 4.4 Other Modalities or Procedures

After CRS/HIPEC, participants will undergo a standardized postoperative care pathway, which is the standard of care at our institution. This includes use of epidural analgesia, early mobilization and ambulation on POD 1-2, liquid diet on POD 1-3, early removal of the foley catheter, and clamping trials of the gastric tube (if present) once bowel function returns.

### 4.5 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03. Dose adjustments are not applicable in this study and will not be made. Participants who have emesis within one hour after taking the study medication or have visible study medication within the gastric tube effluent or who otherwise miss a dose for any other reason, will not be re-dosed, and they will resume standard dosing at the next scheduled dose. Participants or providers may decide to cease the study medication before all doses have been administered per the criteria listed in Section 4.6.

### 4.6 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for a maximum of **seven days** or less if one of the following occurs:

- Participant is discharged home prior to seven days after surgery

- Inter-current illness that prevents further administration of treatment (i.e. participant is unable to tolerate oral medication with gastric tube clamped or the participant is intubated and cannot take oral medication). Participants may resume study drug administration once it can be tolerated without "make-up" doses given (i.e. no study drug will be given beyond postoperative day seven). If more than 50% of the doses are missed, then the participant will be withdrawn from the study (see Section 5.5).
- Unacceptable adverse event(s)
- Participant decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

### 4.7 Duration of Follow Up

Participants will be monitored daily during their postoperative stay by nurses and physicians, per standard of care after CRS/HIPEC. Typical length of stay after this procedure is 10 days. After discharge, participants will be followed (by postoperative visit or telephone call) for 30 days from the date of surgery for adverse events.

## 5.0 STUDY PROCEDURES

### 5.1 Schedule of Events

| | Screening (POD -30 to -1) | Preoperative Day (POD -3 to -1) | Postoperative Admission (POD 1 – Date of Discharge) | Postoperative Clinic Visit ± 5 days | Follow–up visit (POD ≥ 30)[1] |
|---|---|---|---|---|---|
| **Assessment** | | | | | |
| Informed consent | X | | | | |
| Medical history | X | | | | |
| Physical exam, including vitals[2] | X | | | | |
| Demographic | X | | | | |
| Eligibility Criteria | X | | | | |
| ECOG | X | | | | |
| Adverse events[3] | | | X | X | X |
| Concomitant medications[4] | X | X | | | |
| Confirmation that CRS/HIPEC performed and eligibility criteria still met[5] | | | X | | |
| Assessment of return of bowel function[6] | | | X | | |
| Alvimopan administration[7] | | X | X | | |
| Urine Pregnancy Test[8] | X | | | | |

[1]By standard of care clinic visit, or telephone call if no clinic visit at this time (≥ 30 days

after surgery)
[2] Physical exam and vital signs: consist of temperature, heart rate, respiration and blood pressure.
[3]Adverse events: to be collected once patient signs consent form. See Section 7 for more information.
[4]Concomitant medications: to be collected for any subject being followed for a Serious Adverse Event (SAE) occurring up to 30 days after last dose of study drug until resolution of the SAE. (see Section 7).
[5]Confirmed on POD 1, prior to administration of first postoperative dose of study medication.
[6]Includes recording the date and hour of the time of first flatus, bowel movement, and tolerance of solid food (per participant diary); as well as the date/hour of leaving the operating room
[7]Alvimopan administration: see section 8.1 for instructions on administration.
[8]Pregnancy test: A serum or urine pregnancy test is required for all females of childbearing potential.

## 5.2 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

The screening procedures include:

### 5.2.1 Informed Consent

### 5.2.2 Medical history

Complete medical, surgical and oncology history as well as history of infections will be obtained at screening. Any changes from Screening (e.g. worsening severity or abnormal findings) are considered to be adverse events (AEs).

### 5.2.3 Demographics

Demographic information to be collected at screening will include date of birth, gender, race, and ethnicity.

### 5.2.4 Review subject eligibility criteria

Review of eligibility criteria as described in Section 3 to ensure subject qualification for study entry.

### 5.2.5 Review previous and concomitant medications

All prior medication taken by the subject within 4 weeks before starting the study is to be recorded. Concomitant medications taken by the subject during the study are to be recorded up until 30-days after last study dose. If a reportable adverse event (see Section 7) occurs within 30-days after last study dose, recording of concomitant medications should continue until resolution of the adverse event.

### 5.2.6 Physical exam including vital signs, height and weight

Physical exam will include collection of vital signs (temperature, pulse, respirations, blood pressure), height, weight.

### 5.2.7 ECOG performance status

ECOG performance status will be evaluated prior to study entry.

#### 5.2.8 Adverse event assessment

Baseline assessment of subject status for determining adverse events. See Section 7 for Adverse Event monitoring and reporting.

#### 5.2.9 Pregnancy test (for females of child bearing potential)

See section 3.1 for definition.

### 5.3 Procedures During Treatment

Treatment will be administered in the hospital in the postoperative recovery period. There are no additional procedures or visits performed during the treatment period. However, there are some additional data collected during this period, as follows:

#### 5.3.1 Date and Time of Completion of Operation

- To be determined from the electronic medical record (Time is the "Out of Room" time recorded in the chart).

#### 5.3.2 Total Opioid Consumption

- To be measured in morphine equivalents, calculated after discharge.

#### 5.3.3 Assessment of Bowel Function

- To be recorded in patient postoperative bowel function diary (Appendix B)
- An audit of at least 10% of all diaries will be undertaken to compare the patient recorded date of first recorded bowel movement with that from the electronic medical record.

### 5.4 Follow-up Procedures

Patients will be followed for at least 30 days after surgery. Follow-up will consist of postoperative visit or telephone call (in situations where there is no postoperative visit $\geq$ 30 days from surgery).

### 5.5 Removal of Subjects from Study Treatment and Study

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

**5.5.1** Patient completed study treatment;

**5.5.2** Patient voluntarily withdraws from treatment (follow-up permitted);

**5.5.3** Patient withdraws consent (termination of treatment and follow-up);

**5.5.4** Patient is unable to comply with protocol requirements (i.e. the patient is unable to tolerate or misses more than 50% of the study drug doses);

**5.5.5** Patient experiences toxicity that makes continuation in the protocol unsafe;

**5.5.6** Treating physician judges continuation on the study would not be in the patient's best interest;

**5.5.7** Patient becomes pregnant (pregnancy to be reported along same timelines as a

serious adverse event);

**5.5.8** Lost to follow-up.

If a research subject cannot be located to document adverse events after a period of at 60 days after surgery, the subject may be considered “lost to follow-up.” All attempts to contact the subject during this period will be documented.

## 6.0 Measurement of Effect

### 6.1 Effect on Return of Bowel Function

Time to first flatus, time to first BM, time to tolerance of solid diet will all be measured as endpoints for return of bowel function.

Time to flatus is a more subjective and unreliable endpoint for return of lower bowel function versus time to first BM. More recent alvimopan studies have used GI-2 rather than GI-3 endpoints, which consider BM rather than flatus as evidence of lower bowel function. Thus, the current study will use the GI-2 definition, which is the time, in hours, from leaving the operating room to the later of the time of tolerating solid food and having a BM. Tolerance of solid food is defined as the time of solid food ingestion without significant nausea or vomiting for 4 hours. The precise date and hour of first flatus, first BM, and first tolerance of solid diet will be recorded in a participant diary (Appendix B). These dates and times will be corroborated and audited by reviewing the inpatient medical record (in $\geq$ 10% of participants).

#### 6.1.1 Prolonged Ileus

Participants without flatus or BM for more than seven days after surgery, are considered to have a prolonged ileus.

#### 6.1.2 Time to Hospital Discharge

The time, in hours, from leaving the operating room to when the discharge order is signed.

### 6.2 Safety/tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 4.03 (http://ctep.cancer.gov/reporting/ctc.html) for reporting of adverse events.

## 7.0 ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment 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), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

### 7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical

trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

As far as possible, each adverse event should be evaluated to determine:

- duration (start and end dates)
- severity (grade)
- seriousness
- relationship to study agent
- action taken (i.e., none, study agent modification, medical intervention)
- outcome (i.e., resolved without sequelae, resolved with sequelae, ongoing)

All patients experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

### 7.2 Severity

All adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v4.03 is available at http://ctep.cancer.gov/reporting/ctc.html

If no CTCAE grading is available, the severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
Moderate (grade 2): the event causes discomfort that affects normal daily activities.
Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
Life-threatening (grade 4): the patient was at risk of death at the time of the event.
Fatal (grade 5): the event caused death.

### 7.3 Seriousness

A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

1. Results in death.
   If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
2. Is life-threatening.
   (the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).

3. Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
4. Results in persistent or significant disability or incapacity.
5. Is a congenital anomaly/birth defect
6. Is an important medical event
   Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
   For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

### 7.4 Relationship

Attribution categories for adverse events in relationship to protocol therapy are as follows:

Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.
Possible – The AE *may be related* to the study treatment.
Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment.

### 7.5 Prior experience

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is <u>not</u> listed in the current known adverse events listed in the agent clinical experience section of this protocol or the current Product Label.

### 7.6 Reporting Requirements for Adverse Events

#### 7.6.1 Expedited Reporting

- The **Principal Investigator** must be notified <u>within 24 hours of learning of any serious adverse events</u>, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.
- The **UCSD Human Research Protections Program (HRPP)** must be notified <u>within 10 business days</u> of "any unanticipated problems involving risk to subjects or others" (UPR).

  The following events meet the definition of UPR:

  1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
  2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
  3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
  4. Any new information (e.g., publication, safety monitoring report,

updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.

5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

### 7.6.2 Routine Reporting Requirements

- The UCSD HRPP will be notified of any adverse events that are not unanticipated problems involving risk to subjects or others (non-UPRs) at the time of the annual Continuing Review.

## 8.0 AGENT INFORMATION

### 8.1 Agent Alvimopan

Please refer to Prescribing Information for more comprehensive information.

**Other names for the drug:** Entereg®

**Mechanism of action (or Product description):**

Alvimopan is a peripherally acting mu-opioid receptor antagonist, blocking the peripheral effects of opioids on gastrointestinal motility and secretion but not the central analgesic effects of mu-opioid agonists.

**Availability:**

Alvimopan (and placebo) will be provided by the sponsor free of charge.

**How supplied:**

Alvimopan will be supplied as 12 mg oral capsules by the sponsor. Unmatched placebo capsules will also be supplied, and alvimopan and placebo will be over-encapsulated by UCSD pharmacy to maintain double-blinding.

**Storage and stability:**

Alvimopan capsules may be stored at controlled room temperature (77˚ F) with excursions between 59˚ and 86˚ F.

**Preparation:**

Alvimopan and placebo will be over-encapsulated by USCD pharmacy prior to administration.

**Route of administration for this study:**

Study drug (alvimopan or placebo) will be administered orally. If a gastric or nasogastric tube is present, it will be clamped for one hour after oral administration of the study drug.

**Side effects:**

The most common adverse events of alvimopan include the following:

- Hypokalemia (10%)
- Dyspepsia (2-7%)
- Anemia (5%)
- Urinary retention (3%)
- Back pain (3%)
- Myocardial infarction (rate unknown, higher rate than placebo in study with 12 month use of alvimopan)

### 8.1.1 Return and Retention of Study Drug

Remaining drug is to be destroyed, according to Moores Cancer Center Investigational Drug Services destruction policy.

### 8.1.2 Subject Compliance

Subject compliance of study drug will be maintained by directly-observed administration in the hospital.

## 9.0 STATISTICAL CONSIDERATIONS

### 9.1 Study Design/Study Endpoints

The proposed study is a double blind prospective, randomized controlled phase 2 trial.

Subjects will be assigned 1:1 to either placebo or alvimopan groups using a permuted block randomization of block size 4. The block and package in the R statistics software will be used to generate group assignments. The randomization file will be given to the investigational Pharmacy which will carry out the randomization. Patients who do not undergo CRS/HIPEC during surgery are considered screen failures after randomization. Their randomization IDs will not be discarded and will be passed to the next available subjects to keep the 1:1 ratio.

### 9.2 Sample Size and Accrual

Our sample size calculation is based on detecting a difference in distributions of times until GI-2 between groups. Assuming a similar hazard ratio between the Alvimopan 12 mg and placebo groups as Xu et. al. (HR = 1.59, which approximately corresponds to an improvement in the median primary endpoint (GI-2) from 9 days to 5.7 days), a log-rank test for a difference in distributions of times until GI-2 is met will have 80% power at the one sided 0.05 significance level with a total sample size of n = 122. (Note that this does not adjust for a reduction in power due to the interim analysis.) Accounting for a 5% drop-out rate, the total enrolled sample size is 128 participants.

Approximately 60-70 CRS/HIPEC procedures are performed at UCSD annually. Accrual of 128 participants could occur over 2-3 years. Annual target accrual will be 40 participants per year.

| **Accrual Targets** | | | |
|---|---|---|---|
| **Ethnic Category** | **Sex/Gender** | | |
| | **Females** | **Males** | **Total** |
| Hispanic or Latino | 8 | 5 | 13 |
| Not Hispanic or Latino | 63 | 52 | 115 |
| **Ethnic Category: Total of all subjects** | 71 | 57 | 128 |
| **Racial Category** | | | |
| American Indian or Alaskan Native | 0 | 0 | 0 |
| Asian | 8 | 5 | 13 |
| Black or African American | 2 | 1 | 3 |
| Native Hawaiian or other Pacific Islander | 1 | 1 | 2 |
| White | 60 | 50 | 110 |
| **Racial Category: Total of all subjects** | 71 | 57 | 128 |

### 9.3 Protocol Deviations, Data Blind Review, and Unblinding

Classification of deviations from the protocol as minor or major, and decisions regarding exclusion of patients and/or patient data from the statistical analyses, will be decided on a case-by-case basis without knowledge of the treatment assigned and before the database lock (Data Blind Review). After database lock, the responsible statistician will request the treatment codes, the study will be unblinded, and the statistical analysis will be conducted.

### 9.4 Analysis Populations

Analysis populations are defined as follows:

- The Safety population will include all randomized patients who took at least one dose of the study medication, including screen failures after randomization and subjects withdrawn from the study.
- The modified Intent-to-Treat (mITT) population will include all randomized patients who took at least one dose of the study medication and who have at least one efficacy evaluation following baseline.
- The Per Protocol (PP) population will include all mITT patients who:
  - took assigned medication during the treatment period (who received at least 50% of the study drug), and
  - did not have any major protocol deviations.

The primary population for all efficacy analyses is the mITT population, without imputation for missing values. Sensitivity analyses will also be performed using the PP populations

for efficacy endpoints, and using the mITT population with multiple imputation. The safety population will be used for analyses of safety endpoints.

### 9.5 Analyses of the primary endpoint

For our primary endpoint, we will use a log-rank test at 5% level to compare the distributions of times until recovery (GI-2) between groups.

### 9.6 Analyses of secondary endpoints

Log-rank test will also be used to compare the time to return of bowel function outcome. A Cox proportional hazards model will also be considered for this endpoint, controlling for potential confounders such as age and gender. The proportion of patients with prolonged ileus will be compared between groups with a Pearson's chi square test . A logistic regression model will be used to assess the association between prolonged ileus and treatment, controlling for potential confounders. We will compare the time to discharge between groups with a two-sample t-test, and consider a linear regression to control for potential confounders, including opioid use (i.e. total morphine equivalents) +/- epidural placement, bowel resection, and other complications.
.

### 9.7 Exploratory analyses

For any prespecified subgroup analyses, we will include a binary covariate indicating subgroup membership in each of the regression frameworks described. We will also fit models with interactions between each subgroup and treatment group. Descriptive statistics (mean, standard deviation, counts, and percentages) and plots will be produced for all demographic, safety, and outcome variables. All analyses will be conducted using the latest version of R (R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org/).

### 9.8 Interim analysis

When the 64$^{th}$ subject has reached the primary endpoint (or been censored because of loss to follow-up), a futility analysis will be performed.

The futility analysis will use a stochastic curtailment approach (Crowley and Anhkerst, Clinical Trials in Oncology, 2$^{nd}$ ed p 233), as computed in PASS 14.0.6. If at the interim analysis, the conditional power (i.e. the probability that the study will go on to reject the null hypothesis, given the observed data at the interim analysis) is below 20%, the study will stop. This futility analysis will be carried out by the statisticians at the MCC Biostatistics Shared Resource, using a one-sided logrank test at the 5% significance level.

### 9.9 Safety Analysis

Safety will be assessed by summarizing and analyzing AEs during the intervention period. Adverse events will be coded according to established Medical Dictionary for Regulatory Activities (MedDRA) terms and summarized by MedDRA System Organ Class and Preferred Term. Treatment-emergent adverse events (TEAE) will be defined as events that first occurred or worsened on or after randomization.

An overview of AEs, including the number and percentage of participants who died, suffered SAEs, discontinued due to AEs, and who suffered TEAEs, will be provided. A comparison between intervention arms will be performed. Summaries of AEs within system organ class will be provided for: (1) pre-existing conditions, (2) TEAEs, and (3) SAEs. Discontinuations due to AEs will also be listed.

## 10.0 STUDY MANAGEMENT

### 10.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed according to UCSD conflict of interest policy.

### 10.2 Institutional Review Board (IRB) Approval and Consent

The IRB should approve the consent form and protocol prior to any study-related activities. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

### 10.3 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), subjects who have provided written informed consent must also sign a subject authorization to release medical information to the study Sponsor and allow a regulatory

authority, or Institutional Review Board access to subject's medical information relevant to the study.

### 10.4 Data and Safety Monitoring/Auditing

Data and Safety reporting will be supported by the study statisticians according to the attached monitoring plan (Appendix C and D). A series of comprehensive safety and data monitoring reports will be generated every six months for review by the study team in addition to the annual DSMB report described below.

In addition to adverse event monitoring and clinical oversight by the principal investigator and co-investigators, quality assurance of the study will be performed by the clinical trials office internal monitor. Monitoring intervals will be dependent upon the number of patients enrolled and the complexity of the study.

This study will also use the UCSD Moores Cancer Center Data Safety and Monitoring Board (DSMB) to provide oversight in the event that this treatment approach leads to unforeseen toxicities. Data from this study will be reported annually and will include:

1) the protocol title, IRB protocol number, and the activation date of the study.
2) the number of patients enrolled to date
3) the date of first and most recent patient enrollment
4) a summary of all adverse events regardless of grade and attribution
5) a response evaluation for evaluable patients when available
6) a summary of any recent literature that may affect the ethics of the study.

### 10.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

#### **10.5.1** Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, a IRB modification form must be completed within five (5) business days of making the change.

#### **10.5.2** Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.

- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

**Protocol Deviations:** Personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

**Protocol Violations:** Study personnel should report violations within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

### 10.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

### 10.7 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

### 10.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all

the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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## 12.0 APPENDICES

### Appendix A. ECOG Performance Status

| **ECOG Performance Status Scale** | |
|---|---|
| Grade | Descriptions |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). |
| 2 | In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair |
| 5 | Dead. |

## Appendix B. Postoperative Bowel Function Diary

**DIARY INSTRUCTIONS:**

- Note the date and time of day you had each event.
- In the comment section, please include any any uncertainties regarding date or time.
- If you have any questions, please contact your nurse to contact the study staff listed in your informed consent form.

| EVENT | DATE (MO-DD-YYYY) | TIME OF DAY | COMMENTS |
|---|---|---|---|
| *Example.* | *03-15-2017* | *9:00 AM* | |
| First Postoperative Flatus | | | |
| First Postoperative Bowel Movement | | | |
| First Solid Food (without significant nausea or vomiting within 4 hours) | | | |

**Appendix C. Division of Biostatistics and Bioinformatics Report**


Division of Biostatistics & Bioinformatics

Report Type
Trial: The ILEUS Study: A Phase 2 Randomized Controlled Trial **I**nvestigating A**L**vimopan for **E**nhanced Gastrointestinal Recovery after Cytored**U**ctive **S**urgery and Hyperthermic Intraperitoneal Chemotherapy (UCSD IRB 171044)
Protocol Version V2.0 dated 06/10/2019
CONFIDENTIAL DOCUMENT

Date
Principal Investigator: Joel M. Baumgartner, MD, MAS
Statistician: Karen Messer, PhD and Ruifeng Chen, MS

**Contents:**

## 1. Executive Summary

Report Overview
This report reviews enrollment and safety data available in the study VELOS database as of xxxx. Summary tables are provided in sections 6-15. Additional tables and figures referenced in the report are provided in the Appendices.

Study Site Status
This is a single site trial at UCSD. It was activated 02/28/2018.
Enrollment Status
XXX subjects have been screened for this study.
XXX subjects have been enrolled.
Early Discontinuation/Off Treatment Status
XXX treated subjects have been discontinued (withdrawn) from the study. XXX treated subjects have completed treatment. Details are specified in section Early Discontinuation/Off Treatment.
Stopping/Halting Rules
At accrual of 64 patients, a futility analysis will be performed. The stopping rule is stated in section protocol synopsis.

Safety Summary
XXXX adverse events have occurred in XXX subjects. XXX serious adverse events have occurred in XXX subjects.
Of the XX adverse events: XX were mild (grade 1), XX were moderate (grade 2) and XX were severe (Grade 3+).

Deaths

Quality Management
Quality management reviews are performed annually and were last completed on xxxx.

## 2. Protocol Synopsis

Planned Accrual: N= 128; approximately 60-70 CRS/HIPEC procedures are performed annually at UCSD.
Study Design: The proposed study is a prospective, randomized controlled phase 2 trial. Subjects will be assigned to either placebo or alvimopan groups according to a block randomization.
Primary Objective: To determine the efficacy of alvimopan to reduce postoperative ileus in patients undergoing CRS/HIPEC, as measured by the composite of time to recovery of upper and lower GI function.
Treatment Description: Alvimopan (12 mg) or Placebo 30 minutes – 5 hours prior to surgery, then twice daily (BID) starting POD 1 for a maximum of 7 days or until hospital discharge.
Primary Endpoint(s): Time to either 1$^{st}$ solid food or 1$^{st}$ bowel movement postoperatively, whichever is later.
Study Stopping Rules:

At accrual of 64 patients, a futility analysis will be performed. If the conditional power (as computed for log-rank tests) is less than 10% at this halfway point, we will suspend the study. The conditional power threshold of 10% was chosen based on boundaries set in Jennison and Turnbull, as well as with consideration to the probability of stopping early based on a series of effect sizes. If the null hypothesis is true (i.e. a hazard ratio of 1), the study will stop early at the interim to fail to reject the null hypothesis 69.49% of the time. Under the alternative hypothesis, the study will stop early 10.35% of the time while maintaining a type II error rate of 20%.

### 3. Report Overview

The purpose of this report is to review cumulative enrollment and safety data for the subjects enrolled in the ILEUS study. This report reflects data from the study database as of xxx. Within the body of the report are summary tables of enrollment, demographic characteristics, and adverse events. Readers of this report are asked to maintain the confidentiality of the information provided in this report.

### 4. Quality Management

4.1 This study was monitored by the UCSD Moores Cancer Center CTO xxxxx
Protocol deviations/violations:

4.2 Protocol deviations

### 5. **Methods** – Data Set

This report is based on all data downloaded on xxxx from the VELOS portal (https://velos.ucsd.edu).

### 6. Participant Status

This section summarizes the participant status and enrollment by study month. Enrollment is defined as received at least one treatment.

| Study Month | Year & Month | N Subjects Enrolled |
|---|---|---|
| 1 | | |
| 2 | | |
| 3 | | |

XX Subjects have been consented. This trial is accruing at a rate of X subjects per month.

## 7. Subject Consent and Treatment Dates

Consent and Treatment Dates

| Subject ID | Consent Date | Treatment Start Date |
|---|---|---|
| | | |
| | | |

## 8. Screen Failures

This study having two time points where subjects potentiality may fail to initiate (screen fails) or continue treatment (surgical fails). Subjects with a surgical failure will be followed since they are in both the safety and IIT populations.

### 8.1 Screen Failures

| Subject ID | Consent Date | Screen Failure Date | Reason for Screen Failure |
|---|---|---|---|
| | | | |
| | | | |

### 8.2 Surgical Failures

Surgical Failures are still in the intent to treat and safety populations since they were randomized and received at least one dose of medication.

| Subject ID | Consent Date | Surgical Failure Date | Reason for Surgical Failure |
|---|---|---|---|
| | | | |
| | | | |

## 9. Early Discontinuation/Off Treatment

### 9.1 Completed Treatment

| Subject ID | Off Treatment Date | Off Treatment Reason |
|---|---|---|
| | | |
| | | |

### 9.2 Early Discontinuation

| Subject ID | Off Treatment Date | Off Treatment Reason |
|---|---|---|
| | | |
| | | |

## 10. Demographics

This section includes the key demographics for the treated subjects, including surgical failures.
Categorical measures:
- Gender
- Race
- Ethnicity

Continuous measures:
- Age (years)

Continuous variables are summarized with N, mean, standard deviation, median.
Categorical variables are summarized using frequency tables and percentages

Gender, Race, Ethnicity

| | Frequency | Proportion |
|---|---|---|
| **Gender** | | |
| Female | | |
| Male | | |
| **Race** | | |
| White | | |
| Black, African- American | | |
| Asian | | |
| Native America | | |
| Unknown or Not Reported | | |
| **Ethnicity** | | |
| Non-Hispanic | | |
| Hispanic | | |

Continuous measures: Continuous variables are summarized with N, mean, standard deviation, median.

Age (years)

| | N | Mean | SD | Median |
|---|---|---|---|---|
| Age | | | | |

Demographic Information for All Consented Subjects

| Subject ID | Age | Gender | Ethnicity | Race |
|---|---|---|---|---|
| | | | | |
| | | | | |

### 11. Stopping Rules

At accrual of 64 patients, a futility analysis will be performed.

## 12. Deaths

| Subject ID | Date of Death | Reason for Death | On Treatment? |
|---|---|---|---|
| | | | |
| | | | |

## 13. Post-Treatment Adverse Events

### 13.1 Adverse Events Summary

| **Severity** | **N Adverse Events** |
|---|---|
| Mild (grade 1) | |
| Moderate (grade 2) | |
| Severe (grade 3) | |
| Life-threatening (grade 4) | |

| Severity | N Adverse Events |
|---|---|
| Fatal (grade 5) | |
| Total | |

**13.2 AE by Grade**

**13.3 AE by relationship**

Note: A list of all adverse events is in Appendix A. These are all AEs; SAEs are also reported in next section.

**13.4 Serious Adverse Events**

Serious Adverse Events

| Patient Study ID | Serious Adverse Event Name | Severity/Grade | Start Date | Stop Date | Attribution |
|---|---|---|---|---|---|
| | | | | | |

**14. Software**

Statistical software R (version 3.1.3) is used http://www.r-project.org.

**Appendices**

1 Adverse Events
2 Treatment Assessment
3 Response Assessment
4 Issues with data

BSR data checks include verification of doses, number of appropriate drug and response cycles based on treatment start date, redundant and/or missing data, and other data elements as needed based on study protocol.

## Appendix D. UCSD Moores Cancer Center Data Monitoring Plan

### Introduction

This data reporting plan outlines the routine monitoring reports that are to be generated by the study statistician or the study data manager, based on the data that have already been entered into the electronic data capture data base (VELOS).

The purposes of these reports are to monitor the progress of trials and the safety of participants, to assure data accuracy, data completeness and protocol compliance.

All the study personnel listed on the VELOS Clinical study information and personnel contact information page will receive these reports. (see Appendix A).

For an outline of the report see Appendix B.

**I. Table of Contents**

**II. Executive Summary** –

The Executive Summary will be an overarching description of the data analyzed.

**III. Protocol Synopsis** -

The Protocol will be an overarching description of the study.

(note: Study coordinator is to obtain this information from the research plan and the first page of IRB submission for this report. It may be also available on the VELOS study information page.)

**IV. Study Data Report** –

The Study Report will include the following Tables:

- Table 1: Overall Enrollment
- Table 2: Monthly Enrollment
- Table 3: Consent and Treatment Dates
- Table 4: Screen Failures
- Table 5: Early Discontinuations/Off Treatment
- Table 6: Gender, Race, Ethnicity
- Table 7: Age (years)
- Table 8: Subjects Demographics
- Table 9: Deaths
- Table 10: Adverse Events Summary
- Table 11: Serious Adverse Events
- Appendix: Listing of All Adverse Events

The Principal Investigator will receive additional tables in regards to study treatment, response assessment and data completeness as outlined in sections 5-8 below. Additional tables related to stopping rules will be added in the interim futility report. These may include unblinded randomization tables, as well as, response assessments.

Only, the Principal Investigator will received reports of outcome data and appendices that include treatment assessment, response assessment, baseline characteristics and data issues, as determined by study statistician.

Below has details for each of the tables/reports listed above. The frequencies of running the reports was determined by the study protocol. Note: This is a double blind study. All reports, except futility and final, will contain aggregated data.

1. Overall Enrollment - Table 1

- Purpose

To monitor enrollment; to ensure that accrual goals are met in a timely manner; to notify the team when accrual goal is nearing completion

- Components

Accrual (number of patients and percentages) by month.

- Frequency: first two week data analysis, futility, semi-annually, annually

2. Study Status Report – Tables 2-5

- Purpose

To provide a summary of the status of study subjects.

- Components

1) Total number of accrual as of date; number of subjects who are on/off study; number of subjects who are still on study treatment (s); number of subjects who are still on study but off study treatment (s).

2) Listings of off study/off treatment with subject ID, date, week and reason.

- Frequency: first two week data analysis, futility, semi-annually, annually

3. Baseline Characteristics Report –Tables 6-8 and Appendix

- Purpose

To provide a summary of subjects' baseline characteristics

- Components

Baseline variables which are crucial to study design and analysis

For categorical variables frequency tables will be generated.

For continuous variables, mean (range) will be reported.

- Frequency: first two week data analysis, futility, semi-annually, annually

4. Toxicity/Adverse Event Report – Tables 9-11 and appendix

- Purpose:

To monitor toxicities; to evaluate unexpected toxicities; to ensure that toxicity rates are acceptable. All participants receiving investigational agents will be evaluated for safety.

- Components: adverse events reported to the investigator by participants.

    1) Listing of all deaths.

    2) Frequency tables of all the signs and symptoms or laboratory toxicities by grade and across grades

    3) Listing of all adverse events. The list will include patient number, toxicity name, severity/grade of reaction, relationship to study drug.

- Frequency: first two week data analysis, futility, semi-annually, annually

5. Stopping Rules (Tables may vary)

- Components: adverse events reported to the investigator by participants.

- Tables of response times for either 1st solid food or 1st bowel movement, whichever is later.

  - Frequency: first two week data analysis, futility, semi-annually, annually

  - NA

6. Treatment and Dose Modifications Report (Treatment Form)

  - Purpose: To monitor treatment and dose adjustment

  - Components: Listings of study treatment (s) and their corresponding dosages,

  - Frequency: first two week data analysis, semi-annually, annually

7. Response Assessment report

  - Purpose: To monitor responses.

  - Components: Table of responses times.

  - Frequency : first two week data analysis, semi-annually, annually

8. Issues with Data including Data Completeness Report (various data forms)

  - Purpose:

    To ensure that clinic visits and other endpoint-related visits are conducted according to schedule; that endpoint-related data are collected appropriately and in a timely manner; to correct the database; to make sites and site principal investigators (PIs) aware of specific problems and to ensure that the compliance rate for visits and sample acquisition is high enough to satisfy protocol objectives.

  - Frequency: first two week data analysis, semi-annually, annually

**Timeline for Reports**

| Date | Accrual* | Study Status | Baseline Characteristics* | Study Completeness | Toxicity/Adverse Event | Treatment and Dose Modifications | Interim Analysis Response Assessment |
|---|---|---|---|---|---|---|---|
| 4/17/2018 | X | X | X | X | X | X | |
| Xxxxxx *** (futility Analysis) | X | X | X | X | X | X | X |
| 11/21/2018 | X | X | X | X | X | X | |
| 5/1/2019 | X | X | X | X | X | X | |
| 11/1/2019 | X | X | X | X | X | X | |
| 5/1/2020 | X | X | X | X | X | X | |
| 11/1/2020 | X | X | X | X | X | X | |
| 5/1/2021 | X | X | X | X | X | X | |

*****Accrual and Baseline Characteristics Reports may be discontinued following closing the study to accrual
*** Futility Analysis will be completed when necessary