Clinical Study Protocol: LBS-POI-201

Study Title:	A Randomized, Double-Blind, Placebo-Controlled Proof of Concept Study to Evaluate LB1148 for Return of Gastrointestinal Function, Post-Operative Ileus and Intra-Abdominal Adhesions in Subjects Undergoing Elective Bowel Resection (PROFILE)
Study Number:	LBS-POI-201
Study Phase:	2
Product Name:	LB1148
Indication:	Post-Operative Ileus and Adhesions
Investigators:	Multicenter across the United States
Sponsor:	Palisade Bio, Inc. 7750 El Camino Real, Suite 5200 Carlsbad, CA 92009
Medical Monitor:	[redacted]

	Date
Original Protocol:	11 July 2016
Amendment #1:	17 August 2016
Amendment #2:	18 August 2016
Amendment #3:	13 June 2019
Amendment #4:	17 June 2021
Amendment #5:	24 August 2021
Amendment #6:	26 August 2022

SPONSOR SIGNATURE

Study Title:	A Randomized, Double-Blind, Placebo-Controlled Proof of Concept Study to Evaluate LB1148 for Return of Gastrointestinal Function, Post-Operative Ileus and Intra-Abdominal Adhesions in Subjects Undergoing Elective Bowel Resection (PROFILE)
Study Number:	LBS-POI-201
Version Date:	26 August 2022

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Name: [redacted]

Title: VP, Clinical Operations

Signature: _____ Date: _____

Name: [redacted]

Title: Chief Medical Officer

Signature: _____ Date: _____

INVESTIGATOR'S SIGNATURE

Study Title:	A Randomized, Double-Blind, Placebo-Controlled Proof of Concept Study to Evaluate LB1148 for Return of Gastrointestinal Function, Post-Operative Ileus and Intra-Abdominal Adhesions in Subjects Undergoing Elective Bowel Resection (PROFILE)
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I have read the LBS-POI-201 protocol and agree to conduct the study as outlined.

I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

I agree to conduct the study in accordance with the ethical principles that have their origin in the Declaration of Helsinki, are consistent with the Good Clinical Practices guidelines of the International Conference on Harmonization, and according to applicable regulatory requirements.

Principal Investigator:_____
(Print Name/Title)

Signature of Principal Investigator: _____

Date:_____

Affiliation/Company: _____

SYNOPSIS

Study Title: A Randomized, Double-Blind, Placebo-Controlled Proof of Concept Study to Evaluate LB1148 for Return of Gastrointestinal Function, Post-Operative Ileus and Intra-Abdominal Adhesions in Subjects Undergoing Elective Bowel Resection (PROFILE)	
Name of Finished Product: LB1148	**Name of Active Ingredient:** Tranexamic acid (TXA) 7.5 g
Study Number: LBS-POI-201	**Study Phase:** 2
Clinical Sites: Approximately 15 sites in the United States	
Study Rationale: The purpose of this study is to establish preliminary evidence of the efficacy, safety, and tolerability of LB1148 for the treatment of post-operative ileus and intra-abdominal adhesions in subjects undergoing elective bowel resection.	
Primary Objective: To compare the change from baseline in extent and severity of intra-abdominal adhesions among subjects treated with LB1148 or placebo.	
Secondary Objectives: The secondary objectives of this study are to determine the following among subjects treated with LB1148 or placebo: • Compare time from surgical closure to resolution or appearance, as appropriate, of 1 or more of the components common to gastrointestinal (GI) dysfunction following elective bowel resection with a planned stoma. • Compare number of hours to GI2. • Compare number of hours to GI3. • Compare number of hours to resolution of POI. • Compare hospital length of stay (LOS, recorded in hours) through Discharge or Day 14 (whichever comes first). • Compare the incidence of intra-abdominal adhesions following the second surgery among subjects treated with LB1148 or placebo. • Compare the extent and severity of intra-abdominal adhesions following the second surgery among subjects treated with LB1148 or placebo. • Compare change from baseline in incidence, extent, and severity of intra-abdominal adhesions among subjects treated with LB1148 or placebo who had adhesions observed at the time of the first surgery. • Assess the safety and tolerability of LB1148 in subjects undergoing elective bowel resection.	

Exploratory Objectives:

The exploratory objectives of this study are to determine if LB1148 reduces the:

- Post-operative abdominal pain.
- Incidence of bowel obstruction through 30 days post-operatively.
- Incidence of hospital re-admittance through 30 days post-operatively.
- Volume of blood product transfusions on the day of surgery.

Study Design:

This is a multicenter, randomized, double-blind, parallel, placebo-controlled, proof-of-concept, adaptive design, Phase 2 study to evaluate LB1148 for return of GI function, reduction of POI and intra-abdominal adhesions in subjects undergoing elective bowel resection with a planned stoma.

Subjects scheduled for elective bowel resection, aged 18 to 80 years inclusive, will be screened within 42 days of randomization (Study Day -1). Subjects who meet all inclusion and no exclusion criteria, and provide written informed consent, will be stratified by: 1) surgical approach (either minimally invasive technique or laparotomy) and 2) with or without a planned stoma, and then randomized to receive a split oral liquid dose of LB1148 or placebo (polyethylene glycol [PEG], glucose, and electrolytes) in a in a 1:1 ratio.

All subjects will receive 350 mL of study drug 6-10 and 2-6 hours prior to surgery (Study Day 1/2). Subjects will then undergo the first surgery. At the time of surgical closure, the investigator will determine the incidence, extent, and severity of adhesions using the Intra-Abdominal Adhesion Extent and Severity Assessment Worksheet (Appendix 5).

Subjects will be assessed for safety and tolerability, including AEs, physical exam, vital signs, clinical lab tests (chemistry, coagulation, and hematology) while in the hospital and on Day 30. Subjects will be monitored for return of bowel function while in the hospital and discharged following tolerance of solid food and first bowel movement.

Within 8 months of enrollment, subjects will undergo a second surgery for the purpose of ostomy takedown or other planned abdominal surgery, at which time the surgeon will determine the incidence, extent, and severity of adhesions. If a subject is not ready for the second surgery by 8 months, the investigator may consult with Medical Monitor to obtain window approval.

Unless required for safety reasons or protocol compliance, all subjects, Investigators, and study site personnel will remain blinded to the identity of the treatment from time of randomization until final database lock.

Study Population:

Inclusion Criteria:

Subjects will be eligible for participation in the study only if they meet ALL of the following inclusion criteria:

1. Scheduled to undergo an elective (non-emergent) bowel resection with a planned stoma via laparotomy or minimally invasive technique. This includes any subject in which a resection of the small intestine, colon, or rectum is performed for any elected indication.
2. Planned stoma takedown or other planned abdominal surgery within 8 months of the initial surgery.
3. Willing to perform and comply with all study procedures including attending clinic visit as scheduled and completion of a second surgery for stoma takedown or other abdominal surgery and to determine the presence of intra-abdominal adhesions.
4. Has been informed of the nature of the study (either the subject or their legal representative), agrees to its provisions, and has provided written informed consent.

Exclusion Criteria:

Subjects will not be eligible for participation in the study if they meet ANY of the following exclusion criteria:

1. <18 or >80 years of age.
2. Requires emergency bowel surgery.
3. Has had 1 or more abdominal surgeries, excluding the current, for inflammatory bowel disease, including, but not limited to, inflammatory bowel disease (IBD), Crohn's Disease, or ulcerative colitis.
   Note: This does not apply to previous surgery such as hernia repair unrelated to IBD.
4. American Society of Anesthesiologists (ASA) Class 4 or 5.
5. Known inability to take the study drug orally (i.e. complete small bowel obstruction).
6. Has contraindications or potential risk factors to taking TXA. These include subjects with:
   a. Known sensitivity to TXA
   b. Recent craniotomy (past 30 days)
   c. Active cerebrovascular bleed
   d. Active thromboembolic disease (such as deep vein thrombosis, pulmonary embolism, cerebral thrombosis, ischemic stroke, or acute coronary syndrome)
   e. Acute promyelocytic leukemia taking all-trans retinoic acid for remission induction, or
   f. Continuing use of a combined hormonal contraceptive and or combined hormonal replacement therapy (including combined hormonal pill, patch, or vaginal ring)
7. Has peritoneal carcinomatosis.
8. History of or current seizure disorder.
9. Patients with myeloproliferative disorders.
10. Any other condition that, in the opinion of the Investigator, would preclude the subject from being an appropriate candidate for the study, including severe renal or hepatic impairment.

11. Planned treatment with alvimopan (Entereg®) during study participation period.
12. Planned use of 4% icodextrin (Adept®) or SEPRAFILM during the first surgery.
13. Received any other investigational therapy within 4 weeks prior to Randomization
14. Female subjects of childbearing potential with a positive urine or serum pregnancy test or who are not taking (or not willing to take) acceptable birth control measures (abstinence, intrauterine devices, contraceptive implants or barrier methods) through Day 30. Additionally, those women who are lactating and insist on breast feeding within 5 days of the last dose of study drug.
15. Known history of radiation enteritis.

Planned Number of Subjects:

Enrolled: Planned 120 subjects; adaptive design may allow for up to 200 subjects.

Test Product, Dose, and Mode of Administration:

A total of 700 mL of LB1148 will be administered orally as a split dose (350 mL 6-10 hours before surgery and another 350 mL 2-6 hours before surgery).

LB1148 contains 7.5 g TXA, polyethylene glycol (PEG), glucose, and electrolytes.

Reference Product, Dose, and Mode of Administration:

A total of 700 mL of placebo will be administered orally as a split dose (350 mL 6-10 hours before surgery and another 350 mL 2-6 hours before surgery).

The placebo contains PEG, glucose, and electrolytes.

Duration of Treatment:

Subjects will receive study drug over the 10 hours prior to surgery.

Administration:

A total of 700 mL of study drug should be completely consumed orally 2-10 hours prior to induction of surgical anesthesia as a split dose:

- Subject will consume 350 mL 6-10 hours prior to surgery.
- Subject will consume the remaining 350 mL 2-6 hours prior to surgery.

Perioperative Standardization of Care:

Subjects **must** receive:

- Venous thromboembolism (VTE) prophylaxis according to each institute's regional antithombotic guidelines.

Subjects must **not** receive:

- Solid foods consumed for the 8 hours prior to induction of surgical anesthesia;
- Alternative carbohydrate drinks 8 hours prior to induction of surgical anesthesia; study drug will replace carbohydrate drinks within that time period, and

- Anything by mouth for the 2 hours prior to induction of surgical anesthesia (exception: daily oral medication such as anti-hypertensive may be taken with small volume of water as directed by physician)

Duration of Subject Study Participation:
The total duration for subject participation is up to 10 months (screen through second surgery).

Efficacy Assessments:
Intra-Abdominal Adhesions:

- Incidence of intra-abdominal adhesions as determined by the surgeon.
- Extent and severity of intra-abdominal adhesions as determined by the surgeon using the Intra-Abdominal Adhesion Extent and Severity Assessment Worksheet (Appendix 5).

Bowel Function:

- GI2, defined as the time from the end of surgery (the time the last skin staple or suture was placed by the surgeon) to the time of toleration of solid food (the time a patient finished meal that required chewing and experienced no significant nausea/vomiting for four hours after the solid meal) AND the time to first bowel movement.
- GI3, defined as the toleration of solid food and either first flatus or bowel movement.
- Ability to tolerate a liquid oral diet (time subject is able to sustain oral liquid intake without need for IV fluid administration).
- Ability to tolerate a solid oral diet (time subject is able to ingest solid food without significant nausea/vomiting for four hours).
- Flatus.
- Bowel movement.
- Insertion, reinsertion, and/or removal of nasogastric (NG)/orogastric (OG) tube.
- Nausea with a Verbal Rating Score (VRS) ≥3 (moderate to severe).
- Vomiting or retching.
- POI, defined as the inability to tolerate liquid or solids greater than expected post-operative period, confirmed by imaging studies
- Resolution of POI, defined as having resolved when all of the following criteria are met:
  - Absence of nausea AND vomiting for 12 hours without a NG/OG tube
  - Ability to tolerate a solid or liquid oral diet
  - Passage of flatus OR stool over the preceding 24 hours.

Other Endpoints:

- Hospital LOS defined as time of admission to time that discharge order is written. NOTE: Subjects may not be discharged until all of the following criteria are met:
  - Passage of stool
  - Ability to tolerate solid food and drink comfortably
  - Adequate oral analgesia
  - Subject's willingness to be discharged.
- Pain values will be evaluated using

- Values recorded from the Numeric Pain Rating Scale (NPRS);
- Analgesia consumption, including totals for opioid use and morphine equivalents;

- The number of subjects with a recorded bowel obstruction;
- The number of subjects with a hospital re-admission, and
- Blood product transfusion volume on the day of surgery.

Safety Endpoints:

Safety and tolerability will be assessed based on the incidence and severity of treatment emergent adverse events (AE), serious adverse events (SAEs), vital signs, clinical laboratory results. Specific safety sub-analyses will be performed to assess the safety of LB1148 in the following patient populations:

- patients who are on chemotherapy;
- patients with a venous port or catheter;
- patients with varicose veins and superficial vein thrombosis;
- patients with varying degrees of obesity;
- patients who are smokers;
- patients with varying degrees of renal function; and
- patient age groups, including 65-80 years old.

Statistical Methods:

Intra-Abdominal Adhesions:

Comparisons between the LB1148 and placebo groups with respect to change from baseline in extent and severity of intra-abdominal adhesions will be made using the Wilcoxon rank sum test.

Bowel Function:

Bowel function analyses will be a time to event analysis (e.g., Cox proportional hazard model) with a main effect of treatment and stratified by surgery type (laparotomy versus minimally invasive approaches) and stoma (planned stoma versus no stoma). The p-values between the treatment groups will be evaluated using the Wald chi-square test. The magnitude of the treatment effect will be presented as the difference between the LB1148 and placebo groups in mean time to event (estimated by area under the Kaplan-Meier survival curve).

Interim Analyses:

An interim analysis of efficacy, safety, and tolerability will be performed after enrollment of approximately 50-60 subjects. Results from this interim analysis will permit a clearer determination of effect size and may trigger an increase in overall study sample size to up to 200 subjects enrolled.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term or Abbreviation	Definition
AE	adverse event
ASA	American Society of Anesthesiologists
BP	blood pressure
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	electronic case report form
ERAS	Enhanced Recovery After Surgery Society
GCP	good clinical practice
GI	gastrointestinal
HR	heart rate
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
Investigative Team	Investigator and/or designated study site team
IRB	Institutional Review Board
IV	intravenous
IXRS	interactive response system used for randomization.
LBS	Leading BioSciences (the Sponsor)
LB1148	investigational product – the active ingredient, TXA, is formulated in a solution containing PEG, glucose, electrolytes and water.
LOS	length of stay
NCI	National Cancer Institute
NG	nasogastric tube
NPO	nothing by mouth (nil per os)
NPRS	Numeric Pain Rating Scale

Term or Abbreviation	Definition
OG	orogastric tube
PEG	polyethylene glycol
POI	post-operative ileus
PCA	patient-controlled analgesia
RR	respiratory rate
SAE	serious adverse event
TAP	transverse abdominis plane
TXA	tranexamic acid – the active ingredient in LB1148
UADR	unexpected adverse drug reaction
VRS	Verbal Rating Scale (used for nausea)
VTE	venous thromboembolism

INTRODUCTION

1.1. Summary

During abdominal surgery, surgeons handle, manipulate, and often make incisions in the bowel. These actions can create bruising, lesions, and microscopic damage to the bowel (Thomas et al., 2004), which may allow digestive enzymes to cross the intestinal mucosal barrier potentially resulting in injury both locally and remotely. Although normally not life threatening, this digestive enzyme leak during surgery exacerbates local tissue and organ damage. Due to proximity to the leak, the bowel is one of the most seriously affected organs. Leaking digestive enzymes may delay return of normal gastrointestinal (GI) function, lead to a lack of motility in the intestine (ileus), and promote the formation of intestinal scar tissue (adhesions).

LB1148 contains tranexamic acid (TXA) as the active ingredient, a synthetic lysine amino acid derivative that is best known as a plasminogen activator inhibitor (DeLano et al., 2013) in the antifibrinolytic pharmaceutical class. In addition to being an anti-fibrinolytic, TXA is also a broad-spectrum serine protease inhibitor with inhibitory activity against trypsin, chymotrypsin, elastase, enterokinase, as well as others. This activity appears to be independent of plasminogen inhibition or activity. The pharmacology as a serine protease inhibitor is what is believed to allow TXA to preserve GI integrity during periods of mucosal barrier disruption. When administered enterally in preclinical studies, LB1148 inhibits key digestive enzymes in the lumen of the small intestine and helps preserve the gut barrier during acute periods of perturbation, shock, hypoperfusion, and ischemia (refer to the LB1148 Investigator's Brochure [IB] for further detail). The key is the oral/enteral administration of LB1148 allowing TXA to inhibit the digestive enzymes in the lumen of the bowel and to halt the digestive enzymes proteolytic activity against the intestine and villi. Intravenous (IV) administration of TXA does not allow TXA to reach therapeutic levels in the lumen of the small intestine and does not demonstrate a therapeutic benefit to preserving the mucosal barrier during times of perturbation.

All of the components in the LB1148 formulation are approved for use in humans and have well-characterized and established safety profiles. As of April 2016, PubMed lists 534 published clinical trials with TXA in humans. Some of these studies are quite large, such as the CRASH-2 study, which enrolled over 20,000 patients in over 40 countries. Furthermore, oral and parenteral formulations of TXA have 30 years of post-marketing experience. TXA is routinely given in doses up to 10 g by IV and over 8 days of consecutive oral administration in patients undergoing dental surgery with an acceptable safety and tolerability profile (Section 1.4).

The components of LB1148 are reconstituted in water (700 mL final volume) prior to oral or enteral administration. For this study, LB1148 will be orally administered once via a split dose prior to surgery. This clinical study is designed to determine if administration of LB1148 prior to surgery will reduce the GI complications and GI dysfunction following elective bowel resection.

1.2. Post-Operative Ileus

All patients undergoing bowel resection experience some degree of post-operative ileus (POI), a transient cessation of bowel motility. Prolonged POI is a serious complication of abdominal surgery, resulting in increased morbidity, hospital length of stay, and costs. Post-surgical hospital stays for patients who develop POI are 4-6 days longer than for patients who do not develop POI, resulting in a major burden on patients and health care providers each year (Berger et al., 2015; Goldstein et al., 2007; Iyer et al., 2009; Jakobsen et al., 2014).

Although POI is common after abdominal surgery, there is no widely agreed upon definition in the literature. The 2006 Clinical Consensus defines POI as "transient cessation of coordinated bowel motility after surgical intervention, which prevents effective transit of intestinal contents or tolerance of oral intake". The 2006 Clinical Consensus defines primary POI as occurring in the absence of any precipitating complication, whereas secondary POI occurs in the presence of a precipitation complication (bowel obstruction, infection, etc.). The 2006 Clinical Consensus also defined 3 types of POI:

1. Panintestinal ileus (no flatus or bowl movement, presence of nausea and vomiting);
2. Upper GI symptoms (nausea, vomiting and flatus present), and
3. Lower GI (no flatus or bowel movement, tolerance of diet).

The mechanism of POI remains elusive and is likely multifactorial, involving the central nervous system (CNS, specifically the autonomic nervous system), inflammation (mast cell inflammatory process), the enteric nervous system, hormones, neuropeptides, anesthesia, narcotics and digestive enzymes (2006 Clinical Consensus; Gan et al., 2015; Iyer et al., 2009; Jakobsen et al., 2014; Kalff et al., 1998; Kraft et al., 2010; Ludwig et al., 2008; Vather et al., 2013; Vather et al., 2014; Vather et al., 2015; Wolthius et al., 2016).

POI prevention strategies include the type of opioid (Gan et al., 2015; Berger et al., 2015) and anesthesia used (Goldstein et al., 2007). Nursing prevention strategies include early patient ambulation, early introduction of a peroral diet, selective use of a NG tube, and the use of non-opioid analgesics (2006 Clinical Consensus). Additionally, Entereg® (alvimpan) has been approved for use in the US as a gut motility stimulator to restore gut function after surgery.

1.3. Intra-abdominal Adhesion Formation and Impact

The post-operative intra-abdominal adhesions (referenced as adhesions herein) develop in the abdomen following abdominal or pelvic surgery and are found in up to 95% of patients who have subsequent surgery. Adhesions are a normal response to injury of the tissue surfaces during surgery, and although adhesions may have some beneficial effects, they can increase risk for complications, cause significant morbidity, and impose technical difficulties for subsequent abdominal surgeries. Adhesions are fibrous 'bridges' or bands that join intra-abdominal organs

(Ghonge and Ghonge, 2014). Traditionally, adhesion formation is thought to be a result of a complex interaction of cytokines, growth factors, cell adhesion molecules, neuropeptides, and numerous other factors secreted by cells in or near the area of trauma tissue perturbation during surgery.

Adhesions are known to have a significant impact on post-surgical quality of life for people worldwide. Adhesions may result in small bowel obstruction, female infertility, chronic abdominal pain, and increased difficulty with subsequent surgery and intervention costs (Ghonge and Ghonge, 2014; Ward and Panitch, 2011; DeCherney and Kumar, 2015). A number of animal studies and human interventional studies have evaluated a variety of techniques and materials designed to reduce and prevent postsurgical adhesions. Prevention strategies include mechanical (solid), liquid and gel, and pharmaceutical barriers (Ward, 2011). To date, only a handful of agents have been proven safe and effective in clinical trials, and few have generated abundant evidence to be adopted for routine use.

1.4. Rationale for Use of LB1148

The intestinal mucosal barrier plays a key role in both acute critical care medical conditions as well as burdensome chronic diseases. Healthy maintenance of the intestinal mucosal barrier requires oxygenation and blood flow and avoidance of mechanical or physical injury. Potent digestive enzymes are maintained within the intestine as long as normal blood flow continues and no damage or disturbances to the wall occur.

Breakdown of the intestinal mucosal barrier can be produced by wide variety of events. These include prolonged low blood pressure ([BP] e.g. during shock), disruption of blood flow (e.g. during ischemia), and physical and mechanical perturbations (e.g. during trauma or abdominal surgery).

One of the key advances toward the use of LB1148 to reduce post-operative complications was the learning that with more subtle perturbations of the mucosal barriers, such as during abdominal surgery, intraluminal pancreatic digestive enzymes played a role in the pathology of GI dysfunction. When the mucosal barrier was disturbed, the pancreatic digestive enzymes had a profound effect on the tissue the enzymes contacted first, namely, the intestine. Importantly, the enterotomy into the bowel during resection and anastomosis is sufficient to release pancreatic digestive enzymes, which delays the return of gut function. Perioperative enteral administration of LB1148 in preclinical models was sufficient to reduce the delayed return of GI function. Furthermore, the reduction in pancreatic digestive enzyme-induced tissue damage had a profound reduction in post-operative adhesion formation. Together, these preclinical studies provide evidence that blocking pancreatic digestive enzymes with LB1148 in the intestinal lumen reduces local tissue damage, preserves GI function, and reduces adhesion formation.

LB1148 was designed to stop the downstream effects of a disruption of the intestinal mucosal barrier by inhibiting digestive enzymes only in the lumen of the bowel and not systemically. One of the objectives of this study is to determine if a single split dose of LB1148 reduces the mucosal barrier breakdown and the leakage of digestive enzymes, thereby preventing local tissue damage and ultimately decreasing the number of hours from surgical closure to return of normal GI function.

All of the components of LB1148 are approved for use in man, having been administered to tens of thousands of subjects in controlled clinical trials, and used in hundreds of thousands of patients during routine medical care, most notably in the surgical setting. From a safety and tolerability perspective, the use of a single oral, 7.5 g dose is within the amount of TXA routinely used in medical practice. The Canadian Cyklokapron Monograph indicates an oral dose of 100 mg/kg for 8 days for patients undergoing dental surgery. Assuming a patient weighs 75 kg, this would equate to a 7.5 g dose. Since LB1148 contains TXA as the active ingredient, relevant TXA-related safety information from the Canadian Cyklokapron Monograph, the Lysteda Package Insert (oral administration), and the Australian Public Assessment is provided in the LB1148 Investigator's Brochure (IB). Information related to the pharmacokinetics (including absorption, distribution, metabolism and excretion), as well as supporting nonclinical data are provided in detail in the LB1148 IB.

Additionally, Palisade Bio has sponsored a Phase 2 study evaluating the use of LB1148. This was a multicenter, randomized, double blind, parallel, placebo-controlled study evaluating enteral administration of LB1148 in subjects with septic shock. A total of 8 subjects were enrolled and completed the study through Day 28, however the Sponsor terminated this study due to slow enrollment. Details from this study are also provided in the LB1148 IB.

STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

To compare the change from baseline in extent and severity of intra-abdominal adhesions among subjects treated with LB1148 or placebo.

2.1.2. Secondary Objectives

The secondary objectives of this study are to determine the following among subjects treated with LB1148 or placebo:

- Compare time from surgical closure to resolution or appearance, as appropriate, of 1 or more of the components common to gastrointestinal (GI) dysfunction following elective bowel resection with a planned stoma.
- Compare number of hours to GI2.
- Compare number of hours to GI3.
- Compare number of hours to resolution of POI.
- Compare hospital length of stay (LOS, recorded in hours) through Discharge or Day 14 (whichever comes first).
- Compare the incidence of intra-abdominal adhesions following the second surgery among subjects treated with LB1148 or placebo.
- Compare the extent and severity of intra-abdominal adhesions following the second surgery among subjects treated with LB1148 or placebo.
- Compare change from baseline in incidence, extent, and severity of intra-abdominal adhesions among subjects treated with LB1148 or placebo who had adhesions observed at the time of the first surgery.
- Assess the safety and tolerability of LB1148 in subjects undergoing elective bowel resection.

2.1.3. Exploratory Objectives

The exploratory objectives of this study are to determine if LB1148 reduces the:

- Post-operative abdominal pain.
- Incidence of bowel obstruction through 30 days post-operatively.
- Incidence of hospital re-admittance through 30 days post-operatively.
- Volume of blood product transfusions on the day of surgery.

2.2. Study Endpoints

2.2.1. Intra-Abdominal Adhesions

- Incidence of intra-abdominal adhesions as determined by the surgeon.

- Extent and severity of intra-abdominal adhesions as determined by the surgeon using the
- Intra-Abdominal Adhesion Extent and Severity Assessment Worksheet (Appendix 5).

2.3. Bowel Function

- GI2, defined as the time from the end of surgery (the time the last skin staple or suture was placed by the surgeon) to the time of toleration of solid food (the time a patient finished meal that required chewing and experienced no significant nausea/vomiting for four hours after the solid meal) AND the time to first bowel movement.
- GI3, defined as the toleration of solid food and either first flatus or bowel movement.
- Ability to tolerate a liquid oral diet (time subject is able to sustain oral liquid intake without need for IV fluid administration).
- Ability to tolerate a solid oral diet (time subject is able to ingest solid food without significant nausea/vomiting for four hours).
- Flatus.
- Bowel movement.
- Insertion, reinsertion, and/or removal of nasogastric (NG)/orogastric (OG) tube.
- Nausea with a Verbal Rating Score (VRS) ≥3 (moderate to severe).
- Vomiting or retching.
- POI, defined as the inability to tolerate liquid or solids greater than expected post-operative period, confirmed by imaging studies
- Resolution of POI, defined as having resolved when all of the following criteria are met:
  - Absence of nausea AND vomiting for 12 hours without a NG/OG tube
  - Ability to tolerate a solid or liquid oral diet
  - Passage of flatus OR stool over the preceding 24 hours.

2.3.1. Other Endpoints

- Hospital LOS defined as time of admission to time that discharge order is written. NOTE: Subjects may not be discharged until all of the following criteria are met:
  - Passage of stool
  - Ability to tolerate solid food and drink comfortably
  - Adequate oral analgesia
  - Subject's willingness to be discharged.
- Pain values will be evaluated using:
  - Values recorded from the Numeric Pain Rating Scale (NPRS);
  - Analgesia consumption, including totals for opioid use and morphine equivalents;
- The number of subjects with a recorded bowel obstruction;
- The number of subjects with a hospital re-admission, and
- Blood product transfusion volume on the day of surgery.

2.3.2. Safety Endpoints

Safety and tolerability will be assessed based on the incidence and severity of treatment emergent adverse events (AEs), serious adverse events (SAEs), vital signs, clinical laboratory results.

Specific safety sub-analyses will be performed to assess the safety of LB1148 in the following patient populations:

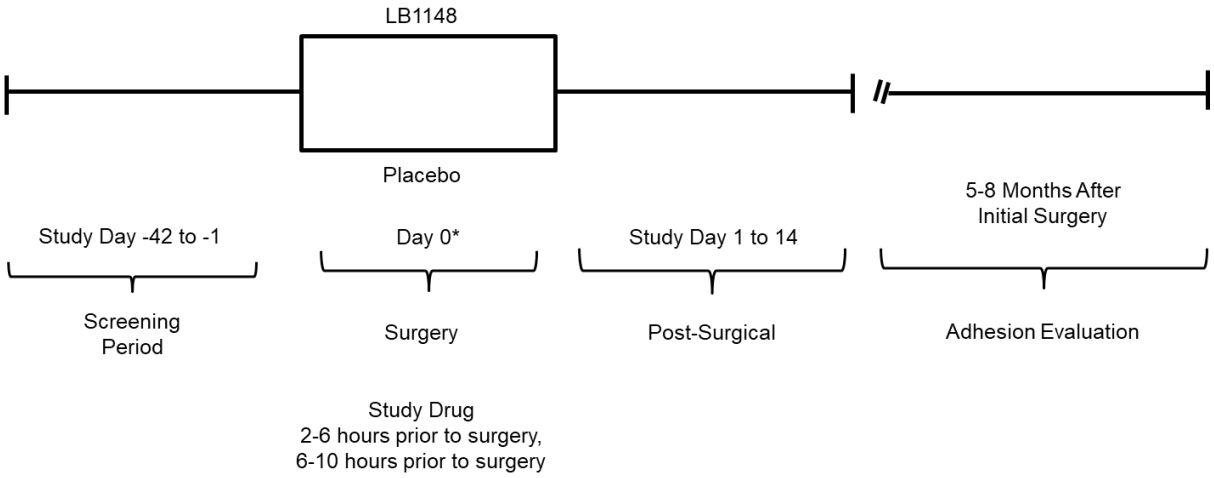
- patients who are on chemotherapy;
- patients with a venous port or catheter;
- patients with varicose veins and superficial vein thrombosis;
- patients with varying degrees of obesity;
- patients who are smokers;
- patients with varying degrees of renal function; and
- patient age groups, including 65-80 years old.

INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is a multicenter, randomized, double-blind, parallel, placebo-controlled, proof-of-concept, adaptive design, Phase 2 study to evaluate LB1148 for return of GI function, reduction of POI and intra-abdominal adhesions in subjects undergoing elective bowel resection with a planned stoma.

Figure 1 Illustration of Study Design for Protocol LBS-POI-201



* Study Day 0 is the day of surgery. Study dosing could occur on Day -1 and/or up to 2 hours prior to surgery on Day 0.

Subjects scheduled for elective bowel resection, aged 18 to 80 years inclusive, will be screened within 42 days of randomization (Study Day -1). Subjects who meet all inclusion and no exclusion criteria, and provide written informed consent, will be stratified by: 1) surgical approach (either minimally invasive technique or laparotomy) and 2) with or without a planned stoma, and then randomized to receive a split oral liquid dose of LB1148 or placebo (polyethylene glycol [PEG], glucose, and electrolytes) in a in a 1:1 ratio.

All subjects will receive 350 mL of study drug 6-10 and 2-6 hours prior to surgery (Study Day 1/2). Subjects will then undergo the first surgery. At the time of surgical closure, the investigator will determine the incidence, extent, and severity of adhesions using the Intra-Abdominal Adhesion Extent and Severity Assessment Worksheet (Appendix 5).

Subjects will be assessed for safety and tolerability, including AEs, physical exam, vital signs, clinical lab tests (chemistry, coagulation, and hematology) while in the hospital and on Day 30. Subjects will be monitored for return of bowel function while in the hospital and discharged following tolerance of solid food and first bowel movement.

Within 8 months of enrollment, subjects will undergo a second surgery for the purpose of ostomy take down or other planned abdominal surgery, at which time the surgeon will determine the incidence, extent, and severity of adhesions. If a subject is not ready for the second surgery by 8 months, the investigator may consult with Medical Monitor to obtain window approval.

Unless required for safety reasons or protocol compliance, all subjects, Investigators, and study site personnel will remain blinded to the identity of the treatment from time of randomization until final database lock.

The Schedule of Assessments is provided in Appendix 1 and the study endpoints are in Section 2.2.

3.2. Rationale for Study Design, Control Group, and Perioperative Standardization

Study Design: This is a multicenter, randomized, double-blind, parallel, placebo-controlled, proof-of-concept, adaptive design, Phase 2 study to evaluate LB1148 for return of GI function, reduction of POI and intra-abdominal adhesions in subjects undergoing elective bowel resection with a planned stoma. The study is randomized to control for factors known and unknown between the treatment groups, and neither the Investigator nor the subject will know which treatment the subject will receive in order to avoid any bias in the study assessments.

Control Group: Placebo, superimposed on current standard of care, is an appropriate control for this study.

Perioperative Standardization of Care: There are no internationally recognized perioperative standards of care for general bowel resection subjects. Although the Enhanced Recovery After Surgery (ERAS) Society has provide suggestions for improved perioperative care for GI surgical patients, these standards have been inconsistently adopted by surgical centers (ERAS website). Often each surgical center has its own, site-specific practices that best fit its patients and standards of care. This has led to heterogeneous perioperative care across sites and countries. To improve the homogeneity of perioperative care in this study and improve the opportunity to detect the effect of treatment, the following standards are being set forth:

- Subjects must receive:
  - Venous thromboembolism (VTE) prophylaxis according to each institute's regional antithombotic guidelines.
- Subjects must **not** receive:
  - Solid foods consumed for the 8 hours prior to induction of surgical anesthesia;
  - Alternative carbohydrate drinks 8 hours prior to induction of surgical anesthesia; study drug will replace carbohydrate drinks within that time period;

- Anything by mouth for the 2 hours prior to induction of surgical anesthesia (exception: daily oral medication such as anti-hypertensive may be taken with small volume of water as directed by physician), and

3.3. Study Duration and Dates

The total duration for subject participation is up to10 months (screen through second surgery).

STUDY POPULATION SELECTION

4.1. Study Population

Inclusion and exclusion criteria are provided below. As stated earlier (Section 3.1), this is an adaptive design study. Currently, 120 subjects are planned for randomization at approximately 15 sites in the United States. Based on the interim analysis results, the adaptive design of this study may allow for up to 200 total subjects enrolled at study completion.

4.2. Inclusion Criteria

Subjects will be eligible for participation in the study only if they meet ALL of the following inclusion criteria:

1. Scheduled to undergo an elective (non-emergent) bowel resection with a planned stoma via laparotomy or minimally invasive technique. This includes any subject in which a resection of the small intestine, colon, or rectum is performed for any elected indication.
2. Planned stoma takedown or other planned abdominal surgery within 8 months of the initial surgery.
3. Willing to perform and comply with all study procedures including attending clinic visit as scheduled and completion of a second surgery for stoma takedown or other abdominal surgery and to determine the presence of intra-abdominal adhesions.
4. Has been informed of the nature of the study (either the subject or their legal representative), agrees to its provisions, and has provided written informed consent.

4.3. Exclusion Criteria

Subjects will not be eligible for participation in the study if they meet ANY of the following exclusion criteria:

1. <18 or >80 years of age.
2. Requires emergency bowel surgery.
3. Has had 1 or more abdominal surgeries, excluding the current, for inflammatory bowel disease, including, but not limited to, inflammatory bowel disease (IBD), Crohn's Disease, or ulcerative colitis.

   Note: This does not apply to previous surgery such as hernia repair unrelated to IBD.
4. American Society of Anesthesiologists (ASA) Class 4 or 5.
5. Known inability to take the study drug orally (i.e. complete small bowel obstruction).
6. Has contraindications or potential risk factors to taking TXA. These include subjects with:
   a. Known sensitivity to TXA

b. Recent craniotomy (past 30 days)
c. Active cerebrovascular bleed
d. Active thromboembolic disease (such as deep vein thrombosis, pulmonary embolism, cerebral thrombosis, ischemic stroke, or acute coronary syndrome)
e. Acute promyelocytic leukemia taking all-trans retinoic acid for remission induction, or
f. Continuing use of a combined hormonal contraceptive and or combined hormonal replacement therapy (including combined hormonal pill, patch, or vaginal ring)

7. Has peritoneal carcinomatosis.
8. History of or current seizure disorder.
9. Patients with myeloproliferative disorders.
10. Any other condition that, in the opinion of the Investigator, would preclude the subject from being an appropriate candidate for the study, including severe renal or hepatic impairment.
11. Planned treatment with alvimopan (Entereg®) during study participation period.
12. Planned use of 4% icodextrin (Adept®) or SEPRAFILM during the first surgery.
13. Received any other investigational therapy within 4 weeks prior to Randomization
14. Female subjects of childbearing potential with a positive urine or serum pregnancy test or who are not taking (or not willing to take) acceptable birth control measures (abstinence, intrauterine devices, contraceptive implants or barrier methods) through Day 30. Additionally, those women who are lactating and insist on breast feeding within 5 days of the last dose of study drug.
15. Known history of radiation enteritis.

STUDY TREATMENTS

5.1. Description of Treatments

5.1.1. Study Drug

LB1148 contains 7.5 g TXA, polyethylene glycol (PEG), glucose, and electrolytes. A dose of 700 mL of LB1148 will be administered orally (refer to Section 5.2).

5.1.2. Placebo

The placebo contains PEG, glucose, and electrolytes. A dose of 700 mL of placebo will be administered orally (refer to Section 5.2).

5.2. Treatment Administration

Eating, bowel prep, and drinking will be held 1 hour before and 1 hour after study drug administration.

A total of 700 mL of study drug should be completely consumed orally 2-10 hours prior to induction of surgical anesthesia. Study drug will be provided to subjects in 2 bottles, approximately 350 mL in each bottle:

- Subject will consume the first 350 mL 6-10 hours prior to surgery.
- Subject will consume the second 350 mL 2-6 hours prior to surgery.

5.3. Selection and Timing of Dose for Each Subjects

The 7.5 g dose was chosen for safety and efficacy reasons. The minimally effective concentrations of TXA in the lumen of the small intestine were 45 mM (Delano et al., 2013) and 56.5 mM (Chang et al., 2012). LB1148 is formulated at a concentration of 68.2 mM (7.5 g TXA per 700 mL solution).

In preclinical testing, LB1148 demonstrated efficacy when administered 2 hours prior to abdominal surgery. For this study, study drug will be administered 2-10 hours prior to abdominal surgery (refer to Section 5.2 and Section 6.8). Additional information regarding dose selection, safety, and preclinical efficacy can be found in the LB1148 IB.

The ASA Practice Guidelines for Preoperative Fasting are based on a synthesis and analysis of the current literature, expert and practitioner opinion, open forum commentary, and clinical feasibility data. These Guidelines are recommendations to assist the practitioner and patient in making health care decisions. The guidelines currently read that patients should fast from clear liquids for 2 hours pre-operatively and fast from regular meals for 8 hours pre-operatively (ASA, 2011; Korpman et al., 2012). This protocol was designed to be in alignment with ASA Practice Guidelines.

5.4. Method of Assigning Subjects to Treatment Groups

Subjects who meet all study criteria for enrollment will be randomly assigned to either the investigational drug (LB1148) or placebo treatment group. Assignment to treatment groups will be determined by a computer-generated randomized sequence using an interactive response system (IXRS). All randomized subjects will be divided between the 2 treatment groups (LB1148 or placebo) in a 1:1 ratio, stratified by: 1) surgical approach (either minimally invasive technique or laparotomy) and 2) with or without a planned stoma.

5.5. Blinding

This is a randomized double-blind study. The subject's coded treatment assignment will be provided to the blinded pharmacist or designee by an IXRS. The randomization code for treatment assignment will be retained by the IXRS.

Unless required for safety reasons or protocol compliance, it is anticipated that there will be little need to unblind a subject's treatment assignment at the site level. Treatment code must not be broken except in medical emergencies when the appropriate management of the subject necessitates knowledge of the treatment randomization. Because no known antidote for LB1148 exists, there should be no medical reason for unblinding at the site.

The Medical Monitor should be contacted if the Investigator requests unblinding a subject's treatment assignment. Emergency unblinding for AEs may be performed through the IXRS. If the treatment code is broken, then the Investigator(s) must document and report it to the Sponsor.

The Sponsor retains the right to break the code for SAEs that are unexpected and suspected to be causally-related to treatment, and that potentially require expedited reporting to regulatory authorities.

The Sponsor or its designee intends to unblind the treatment assignment at the time of the interim analysis; however, the study double blind (subject, Investigator, and/or designated study site team [investigative team]) will remain intact. Care will be taken such that unblinded Sponsor representative will have no contact with the site in regards to any subject data that are not yet collected by the investigative team. Further, the contract research organization (CRO) representatives in direct contact with the investigative team will remain blinded to treatment assignment throughout the study.

5.6. Concomitant Therapy

The subject must <u>not</u> perform any of the following during study participation:

- Receive other medication containing TXA while receiving study drug;
- Receive pancreatic enzyme replacement therapy during the Surgical Period;

- Use a combined hormonal contraceptive and or combined hormonal replacement therapy (including combined hormonal pill, patch or vaginal ring) during the 7 day period prior to Surgery through the 7 day period following surgery;
- Consume solid foods 8 hours prior to induction of surgical anesthesia;
- Receive alternative carbohydrate drinks. Study drug will replace carbohydrate drinks within 8 hours prior to induction of surgical anesthesia.
- Consume anything by mouth (NPO) for the 2 hours prior to induction of surgical anesthesia. (Exception: daily oral medication such as anti-hypertensive may be taken with small volume of water as directed by physician).
- Receive 4% icodextrin (Adept®) or SEPRAFILM during the first surgery
- Use post-operative alvimopan (also known as Entereg®).

Otherwise, there are no restrictions with respect to concomitant therapies for this study. All concomitant medications should be listed in the electronic case report form (eCRF) along with the date therapy was initiated and, if applicable, terminated.

5.7. Restrictions

5.7.1. Fluid and Food Intake

There is no co-administration of food or drink with the study drug. Eating, bowel preparation, and drinking will be held 1 hour before and 1 hour after study drug administration.

5.7.2. Reproduction

Subjects of reproductive capability must agree to use contraception throughout the Follow-Up Period of the study (through Day 30). Acceptable methods include abstinence, intrauterine devices, contraceptive implants, and barrier methods (condom, diaphragm with spermicide).

5.8. Treatment Compliance

Study drug will be administered either by site personnel at the study hospital or by the subject at home prior to surgery. Location for administration is dependent on time of surgery and location for surgical preparation by the subject, and may differ for participating subjects.

5.9. Packaging and Labeling

The Sponsor will provide study materials to the study pharmacy in 120 mL bottles of either active or placebo powder for reconstitution. Glucose powder will be provided in a clearly labeled 60 mL bottle. Reconstitution and labeling instructions are provided in the Pharmacy Manual.

5.10. Study Drug Storage, Preparation, Dispensing, and Accountability

Study drug will be sent to the clinical study site pharmacy. Instructions for requesting additional supplies of product will be provided in the Pharmacy Manual.

Both LB1148 and placebo are to be stored at room temperature. Study drug should be stored carefully at the clinical study site, safely and separately from other drugs. Instructions for the reconstitution of study drug are provided in the Pharmacy Manual.

The site research pharmacist or other authorized site study team personnel will dispense the reconstituted blinded study drug to each subject. The Investigator (or designated pharmacist) will maintain records of:

- The receipt of study drug at the clinical study site;
- The inventory at the site dispensing product to each subject, and
- The return of unused cartons to the Sponsor or destruction at the clinical study site.

During the course of the study, or upon completion or termination of the study, the Investigator/pharmacist will return all unused medication to the Sponsor or destroy all unused medication at the site according to institutional procedures after recording the relevant accountability information. For drug accountability records, the site will provide the Clinical Monitor with a copy of the inventory record and a record of destroyed clinical supplies (on a Drug Accountability Log). The record of destroyed clinical supplies will include information on:

- All dispensed bottles;
- All used and unused bottles returned to the pharmacy;
- All unused bottles;
- All used and unused bottles destroyed in the course of the study;
- Date(s) of destruction, and
- Name and signature of the Investigator/pharmacist.

During and at the end of the study, all study drug will be reconciled against current inventory and the dispensing records as part of routine monitoring visits. After reconciliation, unused (full) bottles will be destroyed at the site per institutional standard operating procedure. At the end of the study, unused, unopened cartons of study drug will be returned or destroyed as instructed by the Sponsor, or its designees.

STUDY PROCEDURES

The schedule of assessments and treatments is provided in Appendix 1. While the subject is in the hospital, all assessments and treatments are to be performed on the study day as indicated.

6.1. Informed Consent

Written informed consent must be obtained from each subject or legal representative designee if subject is unable to sign after the nature of the study has been fully explained in accordance with International Conference on Harmonization (ICH) Good Clinical Practices (GCP). Informed consent must be obtained prior to performing any study-specific procedures.

6.2. Demographics and Medical History

Medical history will include significant medical conditions and surgical history, as well as baseline signs and symptoms occurring within 2 weeks of randomization. Additionally, the subject's diagnosis and reason for requiring a bowel resection will be documented, the planned surgical approach for the bowel resection, the planned use of stoma, and the need for a planned, second surgery. The subject's medical history will be collected during the Screening Period; during this review, a Caprini risk factor score will be calculated (Appendix 8). Each subject's risk factors for VTE will be assessed in order to determine the appropriate VTE regimen according to each institute's regional antithombotic guidelines. The subject's prior or current use of tobacco will also be collected.

On the day of the first surgery (the Surgical Period), any changes to subject's condition that affect inclusion/exclusion criteria will be documented. Subject must meet all inclusion/exclusion criteria at time of the first surgery.

6.3. Physical Examination

A complete physical examination (except for genitourinary unless indicated) will be performed at Screening. Height will be measured at the Screening visit only.

From Day 0 through Post-Operative Day 14, and at Hospital Discharge, or study termination, whichever comes first – a brief, focused examination of the subject will be performed, including lower extremity assessments to identify any clinical symptoms of VTE and assessment for AEs. Each focused examination will include weight measurements.

6.4. Surgery Assessment

During surgery (where applicable), the following data should be recorded:

- The type of operation.
- The type of surgical approach (minimally invasive technique or laparotomy).

- The location of the surgical incision(s).
- Surgical time, recorded as:
  - Surgery start time, defined as the time when the initial incision is made, and
  - Surgery end time, defined as when the last suture or staple was placed.
- Ileostomy mobilization time (defined as the time from skin incision to completion of circumferential mobilization and start of preparation of ileostomy for closure).

6.5. Concomitant Medication Assessments

Concomitant medications, including prescription and over-the-counter drugs, will be recorded within 2 weeks prior to randomization through Post-Operative Day 14, and at Hospital Discharge, or study termination, whichever comes first. Additionally, any perioperative surgical preparation that was given or consumed will be documented, including mechanical bowel prep and nutritional supplements (refer to Section 3.2, Section 5.6, and Section 0).

Blood products administered to the subject will be documented throughout the same timeframe on the Concomitant Medication eCRFs. Documentation will include start and stop dates and reasons for the use.

Unless otherwise specified in the protocol, administration of other concomitant investigational drugs or devices for any indication, other than study drug, is not permitted while on study. Additionally, receiving medication with TXA while taking the study drug is prohibited along with receiving pancreatic enzyme replacement therapy. Any therapeutic or surgical procedures performed during the study period will be documented. Documentation will include information regarding the date(s), indication(s), description of the procedure(s), and/or any clinical or pathological findings.

6.6. Vital Signs

Vital signs will include BP (systolic and diastolic measurements), heart rate (HR), respiratory rate (RR), oxygen saturation, and temperature. Vital signs will be collected daily from Screening through Post-Operative Day 14, and at Hospital Discharge, or study termination, whichever comes first. For study purposes, the vital signs taken the closest to 0800 will be used for data capture.

6.7. Laboratory Tests

6.7.1. Pregnancy Test

A negative urine or serum pregnancy test must be obtained at Screening and confirmed prior to randomization for all females of childbearing potential.

6.7.2. Local Laboratory Tests

Blood samples will be collected during the Screening Period and on Post-Operative Day 3. A lab draw will be performed on Post-Operative Day 7 only if subject is still hospitalized.

Appendix 2 lists the specific laboratory tests that will be performed for this study.

All laboratory evaluations will be conducted at the laboratories located at or associated with the clinical site. Each laboratory will be required to provide up-to-date reference ranges. Laboratory values will be recorded on the eCRF(s).

Unscheduled laboratory results, from tests pre-specified in this protocol, that are both abnormal and clinically significant, as decided by the Investigator, will be recorded on an additional eCRF page(s) and the data will be included in the assessment of out-of-range parameters.

6.8. Study Drug Administration

A total of 700 mL of study drug should be completely consumed orally 2-10 hours prior to induction of surgical anesthesia as a split dose:

- For the first study drug administration, subject will consume 350 mL 6-10 hours prior to surgery.
- For the second study drug administration, subject will consume the remaining 350 mL 2-6 hours prior to surgery.

Eating, bowel preparation, and drinking will be held 1 hour before and 1 hour after study drug administration.

6.9. Perioperative Surgical Preparation

All perioperative items the subject is given or consumed will be recorded during the Screening and Surgical Periods. These include, but are not limited to, mechanical bowel prep, nutritional supplements, carbohydrate drinks, opioids, and analgesia. As indicated in Section 3.2:

- Subjects **must** receive:
  - VTE prophylaxis according to each institute's regional antithombotic guidelines.
- Subjects must **not** receive:
  - Solid foods consumed for the 8 hours prior to induction of surgical anesthesia;
  - Alternative carbohydrate drinks 8 hours prior to induction of surgical anesthesia; study drug will replace carbohydrate drinks within that time period;
  - Anything by mouth for the 2 hours prior to induction of surgical anesthesia (exception: daily oral medication such as anti-hypertensive may be taken with small volume of water as directed by physician), and

Additional information concerning restrictions are provided in Section 5.7.

6.10. Taste Assessment

In the first phase of the study, after the study drug has been consumed and before surgical anesthesia is administered during the Surgical Period, subject satisfaction with the taste of the study drug will be recorded.

6.11. Opioid Use

The use of opioid pain medications will be collected daily from Screening through Day 14, and at Hospital Discharge or study termination, whichever comes first.

6.12. Pain Assessment

The NPRS is an 11-point scale used to evaluate pain based on subject feedback. This scale can be administered either verbally or graphically by the clinician where subjects is asked to rate their current pain intensity from 0 ("no pain") to 10 ("worst possible pain imaginable"). The NPRS is the method recommended by both the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials as well as the Expert Working Group for the assessment of pain intensity during a clinical study (Breivik et al., 2008; Caraceni et al., 2002). A change of approximately 30% (or 2 points) has been shown to represent a clinically meaningful change in pain (Farrar et al., 2001).

Investigator or delegated site personnel should use the following statements to ask the subject to rate their post-operative abdominal pain:

1. I would like you to rate your pain on a scale from 0 to 10.
2. '0' means you have no pain at all.
3. '10' means the worst possible pain you can imagine.
4. What number would you give to your pain?

A pain assessment will be collected daily starting after Surgery Day 0 through Day 14, and at Hospital Discharge, or study termination, whichever comes first (Appendix 4).

6.13. Gastrointestinal Function Assessment

Starting on Post-Operative Day 1, GI function will be assessed to determine return of GI function. Daily GI assessments will be collected until either the subject has had return of GI function or Hospital Discharge. If, while still in the hospital, GI function deteriorates to the point of no longer being able to tolerate an oral diet and pass stool, daily measurements should be collected again until the subject has had return of GI function.

Data for this assessment will include but not be limited to:

- Nausea and vomiting (either subject reported or recorded as presence or absence, date and time, including VRS [Appendix 3]),
- Passing of flatus (either subject reported or Investigator/delegated site personnel reported during a 24-hour calendar day; date and time of first flatus where only the first observance is recorded; in any instance where subject has post-operative complications and experiences ileus as decided by Investigator, the next flatus event should be recorded);
- Passing of stool from anus or ostomy (recorded as presence or absence and date and time);
- Presence of NG/OG tube (including date and time).
- Ability to tolerate liquid diet (liquid diet ordered, subject is able to sustain oral liquid intake without need for IV fluid administration, and total liquid volume over a 24-hour calendar day);
- Ability to tolerate a solid diet (solid diet ordered and date and time of solid food ingestion without significant nausea or vomiting for 4 hours).
- If a subject experiences a POI event during hospitalization, this event will be recorded, including date and time as an AE/SAE.

6.14. Hospital Discharge

Subjects may not be discharged until all of the following criteria are met:

- Passage of stool
- Ability to tolerate solid food and drink comfortably
- Adequate oral analgesia
- Subject's willingness to be discharged.

Information related to Hospital Discharge after the first bowel resection will be recorded during the Post-Surgical period as:

- When discharge order is written (date and time)
- When subject departs from the hospital (date and time)

6.15. Day 30 Follow-Up

On Day 30 (+7 days), site study staff will contact the subject or their legally authorized representative to determine if the subject experienced a hospital readmission due to GI concerns and/or other medical reasons. If readmission did occur, this event should be recorded as a SAE.

As it is vital to obtain follow-up data, every effort must be made to contact the subject or legally authorized representative to collect this information.

6.16. Adhesions Assessment (Day 0 and at time of second surgery)

The surgeon will determine the incidence, extent, and severity of adhesions at the time of surgical closure for the first surgery and at the time of opening for the second surgery. Grading of the adhesions (extent and severity) will be performed by the surgeon during the surgical procedure (Appendix 5).

For each abdominal region, the score of the extent and severity of adhesions are evaluated. The surgeon will grade the intra-abdominal adhesions at 9 abdominal region (right upper, epigastrium, left upper, left flank, left lower, pelvis, right lower, right flank and central) and when appropriate at 4 areas around the ostomy (superior, lateral, inferior, and medial). (Coccolini et al., 2013, Dabrowski et al., 2016, and the Seprafilm Package Insert).

For each abdominal region, extent of adhesion formation is scored for adhesions from the abdominal wall to bowel (including abdominal wall to viscera) and for adhesions from bowel to bowel (including bowel to viscera) as follows:

0 = no adhesion;
1 = minimal (<1/3 of the site is covered);
2 = moderate (1/3 to 2/3 of the site is covered), or
3 = extensive (>2/3 of the site is covered).

The severity of the adhesions in the region are graded using the following score:

0 = no adhesions;
1 = filmy thickness, avascular;
2 = moderate thickness, limited vascularity, or
3 = dense thickness, vascularized.

At the second surgery visit the site study staff will determine if the subject experienced a hospital readmission due to GI concerns and/or other medical reasons. If readmission did occur, this event should be recorded as a SAE.

6.17. Appropriateness of Measurements

All procedures used to measure the safety and efficacy of LB1148 in this study are considered to be appropriate and necessary to obtain the required safety, tolerability, and efficacy data. The safety assessments used in this study, such as physical examination, vital signs, opioid use, laboratory assessments, and GI function assessments are widely used and are considered appropriate for monitoring subjects' health and well-being in this type of study. The measure used to evaluate pain levels is a validated and widely accepted rating scale used for clinical studies evaluating pain.

ADVERSE EVENTS ASSESSMENTS

AE data will be collected from first administration of study drug through Day 14, Hospital Discharge, or study termination, whichever comes first. Following discharge through the second surgery visit, any hospital readmissions will be recorded as SAEs.

AEs/SAEs related to the second surgery will also be collected.

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting the Sponsor or its designees to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

The Investigator is responsible for the appropriate medical care of subjects during the study. The Investigator remains responsible for following, through an appropriate health care option, SAEs or AEs that caused the subject to discontinue before completing the study. The subject should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the Investigator.

7.1. Adverse Events

An AE is any untoward medical occurrence in a subject administered a drug or biologic (medicinal) product; the event does not necessarily have a causal relationship with the administration of the study drug. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug.

This includes any side effect, injury, toxicity, or sensitivity reaction, and may include a single symptom or sign, a set of related symptoms or signs, or a disease. An AE may also be any laboratory abnormality judged to be clinically significant by the Investigator that worsened when compared to baseline.

AEs include the following:

- All suspected adverse drug reactions.
- All reactions from medication overdose, abuse, withdrawal, sensitivity, or toxicity.
- Apparently unrelated illnesses, including the worsening of a pre-existing illness.
- Injury or accidents.
  Note: If a medical condition is known to have caused the injury or accident (e.g., a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate AEs.
- Abnormalities in physiological testing or physical examination (findings that require clinical intervention or further investigation beyond ordering a repeat [confirmatory] test).

- Laboratory abnormalities that are clinically significant and require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event.

An AE **does not** include:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an AE.
- Pre-existing diseases or conditions present or detected at screening/baseline that do not worsen in severity or frequency.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- Overdose of either study drug or concomitant medication without any signs or symptoms.

Throughout the course of the study, every effort should be made to remain alert to possible AEs. Subjects should be encouraged to report AEs spontaneously or in response to general, non-directed questioning.

With the occurrence of an AE, the primary concern is the safety of the subject. If necessary, appropriate medical intervention should be provided and the study drug discontinued. Urgent safety issues may be discussed with Study Medical Monitor.

7.2. Serious Adverse Events

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- Death.
- A life-threatening AE (i.e., immediate risk of death)
  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.
- Prolongation of existing hospitalization or re-hospitalization.
- Results in persistent or significant disability/incapacity.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the AE may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.3. Adverse Events of Special Interest

AEs of special interest can be either serious or non-serious. For this study, 3 events will be calorized as Special Interest: POI, thrombotic events, and conditions that cause a prolongation of existing hospitalization due to a post-surgical complication. AEs of special interest will be reported as either an SAE (refer to Section 7.2) or as an AE (refer to Section 7.1).

7.4. Venous Thrombosis

As indicated in the LB1148 IB, nonclinical toxicology data indicates a possible association between the use of TXA and thrombosis events. However, post-marketing AE reports in humans indicate thromboembolic events are relatively rare. Since TXA is known to have an impact on blood clotting, thrombotic events will be recorded as an AE/SAE and followed to resolution.

7.5. Post-Operative Ileus

Resolution of POI-related symptoms are one of the focuses of this study. As such, any instance of POI will be recorded as an AE/SAE and followed to resolution. POI events post-discharge, but prior to Day 30, will also be recorded as an AE/SAE.

7.6. Post-Surgical Complications

The impact of study drug on LOS is a secondary endpoint for this study. As such, any post-surgical complication that prolongs discharge will be recorded as an AE/SAE.

7.7. Unexpected Adverse Event

An unexpected AE is any AE that is not identified in nature, severity, or frequency in the current LB1148 IB or product information.

7.8. Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction (UADR) is an adverse reaction, the severity of which is not consistent with the applicable product information or IB. All noxious and unintended responses to a medical product related to any dose should be considered an UADR.

- The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility (meaning the relationship cannot be ruled out).
- The expression “causal relationship” is meant to convey that in general there are facts, evidence, or arguments to suggest a reasonable causal relationship. All serious and UADRs will have expedited reporting to regulatory agencies following ICH requirements.

7.9. Adverse Event Reporting Period

AE data will be collected from first administration of study drug through Day 14, Hospital Discharge, or study termination, whichever comes first. Following discharge through the Month 3 visit, any hospital readmissions will be recorded as SAEs.

AEs/SAEs related to the second surgery will also be collected.

If a subject experiences an AE after signing informed consent, but prior to receiving study drug, the event will NOT be collected unless the Investigator feels the event may have been caused by a protocol procedure.

In addition, any known untoward event that occurs subsequent to the AE-reporting period that the Investigator assesses as related to the study drug should also be reported as an AE.

7.10. Recording Adverse Events

All AEs will be documented in the appropriate section of the eCRFs. Among these AEs, all SAEs (refer to Section 7.2) will be additionally documented in the SAE Report.

The following will be recorded for each event in the eCRF:

- A description of the AE in medical terms, not as reported by the subject. Whenever possible, a diagnosis should be given when signs and symptoms are due to common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection").
- The date of onset (start date).
- The date of resolution (stop date).
- The severity as assessed by the Investigator according to the definitions in Section 7.11.
- The causal relationship to study drug as assessed by the Investigator; the decisive factor in the documentation is the temporal relation between the AE and the study drug (refer to Section 7.12).
- Action taken for study drug (none, study drug discontinued, study drug dose reduction, study drug delayed).
- Other action(s) taken (none, concomitant medication given, new or prolonged hospitalization, procedural surgery).
- The outcome according to the following definitions:
  - Recovered with sequelae;
  - Recovered without sequelae;
  - Ongoing, no therapy;
  - Ongoing, therapy;
  - Died, and
  - Change in toxicity grade/severity.

- SAE (as defined in Section 7.2): Yes or No.

If, in any 1 subject, the same AE occurs on several occasions (unless the AE is continuous and of stable grade), then the AE in question will be documented and assessed each time. For an SAE, the information above recorded in the eCRF will also be recorded in the SAE Report. Only AEs that fulfill the criteria for SAEs (refer to Section 7.2) should be recorded in the SAE Report.

7.11. Assessing Adverse Event Severity

To ensure there is no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

All AEs are to be evaluated with respect to severity using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grading system (Appendix 7).

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). *Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. *Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.*
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

7.12. Assessing Adverse Event Relationship to Study Drug

The Investigator must record his/her opinion concerning the relationship of the AE to study therapy on the eCRF. Investigators will determine relatedness of an event to study drug based on

a temporal relationship as well as if the event is unanticipated or unexplained given the subject's clinical course, previous medical conditions, and concomitant medications. An event should be recorded as "drug related" if the Investigator believes it to be reasonably related to study drug.

7.13. Reporting Serious or Unexpected Adverse Events

Any SAE, irrespective of the relationship to study drug that occurs during the course of the study (from the first dose of study drug through Hospital Discharge, completion of Month 3 or early termination) will be reported on the eCRFs and SAE Report as soon as possible (within 24 hours after the site becomes aware of the event).

The Investigator is encouraged to discuss with the Sponsor's pharmacovigilance group any AE for which the issue of reportability is unclear or questioned.

An SAE Report should be prepared containing as much information as is available concerning the event so that a written report can be filed with appropriate regulatory authorities. If causality cannot be definitively assessed at the time of the SAE, it is important to notify Sponsor or its designees within the timelines stated above. When new significant information is obtained and the outcome and attribution of the event is known, the Investigator will communicate this information to the Sponsor or its designees and/or on the appropriate eCRFs. The relevant information will be provided in a timely manner to allow reporting to regulatory authorities within the required reporting period. Any SAE follow-up information requested by the Sponsor or its designees should be provided in a timely manner.

Additional information may be requested by the Sponsor or its designees to ensure that the initial reporting of SAEs is made to regulatory authorities within the requested timeframe. For a follow-up report to the regulatory authorities, the Sponsor or its designees may be required to collect further information for a detailed description and a final evaluation of the case, including copies of hospital reports, autopsy reports, or other relevant documents.

The Investigator, or Sponsor (or its designees) where applicable, will notify the relevant Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of any SAEs and safety reports according to local regulation requirements.

7.14. Pregnancy

All pregnancies that occur during the study must be reported to the Sponsor and followed to conclusion. The outcome of each pregnancy must be reported.

Pregnancy alone is not an AE, nor is an induced elective abortion to terminate a pregnancy without medical reason. However, an induced therapeutic abortion to terminate a pregnancy due to complications or medical reasons must be reported as an SAE. The underlying medical

diagnosis for this procedure should be reported as the SAE term. A spontaneous abortion is always considered an SAE.

7.15. Discontinuation or Withdrawal

The criteria for study entry and enrollment must be followed explicitly. If a subject who does not meet the study entry and enrollment criteria is inadvertently enrolled and study drug administration has been started, the Investigator should consult with the Sponsor or its designees regarding the termination or continuation of the study drug administration.

If study drug is discontinued, the subject will continue in the study and undergo all study assessments per the protocol in order to provide the follow-up data needed for the analysis of the entire intent-to-treat population. Investigator or delegated site personnel will make the effort to collect the necessary data per protocol; however, if the subject is to be completely off the study per the discretion of the subject, Investigator, or Sponsor, study procedures for Early Termination should be completed.

7.15.1. Discontinuation of Study Drug

Discontinuation of study drug administration is defined as termination of the study drug administration without the intent to re-administer at a later time.

Subjects will discontinue the study drug administration in the following circumstances:

- The Investigator decides that study drug should be discontinued. If this decision is made due to a serious or intolerable AE or a clinically significant change in a laboratory value, the study drug is to be discontinued and appropriate measures taken (refer to Section 7.1). The designated Medical Monitor is to be alerted.
- The subject stops taking study drug. If this decision is made because the subject's condition has worsened, the surgical team (doctor) and the designated Medical Monitor should be alerted immediately.

7.15.2. Withdrawal from the Study

In the event that the subject, the subject's legal representative, the Investigator, or the Sponsor decides that the subject should be withdrawn from the study, all scheduled study assessments will be discontinued.

A subject may decide to withdraw from the study at any time. If a subject refuses to take study drug, the subject should be withdrawn from study participation. If the subject did take a portion of the study drug, the subject should remain in the study unless consent is withdrawn.

The Sponsor or its designees must be alerted if a subject is withdrawn from the study. A subject will be withdrawn from the study in the following situations:

- The subject or the subject's legal representative withdraws consent.
- The subject did not take any portion of study drug prior to surgery.
- The Investigator or the Sponsor, for any reason, stops the subject's participation in the study.

7.15.3. Discontinuation of Study Sites

Study site participation may be discontinued if the Sponsor, Investigator, or the IRB or IEC of the study site judges it necessary for any reason.

7.15.4. Institutional Review Board/Independent Ethics Committee Approval

The study protocol and Informed Consent Form (ICF), as well as any amendments, will be approved by an IRB or IEC as necessary for each study site.

7.15.5. Discontinuation of the Study

The study will be discontinued if the Sponsor judges it necessary for any reason.

QUALITY CONTROL AND ASSURANCE

Study training will be held for all sites prior to first subject enrollment. To ensure accurate, complete, and reliable data, the Sponsor or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate.
- Conduct a start-up training session/Site Invitation Visit to instruct the Investigators and appropriate site staff. This session will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- Make periodic visits to the study site.
- Be available for consultation and stay in contact with the study site personnel by mail, email, telephone, and/or fax.
- Review and evaluate eCRF data and use standard computer edits and/or source verification to detect errors in data collection.
- Conduct a quality review of the study database.

In addition, the Sponsor or its representatives may periodically check subject data recorded against source documents at the study site. The study may be audited by the Sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of subjects in the study, and to ensure accurate, complete, and reliable data, the Investigator will keep records of laboratory tests, clinical notes, and subject medical records in the subject files as original source documents for the study. If requested, the Investigator will provide the Sponsor, applicable regulatory agencies, and applicable ethical review boards with direct access to original source documents and supporting study documentation.

PLANNED STATISTICAL METHODS

9.1. General Considerations

This study employs an adaptive clinical study design feature (interim analyses with possible sample size re-estimation). A comprehensive description of the statistical methods and analyses planned for this study will be provided in a Statistical Analysis Plan (SAP) prior to the planned interim analysis.

9.2. Determination of Sample Size

Although this study is not formally powered to detect a significant treatment effect, a sample size of 120 subjects is planned for enrollment/randomization and is considered adequate to establish proof-of-concept. The adaptive design of this study may allow for up to 200 total subjects enrolled at study completion.

9.3. Statistical Methods

Specific details about the statistical methods for all assessments, the treatment of missing data, and the method of control of the Type I error rate will be provided in the Statistical Analysis Plan (SAP).

9.3.1. Adhesions

Comparisons between the LB1148 and placebo groups with respect to change from baseline in extent and severity of intra-abdominal adhesions will be made using the Wilcoxon rank sum test.

9.3.2. Bowel Function

The primary efficacy analysis will be a time to event analysis (e.g., Cox proportional hazard model) with a main effect of treatment and stratified by surgery type (laparotomy versus minimally invasive approaches) and stoma (planned stoma versus no stoma). The p-values between the treatment groups will be evaluated using the Wald chi-square test. The magnitude of the treatment effect will be presented as the difference between the LB1148 and placebo arms in mean time to event (estimated by area under the Kaplan-Meier survival curve).

9.4. Interim Analysis

The interim analysis serves to inform the Sponsor about the assumptions that underlie the trial procedures, endpoints, and sample size. The interim analysis will be performed after enrollment of approximately 50-60 subjects. The decision rules for increasing the sample size as well as the clinical and statistical considerations required for proper control and minimization of bias will be provided in the SAP.

ADMINISTRATIVE CONSIDERATIONS

10.1. Regulatory Considerations

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCPs and the applicable laws and regulations. The Investigator, head of the medical institution, or designee will promptly submit the protocol to applicable ethical review boards.

LB1148 is being studied in the U.S. under an IND application. Study sites will include approximately up to 15 sites in the United States.

All or some of the obligations of the Sponsor will be assigned to CRO(s).

10.2. Institutional Review Board or Independent Ethics Committee Approval

The study protocol and ICF, as well as any amendments, will be approved by the appropriate ethical review board (IRB or IEC) prior to initiation of the study at a particular site. All subjects will sign an ICF prior to any study-specific procedures. Site performance during the study will be routinely monitored by a study monitor (refer to Section 10.7).

Documentation of ethical review board approval of the protocol and ICF must be provided to the Sponsor *before* the study may begin at the study sites. The IRB/IEC will review the protocol and ICF as required in accordance with the ICH GCP guidelines. Any member of the IRB/IEC who is directly affiliated with this study as an Investigator or as site personnel must abstain from the vote on the approval of the protocol.

10.3. Subject Information and Consent

Written informed consent must be obtained from each subject or legal representative designee if subject is unable to sign after the nature of the study has been fully explained in accordance with ICH GCPs. Informed consent must be obtained prior to performing any study-specific procedures.

The subject (or surrogate) and the individual explaining the study will sign the current IRB/IEC-approved version of the consent form. A copy of the signed ICF will be given to the subject. The date that consent was obtained will be recorded on the eCRF as well as in the subject's chart.

A copy of the IRB/IEC approved version of the consent form will be provided to the Sponsor. The original signed consent form must be maintained at the site and made available for inspection, as appropriate.

10.4. Subject Confidentiality

The anonymity of subjects participating in this study must be maintained. Subjects will be identified by their assigned subject number in all written communications between the Investigator and Sponsor or its designees. Site documents that are not submitted to the Sponsor or its designees and that identify the subject (e.g., signed informed consent; source documents/charts) will be made available to the Sponsor (or its designees) or regulatory authorities for inspections, but will be maintained in confidence.

All study-related information provided by the Sponsor or its designees to the Investigator and not previously published, including but not limited to the active study agent identity, the Investigator's Brochure, the study protocol, verbal and written communication, study data, assay methods and scientific data, will be considered confidential. In addition, all information developed during the conduct of the clinical investigation of the study agent is also considered confidential. Neither the Investigator nor any of his/her employees or agents shall disclose or use this information for any purpose other than the performance of the clinical study. Such information shall remain the confidential and proprietary property of the Sponsor, and disclosure to others will be limited to other physicians who are conducting studies with the same active study agent, the IRB/IEC, and the applicable regulatory authorities except by prior written permission of the Sponsor or its agents. At such time, that information becomes widely and publicly available through no fault of the Investigator, the obligation of nondisclosure toward that particular information will cease.

10.5. Case Report Forms and Study Records

Data collected through the completion of study procedures required by this protocol will be recorded in the subject's chart as source documentation. This data will then be transcribed onto the appropriate eCRFs.

All information in the eCRFs must be supported by original data in the subject's medical records. All medical records, laboratory printouts, notes made by the physician, and other materials will be considered source data and must be available for inspection by the Sponsor, the Sponsor's designees, or governmental representatives.

Appropriate site personnel training will occur prior to subject enrollment for the study. The Investigator remains responsible for the accuracy and adequacy of all study data.

Study data will be monitored as described in Section 10.6 and Section 10.7.

Upon further data processing, queries may be generated and sent to the Investigator for clarification or correction. The Investigator and/or delegated site personnel will address any queries and forward resolutions as directed by the site monitor.

10.6. Safety Monitoring

The Sponsor or their designated Medical Monitor will review blinded safety data throughout the course of the study. All SAEs will be reviewed within time frames mandated by company procedures and local regulatory requirements. The Sponsor or their designee will review safety trends and laboratory analytes at periodic intervals.

All deaths and SAE reports will be reviewed in a blinded manner by the Sponsor or its designee(s) during the study. These reports will be reviewed to assure completeness and accuracy, but will not be unblinded to the clinical team during the study. If a death or clinical AE is deemed serious, unexpected, and possibly related to study drug (refer to Section 0), only the Sponsor or its designees will be unblinded for regulatory reporting and safety monitoring purposes (refer to Section 5.5). The clinical site will have the ability to do an emergency code break on an individual subject at their site. These measures will preserve the integrity of the data collected during this study and minimize any potential for bias while providing for appropriate safety monitoring.

10.7. Protocol Deviations

Sites are responsible for abiding by their IRB rules and regulations for reporting protocol deviations. Additionally, the following important protocol deviations will be reported to the Sponsor:

- Subject did not meet study eligibility criteria
- Subject did not receive the correct treatment assignment
- Subject received the wrong amount of a dose IP (i.e., ± 20% of assigned dose)
- Subject received a prohibited concomitant medication
- Subject was not assessed for intra-abdominal adhesions

10.8. Study Monitoring and Access to Source Documentation

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the Investigator will keep records of laboratory tests, clinical notes, and subject medical records in the subject files as original source documents for the study. If requested, the Investigator will provide the Sponsor, applicable regulatory agencies, and applicable ethical review boards with direct access to original source documents.

The Sponsor or its designees (e.g., CRO) will assure the accuracy of data, the selection of qualified Investigators, appropriate study centers, and review protocol procedures with the Investigators and associated personnel prior to the study and during periodic monitoring visits. The Sponsor or its designee will review study data for accuracy and completeness during monitoring visits. Discrepancies will be resolved with the Investigator as appropriate.

The Sponsor or its designees will monitor the study using any of the following methods:

- Frequent telephone contacts;
- Email;
- Periodic site visits;
- Review of original subject records, eCRFs, study drug accountability, and
- Storage, and general study documentation.

So that the study may be adequately monitored, the Investigator or delegated site personnel will cooperate in providing the Sponsor or its designees with all study documents (e.g., subject charts and study files) and responding to inquiries that may arise as a result of the document review.

Review of these documents will usually occur during a routine monitoring visit, but may also be required during a visit by a quality assurance auditor. The Sponsor reserves the right to terminate the study if access to source documentation is denied to the Sponsor or quality assurance representatives.

10.9. Retention of Data

Source documents are the original documents, data, and records from which the subject's eCRF data are obtained. These include, but are not limited to, hospital records, clinical and office charts, laboratory and pharmacy records, radiographs and correspondence. eCRF entries may be considered source data if the eCRF is the site of the original data recording (i.e. no other written or electronic record of the data exists). All source documents and study documentation will be kept by the Investigator for the appropriate retention period as stipulated by the site IRB or FDA guidelines, whichever is longer.

Investigator shall retain study records required until **at least 2 years** after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. In the event that study records are relocated to a different location from the site location during this study retention period, Investigator must notify the Sponsor or its designees.

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Appendix 1 Schedule of Assessments Protocol LBS-POI-201

	Screening	Surgical	Post-Surgical				Follow-Up	Second Surgery
Study Day	**(-42 to -1 Days)[1,2]**	**Pre-Surgery / Surgery Day 0[2]**	**Post-Operative Days 1-6[3]**	**Post-Operative Day 7[3]**	**Post-Operative Days 8-14[3]**	**Hospital Discharge (Early Termination)**	**Day 30 (+7 Days)**	**Up to 8 Months after Day 0**
Informed Consent	X							
Surgery Assessment		X						X
Study Eligibility Assessment[4]	X	X[5]						
Demographics & Medical History[5]	X	X						
Concomitant Medication and Blood Products Review[5,6]	X	X	X	X	X	X		
Randomization[1]	X	X						
Taste Assessment		X						
Physical Exam[7]	X	X	X	X	X	X		
Vital Signs[8]	X	X	X	X	X	X		X
Study Drug Administration[2,9,10]	X	X						
Perioperative Surgical Preparation[11]	X	X						
Record Opioid Use	X	X	X	X	X	X		
Pain Assessment		X	X	X	X	X		X

Study Day	Screening (-42 to -1 Days)[1,2]	Surgical Pre-Surgery / Surgery Day 0[2]	Post-Surgical Post-Operative Days 1-6[3]	Post-Surgical Post-Operative Day 7[3]	Post-Surgical Post-Operative Days 8-14[3]	Post-Surgical Hospital Discharge (Early Termination)	Follow-Up Day 30 (+7 Days)	Second Surgery Up to 8 Months after Day 0
GI Function Assessment								
Nausea			X	X	X	X		
Vomiting or Retching			X	X	X	X		
Flatus[12]			X	X	X	X		
Stools[12]			X	X	X	X		
NG/OG Tube			X	X	X	X		
Liquid Diet[12]			X	X	X	X		
Solid Diet[12]			X	X	X	X		
Adhesions Count		X						X
Hospital Discharge								
Hospital Discharge Order Written			X	X	X	X		
Hospital Departure			X	X	X	X		
Subject's Willingness To Discharge			X	X	X	X		
Adverse Events (AE)	X	X	X	X	X	X	X[13]	X[14]
Local Laboratory Tests[15]								
Urine or Serum Pregnancy Test[4,5]	X	X						
Labs (CBC, coagulation, and metabolic)[15]	X		X	X				

Abbreviations: GI = gastrointestinal.

[1] Screening and Day 0 (Pre-Operative/Pre-Surgery) can be combined if the visit is on the day of first surgery. If this is the case, randomization will be performed during this study visit.

[2] Study Day 0 starts on the calendar day of the surgery; study dosing could occur Day -1 and/or up to 2 hours prior to surgery on Day 0.

[3] Subject will be monitored from Screening through Post-Operative Days 14 until Hospital Discharge or Study Termination (whichever occurs first).

[4] Eligibility assessment will include, if applicable, a negative pregnancy test.

[5] Document any changes to subject's condition that affect inclusion/exclusion criteria. Subject must meet all inclusion/exclusion criteria at time of the surgery. As part of medical history review, Caprini risk factor score will be calculated and tobacco use recorded.

[6] Concomitant medications taken within 14 days of randomization will be recorded during the Screening visit and through Post-Operative Day14 or Hospital Discharge or Study Termination (whichever comes first).

[7] Screening physical exam includes weight measurement and height measurements, lower extremity assessment to identify any clinical symptoms of VTE, assessment of venous port or venous catheter, varicose veins, superficial vein thrombosis, and BMI. Focused examinations include lower extremity assessment to identify any clinical symptoms of VTE and weight measurements from Day 0 through Post-Operative Days 14 until Hospital Discharge or Study Termination (whichever comes first).

[8] For data capture, use the vital signs (BP - systolic and diastolic measurements, HR, RR, oxygen saturation, and temperature) taken the closest to 0800 during the Surgical and Post-Surgical periods. For the re-operation Adhesion Evaluation, vitals should be recorded prior to surgery.

[9] The study drug (a total of 700 mL) is administered orally prior to surgery as a split dose. For the first study drug administration, subjects will consume 350 mL (at any rate of consumption) 6-10 hours prior to surgery. The second study drug administration, subject will consume the remaining 350 mL (at any rate of consumption) 2-6 hours prior to surgery. Note: There is no co-administration of food or drink with the study drug. Eating, bowel preparation, and drinking should be withheld 1 hour before and 1 hour after study drug administration.

[10] Please refer to Section 9.4 for information regarding possible changes to the study after interim analysis evaluation.

[11] Capture all perioperative items the subject was given or consumed, including but not limited to, mechanical bowel prep, nutritional supplements, carbohydrate drinks, opioids, and analgesia.

[12] For flatus and stool, record the first noted event; if subject experiences POI, record the next event of flatus, and/or stool until resolution. Diet changes (liquid, solid, NPO) will be monitored.

[13] Phone call for follow-up to gather any hospital readmission and vital status after initial hospital discharge information. Only readmissions (SAEs) should recorded and reported.

[14] Only AE/SAEs related to the surgical procedure will be recorded and reported.

[15] Refer to **Error! Reference source not found.** for a list of Laboratory Tests. Labs are collected on Screening and Post-Operative Day 3. Post-Operative Day 7 labs will only need to be performed only if subject is still hospitalized.

Appendix 2 List of Laboratory Tests

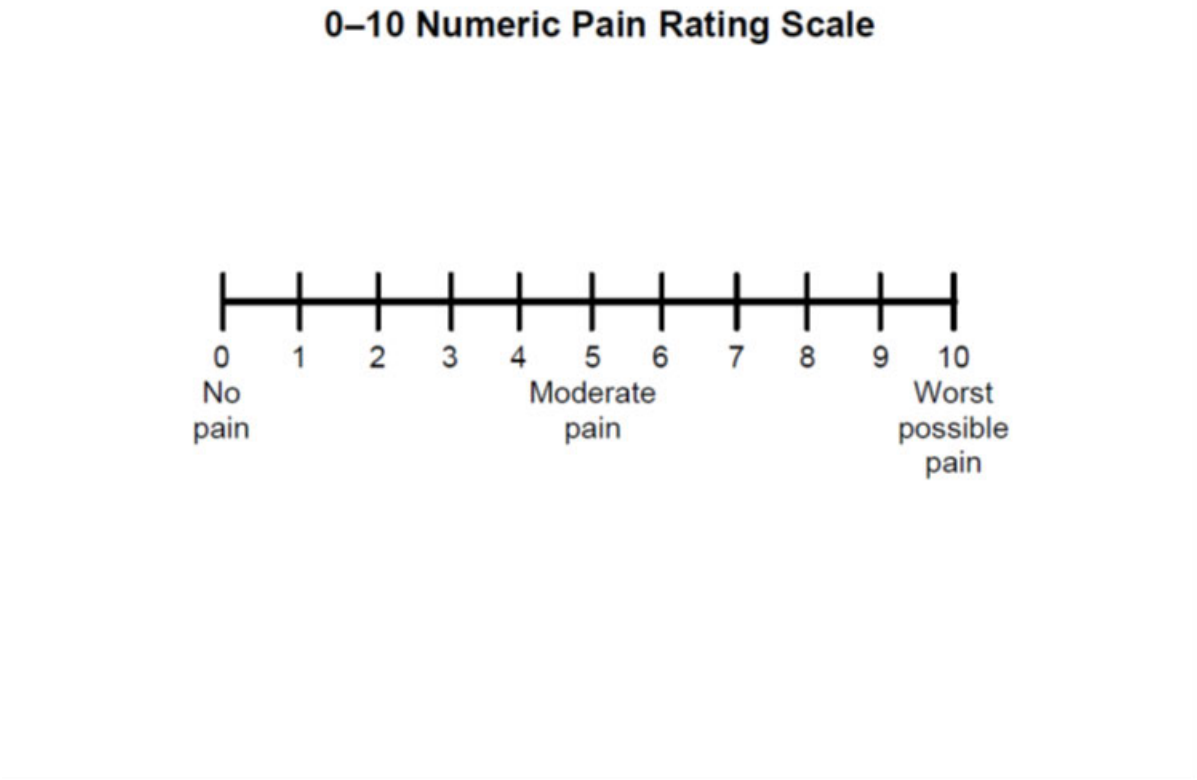
Hematology (CBC) without differential: Hematocrit (Hct) Hemoglobin (Hgb) Red blood cell (RBC) count White blood cell (WBC) count Liver Function Tests: Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Bilirubin Urine or serum human chorionic gonadotropin (hCG) – collected only at Screening and prior to Surgery (Day 0)	Basic Metabolic Panel (BMP): Serum chloride Creatinine Glucose Serum sodium Serum potassium Carbon dioxide (CO_2) Blood urea nitrogen (BUN) Coagulation: Partial Thromboplastin Time (PTT) Prothrombin Time and International Normalized Ratio (PT-INR)

Appendix 3 Nausea Verbal Rating Scoring (VRS) Scale

Score	Measure	Definition
0	None	No nausea
1	Anticipated	Nausea is anticipated and prophylaxis medications may be given.
2	Mild	Nausea reported. Able to tolerate food or medications by mouth.
3	Moderate	Nausea persisting. Lacks appetite. Able to eat small meals occasionally.
4	Great	Nausea ongoing. No appetite. Unable to tolerate food/medications by mouth.
5	Severe	Nausea with dry heaves reported.

Source: Halpin et al., 2010.

Appendix 4 Pain Scoring



Source: NPRS website.

Appendix 5 Intra-Abdominal Adhesion Extent and Severity Assessment Worksheet

Abdominal Regions	Abdominal Wall to Bowel Extent Score	Abdominal Wall to Bowel Severity Score	Bowel to Bowel (or Viscera) Extent Score	Bowel to Bowel (or Viscera) Severity Score
A Right upper				
B Epigastrium				
C Left upper				
D Left flank				
E Left lower				
F Pelvis				
G Right lower				
H Right flank				
I Central				

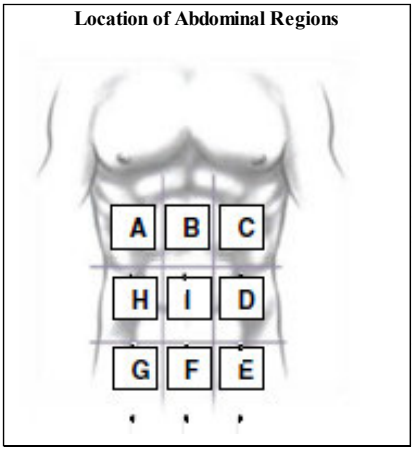
Adhesion Extent Score

0 = no adhesion
1 = minimal (<1/3 of the site is covered)
2 = moderate (1/3 to 2/3 of the site is covered)
3 = extensive (>2/3 of the site is covered)

Adhesion Severity Score

0 = no adhesions
1 = filmy thickness, avascular
2 = moderate thickness, limited vascularity
3 = dense thickness, vascularized

Location of Abdominal Regions



References: Coccolini et al., 2013, Dabrowski et al., 2016, and the Seprafilm Package Insert.

Appendix 6 American Society of Anesthesiologists Classification System

The ASA Physical Status Classification System was last approved by the ASA House of Delegates on 15 October 2014.

ASA PS Classification	Definition	Examples, including but not limited to:
ASA I	A normal healthy patient.	Healthy, non-smoking, no or minimal alcohol use.
ASA II	A patient with mild systemic disease.	Mild diseases only without substantive functional limitations. Examples: current smoker, social alcohol drinker, pregnancy, obesity (30< BMI <40), well controlled DM/HTN, mild lung disease.
ASA III	A patient with severe systemic disease.	Substantive functional limitations; One or more moderate to severe diseases. Examples: poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant post-conceptional age <60 weeks, history (>3 months) of MI, CVA, TIA, or CAD/stents.
ASA IV	A patient with severe systemic disease that is a constant threat to life.	Examples: recent (<3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis.
ASA V	A moribund patient who is not expected to survive without the operation.	Examples: ruptured abdominal/thoracic aneurysm; massive trauma; intracranial bleed with mass effect; ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction.
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes.	

Abbreviations: ARD = advanced renal disease; BMI = body mass index; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; DIC = disseminated intravascular coagulation; DM= diabetes mellitus; ESRD = end stage renal disease; HTN = hypertension; MI = myocardial infarction; TIA = transient ischemic attack.

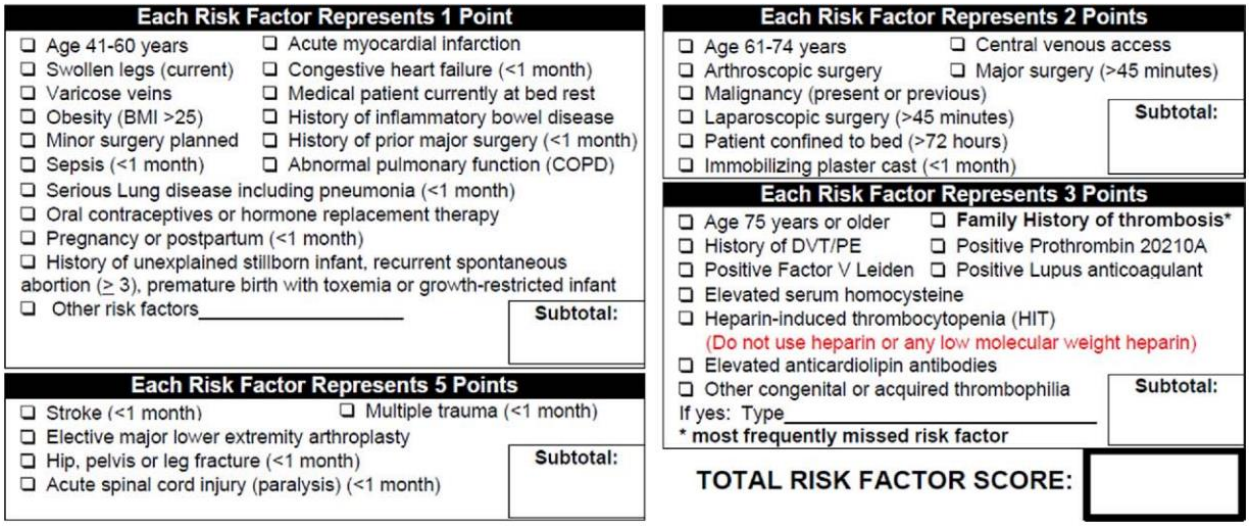
*The addition of "E" denotes Emergency surgery: An emergency is defined as existing when delay in treatment of the patient would lead to a significant increase in the threat to life or body part.

Source: ASA website.

Appendix 7 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)

The following is a link to the full CTCAE, v 5:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Appendix 8 American College of Chest Physicians (ACCP) Guidelines - Caprini Risk Factor Score



Each Risk Factor Represents 1 Point

- ❑ Age 41-60 years
- ❑ Swollen legs (current)
- ❑ Varicose veins
- ❑ Obesity (BMI >25)
- ❑ Minor surgery planned
- ❑ Sepsis (<1 month)
- ❑ Acute myocardial infarction
- ❑ Congestive heart failure (<1 month)
- ❑ Medical patient currently at bed rest
- ❑ History of inflammatory bowel disease
- ❑ History of prior major surgery (<1 month)
- ❑ Abnormal pulmonary function (COPD)
- ❑ Serious Lung disease including pneumonia (<1 month)
- ❑ Oral contraceptives or hormone replacement therapy
- ❑ Pregnancy or postpartum (<1 month)
- ❑ History of unexplained stillborn infant, recurrent spontaneous abortion (≥ 3), premature birth with toxemia or growth-restricted infant
- ❑ Other risk factors_____

Subtotal:

Each Risk Factor Represents 5 Points

- ❑ Stroke (<1 month)
- ❑ Multiple trauma (<1 month)
- ❑ Elective major lower extremity arthroplasty
- ❑ Hip, pelvis or leg fracture (<1 month)
- ❑ Acute spinal cord injury (paralysis) (<1 month)

Subtotal:

Each Risk Factor Represents 2 Points

- ❑ Age 61-74 years
- ❑ Arthroscopic surgery
- ❑ Malignancy (present or previous)
- ❑ Laparoscopic surgery (>45 minutes)
- ❑ Patient confined to bed (>72 hours)
- ❑ Immobilizing plaster cast (<1 month)
- ❑ Central venous access
- ❑ Major surgery (>45 minutes)

Subtotal:

Each Risk Factor Represents 3 Points

- ❑ Age 75 years or older
- ❑ History of DVT/PE
- ❑ Positive Factor V Leiden
- ❑ Elevated serum homocysteine
- ❑ Heparin-induced thrombocytopenia (HIT) (Do not use heparin or any low molecular weight heparin)
- ❑ Elevated anticardiolipin antibodies
- ❑ Other congenital or acquired thrombophilia
- ❑ **Family History of thrombosis***
- ❑ Positive Prothrombin 20210A
- ❑ Positive Lupus anticoagulant

If yes: Type_____

*** most frequently missed risk factor**

Subtotal:

TOTAL RISK FACTOR SCORE:

Abbreviations: BMI = Body Mass Index; COPD = Chronic Obstructive Pulmonary Disease; DVT = Deep Vein Thrombosis; PE = Pulmonary Embolism.

References: Bahl et al., 2010, Caprini et al., 2010, and Lobostov et al., 2015.

Appendix 9 Protocol Amendment Summary

Amendment #1 - 17 August 2016

Amendment 1 to the protocol includes revisions requested by FDA. Changes are summarized as follows:

- Assessments of respiratory rate and pluse oximetry were added to the vital signs to evaluate for respiratory signs associated with pulmonary embolism/thromboembolism.
- Specific venous thrombosis examinations were added to the schedule of study events,such as lower extremity examination for DVT and other clinical signs of venous thrombosis in major organs, such as cardiac, cerebral, pulmonary and GI.
- Exclusion criteria were updated to exclude patients with the following risk factors for thromboembolic disease: known medical history of thrombophilia (e.g. Factor V Leiden, prothrombin gene mutation); Stage IV malignant neoplasm; neurologic paresis, partial paralysis, or paralysis; pacemaker; and history of pulmonary embolism, deep vein thrombosis, cerebrovascular accident or rental venous/artierial occlusion.
- Exclusion critieria updated to exclue patients patients with a history of or current seizure disorder.
- Specific safety sub-analyses included to assess the safety of LB1148 in the following patient populations: patients who are on chemotherapy; patients with a venous port or catheter; patients with varicose veins and superficial vein thrombosis; patients with varying degrees of obesity; patients who are smokers; patients with varying degrees ofrenal function; and patient age groups, including 65-80 years old.
- Calculation of Caprini risk factor score during the medical history collection.
- Inclusion of weight measurements and lower extremity assessments to identify any clinical symptoms of venous thromboembolic.
- Inclusion of respiratory rate, oxygen saturation and pulse rate during vital sign collection.
- Adverse events to be evaluated with respect to severity using the National CancerInstitute Common Terminology criteria for Adverse Events grading system

Amendment #2 - 18 August 2016

Amendment 1 to the protocol includes revisions requested by FDA. Changes are summarized as follows:

- Exclusion criteria were updated to exclude patients with BMI >40.
- Exclusion criteria were updated to exclude patients with congenital or acquired thrombophilia such as, but not limited to, patients with sickle cell disease, nephrotic syndrome, Factor V Leiden, prothrombin gene mutation, Protein C or S deficiency, antithrombin III deficiency, and antiphospholipid syndrome.
- Exclusion criteria were updated to exclude patients with myeloproliferative disorders.

- Added assessment for risk factors of VTE to Demographics and Medical History.
- Added VTE prophylaxis to perioperative standardization of care.

Amendment #3 - 13 June 2019

Amendment 3 includes revisions to the study objectives and associated endpoints, as well as updates to perioperative care. The objectives were change to be in alignment with other key clinical studies, and the perioperative care requirements were updated to be in alignment with current standard of care. Changes are summarized as follows:

- The time (hours) to recovery of GI function as defined by achieving GI2 was moved from a secondary objective to a primary objective.
  - The associated endpoints for GI2 were moved to be primary endpoints.
- The previous primary objective was moved to a secondary objective (time [hours] from surgical closure to resolution or appearance, as appropriate, of 1 or more of the components common to GI dysfunction following elective bowel resection with or without a planned stoma).
  - The endpoints associated with GI dysfunction were moved to be secondary endpoints.
- The requirement for the use of acetaminophen and a planned morphine or fentanyl PCA were removed from the perioperative care requirements for what a subject must receive.
- The use of planned edidural anesthesia or TAP was removed from the perioperative care requirements for what a subject must **not** receive.

Amendment #4 – 17 June 2021

The overall purpose of the amendment is to:

- Change the primary endpoint from return of bowel function to extent and severity of adhesions
- Add a planned laproscopic surgery (second surgery) at Month 3 for the purpose of ostomy take down and/or adhesiolysis, and for the surgeon to determine the incidence, extent, and severity of adhesions.
- Make Adverse Events Assessments its own section (Section 7)
- Change the company name from Leading Biosciences, Inc. to Palisade Bio, Inc.
- Add the name and contact information of the Medical Monitor.
- Fix minor/administrative errors and inconsistencies.

Impact on the Informed Consent Form: the ICF will be updated to reflect the planned laproscopic surgery at Month 3.

Refer to the table below for a detailed list of changes.

Section	Change	Rationale
General	Changed company name from Leading Biosciences, Inc. to Palisade Bio, Inc. throughout the document	• Reflects new company name
Title Page	Changed sponsor name and contact information to that of the Medical Monitor	• Medical Monitor will be primary point of contact for the sponsor
Synopsis – Clinical Sites	• Changed North America and Europe to United States	• Study will be performed in the United States only
Synopsis – Primary Objective	• Changed to: "To compare the change from baseline in extent and severity of intra-abdominal adhesions among subjects treated with LB1148 or placebo."	• Made original exploratory objective the primary
Synopsis – Secondary Objectives	• Moved original primary objective to secondary: "Compare time from surgical closure to resolution or appearance, as appropriate, of 1 or more of the components common to gastrointestinal (GI) dysfunction following elective bowel resection with or without a planned stoma." • Added the following secondary objectives: o Compare the extent and severity of intra-abdominal adhesions following the second surgery among subjects treated with LB1148 or placebo. o Compare change from baseline in incidence, extent, and severity of intra-abdominal adhesions among subjects treated with LB1148 or placebo who had adhesions observed at the time of the first surgery. • Minor edits to clarify objectives	• Made original exploratory objective the primary • Additional analyses of adhesions
Synopsis – Exploratory Objectives	• Moved adhesion objective to primary • Removed language "For subjects who undergo a planned second abdominal reoperation, the	• NA • All subjects will now undergo second surgery

Section	Change	Rationale
	exploratory objectives of this study are to determine if LB1148 decreases…."	
Synopsis – Study Design	• Provided additional detail to the study design description • Specified timing of adhesion determination by surgeon • Added a second surgery for all subjects, regardless of presence of stoma: "Within 3 months (± 1 month) of enrollment, subjects will undergo a laproscopic surgery (second surgery) for the purpose of ostomy take down and/or adhesiolysis, the surgeon will determine the incidence, extent, and severity of adhesions."	• To specify procedures and timepoints • To provide specificity around timing of adhesion measurement • To obtain data for new primary endpoint
Synopsis – Inclusion Criteria	• Added: (2) "Willing to perform and comply with all study procedures including attending clinic visit as scheduled and completion of a second surgery for ostomy or adhesiolysis and to determine the presence of intra-abdominal adhesions."	• To ensure subjects agree to second surgery
Synopsis – Exclusion Criteria	• Added (14) "Planned use of 4% icodextrin (Adept®) or SEPRAFILM during the first surgery."	• Use of these devices could confound interpretation of adhesion analyses
Synopsis – Duration of Subject Participation	• Changed to a total of 5 months: screen through second surgery)	• All subjects will have a second surgery, therefore participation will be the same for all subjects
Synopsis – Efficacy Assessments	• Grouped by type (e.g., adhesion, bowel function) • Adhesions: added incidence • Bowel function: edited language for clarity • Added "Other Endpoints" category • Added "NOTE: Subjects may not be discharged until all of the following criteria are met:"	• For clarity • Will now include analysis of adhesion incidence • For clarity • For clarity • To ensure data for secondary endpoints are collected before discharge

Section	Change	Rationale
Synopsis – Safety Endpoints	• Added vital signs and move clinical laboratory results to first paragraph	• For clarity
Synopsis – Statistical Methods	• Added methods for analyzing adhesion data	• To provide methods for analyzing new primary endpoint
2. Study Obectives and Endpoints	• Added "Endpoints" to section title • Updated per changes described for the synopsis above for primary, secondary, exploratory objectives • Updated per changes described for the synopsis above for primary, secondary, other, and safety endpoints	• For clarity • See above • See above
3.1 Overall Study Design and Plan	• Updated per changes described for the synopsis above for study design • Revised schematic to show second surgery at Month 3 for adhesion assessment	• See above • To reflect change to timing of adhesion assessment
3.2 Rationale for Study Design, Control Group, and Perioperative Standardization	• Added rationale for laproscopic surgery at Month 3 for assessment of adhesions	• To support data collection for adhesion assessment
3.3 Study Duration and Dates	• Updated per changes described for the synopsis above for duration of subject participation	• See above
4.1 Study Population	• Changed North America and Europe to United States	• Study will be performed in the United States only
4.2 Inclusion Criteria	• Updated per changes described for the synopsis above for inclusion criteria	• See above
4.3 Exclusion Criteria	• Updated per changes described for the synopsis above for exclusion criteria	• See above
5.6 Concomitant Therapy	• Added prohibition of "Receive 4% icodextrin (Adept®) or SEPRAFILM during the first surgery"	• Use of these devices could confound interpretation of adhesion analyses

Section	Change	Rationale
Original 6.5 Second Surgical Reoperation Assessment	• Moved to Section 6.16 and combined with Adhesions Assessment	• All subjects will have second surgery for adhesion assessment
6.16 Adhesion Assessment (Day 0 and Month 3 ± 1 month	• ¶-1 Added timing and purpose of adhesion assessment at first and second surgeries • ¶-2 Removed assessment of adhesions at ostomy	• For clarity • To provide consistency in adhesion assessment among all subjects (not all will have ostomy)
Original 6.18	• Removed Adhesions Evaluation for Planned Second Reoperation	• Replaced with updated section 6.16
New Section 7 Adverse Events Assessments	• Separated out Adverse Events Assessmentst to it's own section • ¶-1 updated period of SAE reporting to first administration of study drug through Month 3 visit • ¶-2 Edited to reflect all subjects will have AEs/SAEs related to second surgery reported	• For clarity • To collect all SAEs, including hospital readmissions, through second surgery • For clarity
7.9 Adverse Event Reporting Period	• To make consistent with ¶-1 and 2, as described above	• For clarity
7.13 Reporting Serious or Unexpected Adverse Events	• Specified duration of reporting through Month 3 (second surgery)	• For consistency throughout section 7
9.3.1 Adhesions	• Added methods for analyzing adhesion data (9.3.1)	• To provide methods for analyzing new primary endpoint
10.1 Regulatory Considerations	• ¶-2 Changed North America and Europe to United States	• Study will be performed in the United States only
11 References	• Added: o Adept Package Insert o Brown, et al. 2007	• References relevant to second surgery
Appendix 1 – Schedule of Assessments	• Updated to relect Month 3 visit (second surgery) for all subjects • Edited footnote 14 to reflect AE/SAE reporting for second surgery	• To reflect changes to protocol text
Appendix 5 - Intra-Abdominal Adhesion Extent and	• Removed scoring for ostomy regions	• No longer scoring ostomy regions

Section	Change	Rationale
Severity Assessment Worksheet		
Appendix 7 - National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)	• Removed text and added hyperlink to the NCI-CTCAE website	• For clarity

Amendment #5 – 24 August 2021

The overall purpose of the amendment is to:

- Limit enrollment to only subjects who will undergo an elective (non-emergent) bowel resection with a planned stoma and a planned stoma takedown or other planned abdominal surgery within 8 months after the initial surgery
- Clarified Physical Exam procedure
- Added section on Pregnancy Reporting
- Added section on Protocol Deviations
- Removed references no longer referred to
- Corrected minor typographical errors

Impact on the Informed Consent Form: the ICF will be updated to reflect the changes to study population and planned second surgery

Refer to the table below for a detailed list of changes.

Section	Change	Rationale
Synopsis – Secondary Objectives	• Removed "or without"… a planned stoma	• Excluding subjects who will not have a planned stoma and therefore will not have a planned second surgery
Synopsis – Study Design	• Changed ¶1 to reflect that only subjects with planned stoma or other planned abdominal surgery will be enrolled	• Exclude subjects who will not have a planned stoma or other abdominal surgery and therefore will not have a planned second surgery
	• Changed ¶5 to address timing and purpose of second surgery	• This time period allows for a subject to undergo and recover from cancer treatment prior to a second surgery for stoma takedown

Section	Change	Rationale
Synopsis – Inclusion Criteria	• Criteria #1 – removed subjects without a planned stoma	• Exclude subjects who will not need a second surgery
	• Added criteria #2 for having a planned stoma takedown or other planned abdominal surgery (second surgery) within 8 months of the initial surgery	• To ensure subjects will be evaluable for adhesions
	• Added to criteria #3 "…or other abdominal surgery" • Removed "and/or adhesiolysis" from criteria #3	• Consistency with other criteria • No longer relevant
Synopsis – Duration of Subject Study Participation	• Changed from 5 months to "up to 10 months"	• To reflect change to timing in second surgery
2.1.2 Secondary Objectives	• Removed "or without"… a planned stoma	• As stated above
3.1 Overall Study Design and Plan	• Changed ¶1 to reflect that only subjects with planned stoma or other planned abdominal surgery will be enrolled	• As stated above
	• Changed ¶5 to address timing and purpose of second surgery	• As stated above
3.2. Rationale for Study Design, Control Group, and Perioperative Standardization	• Changed ¶1 to reflect that only subjects with planned stoma or other planned abdominal surgery will be enrolled	• As stated above
	• Removed rational for second surgery in non-stoma subjects	• No longer relevant
3.3. Study Duration and Dates	• Changed from 5 months to "up to10 months"	• As stated above
4.2 Inclusion Criteria	• Criteria #1 – removed subjects without a planned stoma	• As stated above
	• Added criteria #2 for having a planned stoma takedown or other planned abdominal surgery within 8 months of the initial surgery	• As stated above
	• Added to criteria #3 "…or other abdominal surgery" • Removed "and/or adhesiolysis" from criteria #3	• As stated above

Section	Change	Rationale
6.16 Adhesions Assessment	• Changed ¶5 from "at the Month 5-8 visit" to "At the second surgery"	• Consistency
6.3 Physical exam	• To modify type of physical exam performed at Screening (Complete) and from Days 0-Day 14/discharge from hospital (Focused)	• To better reflect standard of care and required safety assessments
6.16 Adhesion Assessment	• Change second assessment timing to 5-8 months (Section Title and ¶5)	• As stated above
7 Adverse Events	• Changed hospital readmission reporting period to the "second surgery" and removed "(Months 5-8)"	• Consistency
7.14 Pregnancy	• Added section to require reporting of pregnancies and clarify when a pregnancy is an AE	• Data were being collected but not stated in original protocol
10.7 Protocol Deviations	• Added definition of "important protocol deviations" and reporting requirements	• Not included in original protocol
11. References	• Removed ADEPT Package Insert and Brown reference	• No longer relevant
Appendix 1 – Schedule of Assessments	• Changed "Adhesion Evaluation" column header to "Second Surgery	• Adhesion Evaluation is required on Day 0 and second surgery
	• Changed timing of second surgery to "Up to 8 Months after Day 0"	• To reflect changes in amended protocol
	• Removed word "Complete" from physical exam row	• To reflect change in amended protocol

Amendment #6 – 26 August 2022

The overall purpose of the this amendment was to:

- Update the exclusion criteria to align this with the recently cleared phase 3 Return of Bowel Function clinical trial, IND #158008
- Update typographical errors
- Update Sponsor address

Refer to the table below for a detailed list of changes.

Section	Change	Rationale
Title Page	• Removed 'North America and Europe'and replaced with United States • Updated Sponsor address	• This was updated per Amendment 4 but was not updated on this page • This is Sponsor's current business address
Sponsor Signature	• Added [redacted] and removed [redacted]	• Reflects Sponsor's current process for protocol sign-off
Synopsis – Study Design	• Updated ¶2, 1st sentence to reflect when randomization should occur (Day -1 instead of Day 0)	• Reflects the timing per the Schedule of Assessments when the site should randomize a subject
Synopsis – Exclusion Criteria	• Removed exclusion 5 'insulin dependent diabetes mellitus' • Removed exclusion 8 'risk factors for thromboembolic events' • Removed exclusion 11 'body mass index (BMI) > 40' • Removed exclusion 16 'chronic opioid usage' • Added new exclusion 7 'has peritoneal carcinomatosis'	• For the removal of exclusion criteria 5, 7 and 11, these were removed to align this with the recently cleared phase 3 'INTEGRITY' clinical trial • Chronic opioid usage was removed as the study is enrolling only subjects that require a stoma and the primary endpoint is assessing adhesions per amendment 4 • Added exclusion criteria 7, has peritoneal carcinomatosis, as this would not be suitable subject to receive study drug
Synopsis – Perioperative Standardization of Care	• Removed NPO and updated with 'Anything by mouth'	• The lead-in sentence started with 'not' so removed the double negative
3.1 Overall Study Design and Plan	• Updated ¶2, 1st sentence to reflect when randomization should occur (Day -1 instead of Day 0)	• Reflects the timing per the Schedule of Assessments when the site should randomize a subject
3.2 Perioperative Standardization of Care	• Removed NPO and updated with 'Anything by mouth'	• The lead-in sentence started with 'not' so removed the double negative
4.3 Exclusion Criteria	• Removed exclusion 5 'insulin dependent diabetes mellitus' • Removed exclusion 8 'risk factors for thromboembolic events'	• For the removal of exclusion criteria 5, 7 and 11, these were removed to align this with the recently cleared phase 3 'INTEGRITY' clinical trial

Section	Change	Rationale
	• Removed exclusion 11 'body mass index (BMI) > 40' • Removed exclusion 16 'chronic opioid usage' • Added new exclusion 7 'has peritoneal carcinomatosis'	• Chronic opioid usage was removed as the study is enrolling only subjects that require a stoma and the primary endpoint is assessing adhesions per amendment 4 • Added exclusion criteria 7, has peritoneal carcinomatosis, as this would not be suitable subject to receive study drug
5.6 Concomitant Therapy	• Removed 'receive a planned epidural anesthesia or TAP block anesthesia	• This was updated per Amendment 3 but was not previously removed on this page
6.2 Demographic and Medical History	• Added to collect the subject's prior or current use of tobacco	• This was to be collected per the original protocol's Schedule of Assessments
6.3 Physical Examination	• Updated ¶1 to delineate height to collect at the Screening visit only • Updated ¶2 to delineate the focused physical exam	• This was the intent of the original protocol and updates were made for clarification when each assessment should be completed
6.6 Vital Signs	• Removed pulse rate	• The protocol is capturing heart rate so this is redundant
6.7.1 Pregnancy Test	• Removed the language after the 1st sentence	• Clarified when the pregnancy test, whether serum or urine, need to be completed
6.9 Perioperative Surgical Preparation	• Removed NPO and updated with 'Anything by mouth'	• The lead-in sentence started with 'not' so removed the double negative
6.12 Pain Assessment	• Updated last paragraph for when the first pain assessment should be collected	• Clarified when the first pain assessment should be collected post-surgery
Appendix 1 Schedule of Assessments	• Removed physical exam at the 2nd surgery • Removed collecting opiod use at the 2nd surgery • Removed collecting pregnancy test at the 2nd surgery • Updated footer note 4, 6, 7, and 9	• This prior protocol amendment 4 and 5 updates should have removed the physical exam, recording opioids and obtaining a pregnancy test at the 2nd surgery • Footers were updated for clarification and consistency
Appendix 2 List of Laboratory Tests	• Updated when the urine or serum hCG tests should be collected	• Clarified for consistency