Clinical Research Protocol

Minimally Invasive Thoracic Surgery Intercostal Nerve Block Trial

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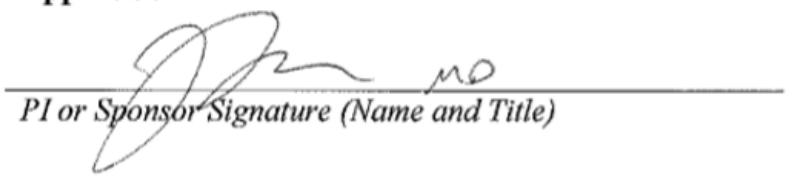
Coordinating Center:	UCSF Cardiothoracic Surgery

Approval:



PI or Sponsor Signature (Name and Title)

11/5/2019

Date

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PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: 18-25152

Protocol Title: Minimally Invasive Thoracic Surgery Intercostal Nerve Block Study

Protocol Date: 11/5/2019

Investigator Signature	11/5/2019 *Date*
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LIST OF ABBREVIATIONS

AE	Adverse event
CC	Cubic Centimeter
CFR	Code of Federal Regulations
CRF	Case report form
CT	Computed Tomography
DMC	Data Monitoring Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
IV	Intravenous Administration
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
KG	Kilogram
MG	Milligrams
MRI	Magnetic Resonance Imaging
PET-CT	Positron Emission Tomography-Computed Tomography
PI	Principal Investigator
PO	Oral Administration
SAE	Serious adverse experience

PROTOCOL SYNOPSIS

TITLE	Minimally Invasive Thoracic Surgery Intercostal Nerve Block Trial
SPONSOR	Sponsor-Investigator
FUNDING ORGANIZATION	Internal – UCSF Department of Surgery, Division of Cardiothoracic Surgery
NUMBER OF SITES	1
RATIONALE	Subjects who undergo minimally invasive lung surgery have postoperative surgical pain. Uncontrolled surgical pain of the chest wall can result in splinting, atelectasis, and pneumonia. The optimal strategy to manage surgical pain from minimally invasive thoracic surgery is unknown. With the development of Liposomal Bupivacaine, a sustained-release formulation of Standard Bupivacaine, there has been renewed interest in regional intercostal nerve blockade. While Standard Bupivacaine loses efficacy after 8 hours, Liposomal Bupivacaine has the potential efficacy of 96 hours. The trial data supporting Liposomal Bupivacaine were performed outside of thoracic surgery in local wound infiltration (not regional nerve blockage), and the data within thoracic surgery are limited and based upon observational studies.
STUDY DESIGN	Randomized, double-blind, active-comparator controlled clinical trial
PRIMARY OBJECTIVE	To assess the analgesic efficacy of intraoperative intercostal nerve block and wound infiltration by Liposomal Bupivacaine versus Standard Bupivacaine in subjects undergoing minimally invasive lung resection.
SECONDARY OBJECTIVES	To assess if there are changes in perioperative outcomes in intercostal nerve block by Standard Bupivacaine versus Liposomal Bupivacaine: pulmonary complications, length of stay, direct hospital costs, quality of life.
NUMBER OF SUBJECTS	80
SUBJECT SELECTION CRITERIA	Inclusion Criteria: - Robotic or video-assisted lung resection for all indications - Surgeons: Johannes R. Kratz MD, David M. Jablons MD, Melissa H. Coleman MD Exclusion Criteria: - Additional thoracic procedures and/or extra-thoracic procedures - Reported hypersensitivity to amide local analgesia - Cardiac Conduction Abnormalities

	- Hepatic Dysfunction - Renal Dysfunction - Preoperative Neuropathic Pain requiring tricyclic antidepressants or calcium channel alpha 2-delta ligands - Preoperative Daily Opioid Usage - <18 years of age
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	**Liposomal Bupivacaine** - 5cc of drug preparation will be percutaneously injected into each intercostal space 3-10 under direct intrathoracic vision and subcutaneously into each surgical wound at the conclusion of the surgery.
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	**Standard Bupivacaine** - 5cc of drug preparation will be percutaneously injected into each intercostal space 3-10 under direct intrathoracic vision and subcutaneously into each surgical wound at the conclusion of the surgery.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on study for up to 30 days following their surgery. **Screening:** Preoperative Clinic Visit **Treatment:** Conclusion of surgery (all subjects admitted to the hospital for standard postoperative care) **Follow Up:** Postoperative Clinic Visit The total duration of the study is expected to be 8 months.
CONCOMMITANT MEDICATIONS	Allowed: *Standardized Hospital Pain Medication Regimen* All subjects will receive a standardized postoperative pain regimen. Goal pain management is to allow the subject to ambulate and perform incentive spirometry per standard care. Escalation of opioid dosing if needed will be at the discretion of the inpatient surgery team. *Standardized Discharge Pain Medication Regimen* All subjects to be discharged on a standardized pain regimen. Prohibited: None
EFFICACY EVALUATIONS	
PRIMARY ENDPOINT	• Cumulative Daily In-Hospital Use of Opioids (morphine equivalents in mg)
SECONDARY ENDPOINTS	• Cumulative Daily In-Hospital Pain Score (0-10) • Mean Time to First Opioid Use (hours)

	• Mean Time to Ambulation (hours) • Pulmonary Complications (y/n) • Liposomal & Standard Bupivacaine Adverse Events (y/n) • Total Opioid Prescription at Discharge (morphine equivalents in mg) • Total Opioid Use as Outpatient (morphine equivalents in mg) • Length of Stay (days) • Direct Costs of Hospital Encounter (dollars) • Quality of Life: Short-Form-8 Health Survey
OTHER EVALUATIONS	n/a
SAFETY EVALUATIONS	- All subjects will be monitored with continuous cardiac telemetry throughout the entirety of their hospitalization. - Nursing staff will assess the mental status of each participant at the start of each shift. - Surgical wounds will be monitored daily by the surgery inpatient team. - The minimum duration of inpatient monitoring is 24 hours. For subjects that are discharged on POD1 after 24 hours of monitoring, a safety assessment will be performed on POD2. - Adverse events will be assessed continuously, starting with the first patient enrollment and until study completion, and will be immediately reported to the Medical Monitor. - Serious and severe adverse events, regardless of causality, will be followed until resolution or stabilization. - Subjects will be discharged with specialized discharge instructions to alert them of potential adverse effects and instruct them when to call the clinic.
PLANNED INTERIM ANALYSES	When the study has reached 1/3 and 2/3 goal enrollment, interim analysis for safety will be conducted by an independent data monitoring committee. Serious and severe adverse events will be monitored by the committee on an ongoing basis throughout the study.
STATISTICS **Primary Analysis Plan & Rationale**	Null Hypothesis: There is no difference in cumulative daily in-hospital use of opioids in subjects who receive intercostal nerve block and wound infiltration with Liposomal Bupivacaine or Standard Bupivacaine during minimally invasive lung resection. Statistical Method: Student's t-test. Rationale: 80 subjects will provide 80% power to detect a statistically significant effect with 2-sided alpha error set at 0.05 if the measured effect is 19% absolute reduction in cumulative daily in-hospital use of opioids.

	The mean cumulative daily in-hospital usage of opioids is 35mg morphine equivalents with standard deviation of 12mg. This was estimated by review of previously published studies and corroboration with UCSF clinical practice patterns. A 19% reduction in cumulative daily in-hospital use of opioids corresponds to 1 fewer oxycodone dose per day, which was considered clinically significant.

1 BACKGROUND

In the study, subjects undergoing minimally invasive lung surgery will receive a one-time intraoperative intercostal nerve block and wound infiltration with Standard Bupivacaine or Liposomal Bupivacaine.

Standard Bupivacaine

Standard Bupivacaine (*Marcaine*®; Hospira Inc; Lake Forest, IL) is an amide local anesthetic that is commonly used in the operating room for wound infiltration and regional nerve block. Onset of action is 5-10 minutes and duration is up to 8 hours [1].

Liposomal Bupivacaine

Liposomal Bupivacaine (*Exparel*®; Pacira Pharmaceuticals Inc; Parsippany, NJ) is a sustained-release formulation of Standard Bupivacaine [2]. Onset of action is within 10 minutes and duration is up to 96 hours [3]. Liposomal Bupivacaine is FDA-approved for single-dose infiltration into the surgical site to produce postsurgical analgesia since 2015 and brachial plexus regional nerve block since 2018. In clinical practice and research, it is also being used off-label for other forms of regional nerve block (including intercostal nerve block). Liposomal Bupivacaine is being used at UCSF for all procedures associated with an enhanced recovery program, which includes thoracic surgery.

1.1 Overview of Non-Clinical Studies

Liposomal Bupivacaine is a novel formulation of Standard Bupivacaine that is designed to provide sustained-release. Multivesicular liposomes release Standard Bupivacaine over an extended period of time due to diffusion, lipid membrane erosion, and lipid membrane reorganization [4]. 266mg Liposomal Bupivacaine (planned dose for the study) reaches peak plasma levels at 12 hours and levels can be detected up to 96 hours after administration. About 3% of the Liposomal Bupivacaine formulation contains extra-liposomal Standard Bupivacaine to provide immediate analgesic coverage until there is adequate liposomal release [3]. The active component Standard Bupivacaine is an amide local anesthetic that binds the voltage-gated sodium channels of the neuron and inhibits conduction of pain. Standard Bupivacaine is metabolized in the liver by cytochrome P450 and excreted by the kidneys [5]. The remnant liposomes and lipid membranes slowly degrade and are eliminated through systemic absorption [4].

1.2 Overview of Clinical Studies

Liposomal Bupivacaine has been studied in a variety of surgical specialties in both wound infiltration and regional nerve block. Comparison of studies is limited by different surgical procedures, placebo versus active control, and varied primary and secondary outcomes.

The initial trials of Liposomal Bupivacaine were in wound infiltration [6]. In comparison to placebo, subjects undergoing hemorrhoidectomy had lower cumulative pain score and lower cumulative opioid consumption in the first 72 hours after surgery [7]. In comparison to Standard Bupivacaine, subjects undergoing breast augmentation had lower mean pain score at 12 hours and no difference for the remaining hospital stay [8]. Subsequent trials have evaluated Liposomal Bupivacaine in regional nerve block [9]. In

comparison to Standard Bupivacaine, subjects undergoing robotic-assisted hysterectomy with abdominal wall nerve block had lower cumulative opioid use in the first 72 hours after surgery and subjects undergoing shoulder arthroplasty had reduced pain scores and opioid consumption in the first 48 hours [10, 11]. The most common adverse events associated with Liposomal Bupivacaine from these studies were nausea, emesis, and/or constipation. Cardiac and neurologic toxicity were not reported [6, 9].

Liposomal Bupivacaine is FDA-approved for single-dose infiltration into the surgical site to produce postsurgical analgesia since 2015 and brachial plexus regional nerve block since 2018. In clinical practice and research, it is also being used off-label for other forms of regional nerve block (including intercostal nerve block).

In thoracic surgery, there are two published studies that were both observational and retrospective. They evaluated intercostal nerve block versus epidural analgesia in subjects undergoing lung resection by both thoracotomy and minimally invasive techniques [12, 13]. Rice et al showed that there was no difference in pain scores, opioid use, or postoperative complications between groups. However, Khalil et al showed that there were lower mean pain scores on postoperative day one and three, no difference in opioid usage, and lower pulmonary complications in subjects that received Liposomal Bupivacaine [**Error! Bookmark not defined.**]. There is also an unpublished randomized, placebo-controlled trial in subjects that underwent thoracotomy and intercostal nerve block. They did not find a difference in pain scores or total opioid consumption.

There are currently three registered clinical trials at ClinicalTrials.gov evaluating Liposomal Bupivacaine in lung resection surgery. The Mayo Clinic is performing a non-inferiority trial of epidural analgesia versus intercostal nerve block with Liposomal Bupivacaine in subjects undergoing open lung resection [14]. Inova Health Care Services is performing a trial assessing local wound infiltration with Liposomal Bupivacaine versus Standard Bupivacaine in subjects undergoing thoracoscopy [15]. Massachusetts General Hospital is performing a trial evaluating intercostal nerve block with Liposomal Bupivacaine, Standard Bupivacaine, Standard Bupivacaine with epinephrine, and normal saline in subjects undergoing video-assisted lung resection [16]. Each of these studies address questions different from this proposal. Moreover, the results from these studies are not expected within the next year.

2 STUDY RATIONALE

Subjects who undergo minimally invasive thoracic surgery have acute, postoperative surgical pain. Uncontrolled surgical pain of the chest wall can result in splinting, atelectasis, and pneumonia [17]. There are a variety of multimodality analgesic strategies currently employed in the clinical setting; however, the optimal strategy to provide analgesia while minimizing analgesic-related complications is unknown. With the development of Liposomal Bupivacaine, a sustained-release formulation of Standard Bupivacaine, there has been renewed interest in regional intercostal nerve blockade.

Currently, most centers utilize some combination of epidural analgesia, systemic opioids, acetaminophen, nonsteroidal anti-inflammatory drugs, and gabapentin [18]. While this approach has proven effective, systemic opioids and epidural analgesia have many limitations. In the hospital, over 15% of patients receiving oxycodone will experience

altered mental status, nausea, or constipation [19]. In addition, it is essential to investigate other pain control strategies in consideration of the ongoing opioid abuse epidemic [20]. In regard to epidural analgesia, its placement is operator dependent, is limited by subject habitus, cannot be used in subjects on antiplatelets or anticoagulants, requires frequent postoperative monitoring, is associated with postoperative hypotension and urinary retention, and can result in epidural hematomas and abscesses that can be life-threatening [21, 22].

Intercostal nerve blockage with Liposomal Bupivacaine is an alluring alternative analgesic strategy as it is a sustained-release formulation of Standard Bupivacaine. Standard Bupivacaine loses efficacy after 8 hours, but Liposomal Bupivacaine has the potential efficacy of 96 hours [3]. Liposomal Bupivacaine is FDA-approved for single-dose infiltration into the surgical site to produce postsurgical analgesia since 2015 and brachial plexus regional nerve block since 2018. Its use for other forms of regional nerve block (including intercostal nerve block) is considered off-label.

Liposomal Bupivacaine is being used for local wound infiltration and regional nerve blocks across the surgical subspecialties, including thoracic surgery. The actual volume and breakdown of use in thoracic surgery is unknown; nonetheless, over the half the audience at the Society of Thoracic Surgery Annual Conference in January 2018 indicated that they routinely used Liposomal Bupivacaine in their practice. However, there is a clear deficit in data for thoracic surgery. There have been only two observational studies within thoracic surgery [12, 13]. They compared Liposomal Bupivacaine to epidural analgesia and found equivalence between the techniques. The results from these studies are subject to systematic error with selection bias and confounding. In addition, as the proportion of minimally invasive to open surgery has increased with the use of robotic-assisted thoracic surgery [23], many centers have eliminated epidural analgesia for the aforementioned reasons and the more pertinent question is Liposomal Bupivacaine versus Standard Bupivacaine.

As discussed in Section 1.2, there are ongoing trials that will provide less biased evidence in thoracic surgery assessing both local wound infiltration and intercostal nerve block with Liposomal Bupivacaine. The Minimally Invasive Thoracic Surgery Intercostal Nerve Block Study is unique, because it will assess intercostal nerve block and wound infiltration with Standard Bupivacaine and Liposomal Bupivacaine in both video-assisted and robotic-assisted lung resection.

A final consideration is the economic impact of Liposomal Bupivacaine. The direct costs of Liposomal Bupivacaine are 100 times the costs of Standard Bupivacaine, and at UCSF, the direct costs of Liposomal Bupivacaine are $340 [24]. If Liposomal Bupivacaine is found to be efficacious, there could be cost savings through a reduction in use of other pain medications and postoperative complications. Alternatively, if Liposomal Bupivacaine is not found to be efficacious, it will only add to the economic burden on the health care system.

2.1 Risk / Benefit Assessment

The risks associated with Liposomal Bupivacaine and Standard Bupivacaine are similar. The most common adverse events include nausea, emesis, and/or constipation and are

expected to occur in >10% of subjects. Less common adverse events include dizziness, altered mental status, and hypersensitivity reactions with urticaria and/or pruritis. Very rare, but serious adverse events include neurologic toxicity with seizures and apnea, cardiac toxicity with atrioventricular nodal conduction abnormalities and cardiac arrest, and hypersensitivity reaction with anaphylaxis. Serious adverse events can be preventable with appropriate education, dosing, and administration. Most serious adverse events are found to be dose-related due to improper intravascular injection, inappropriate dosing, or slow metabolic degradation in patients with hepatic dysfunction [6]. For more information regarding adverse events, see prescribing information [2].

To minimize risk and limit the occurrence of serious adverse events, subjects will not be eligible for the study if they have evidence of hepatic dysfunction. In the operating room, dosing of Standard Bupivacaine will be based upon subject weight (See Section 8.3.2). The medication will be administered with proper technique by drawing back before injection to ensure the tip of the needle is not located within the lumen of a blood vessel. On the hospital ward, continuous cardiac telemetry will be used on all subjects and nursing will assess the mental status of each subject per shift.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to assess the analgesic efficacy of intercostal nerve block and wound infiltration by Liposomal Bupivacaine versus Standard Bupivacaine in subjects undergoing minimally invasive lung resection by robotic or video-assisted thoracoscopic surgery.

3.2 Secondary Objectives

The secondary objective is to assess if analgesia from the aforementioned interventions improve perioperative outcomes with reduction in pulmonary complications, length of stay, and direct hospital costs as well as improvement in quality of life.

4 STUDY DESIGN

4.1 Study Overview

This is a single center, double-blind, randomized, active-comparator controlled clinical trial. 80 subjects undergoing minimally invasive lung resection will be randomly assigned to one of two study groups: a one-time intraoperative intercostal nerve block and wound infiltration by Standard Bupivacaine or by Liposomal Bupivacaine. Each subject will receive standardized postoperative pain management. Evaluations will be taken at three-time points - preoperative clinic visit, index hospitalization following surgery, and postoperative clinic visit. Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study. Total duration of subject participation will be 30 days. Total duration of the study is expected to be 8 months. The treatment regimens are outlined below.

Study Treatment - *Liposomal Bupivacaine*

- 5cc of prepared drug will be percutaneously injected into each intercostal space 3-10 with a 22-gauge spinal needle under direct intrathoracic vision and subcutaneously into each wound at the conclusion of the surgery.

Active Comparator - *Standard Bupivacaine*

- 5cc of prepared drug will be percutaneously injected into each intercostal space 3-10 with a 22-gauge spinal needle under direct intrathoracic vision and subcutaneously into each wound at the conclusion of the surgery.

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

- Cumulative Daily In-Hospital Use of Opioids measured in mg of Oral Morphine Equivalents

The subjective sensation of pain is challenging to measure. Cumulative daily in-hospital opioid use measured in mg of oral morphine equivalents acts as a surrogate endpoint of pain and is commonly used in the literature. It provides objective data that are recorded on every subject in the medication administration record.

5.2 Secondary Efficacy Endpoints

- Cumulative Daily In-Hospital Pain Score: 0 (no pain) – 10 (most pain)

Pain Scores are a measure of the subject's postoperative pain that are recorded every four hours by the nursing staff. They are limited by the subject's perception of pain, concomitant pain medication use, and correlation with an abstract scaling system.

- Mean Time to First Opioid Use (hours)

Time to first opioid use is a surrogate marker of postoperative pain. It is limited by variations in anesthesiologist intraoperative analgesia techniques.

- Mean Time to Ambulation (hours)

Time to ambulation is a downstream marker of postoperative pain control. Ambulation is limited by subject motivation and/or physical disability.

- Pulmonary Complications: Pneumonia and Atelectasis requiring Bronchoscopy (y/n)

Pulmonary complications are a downstream marker of postoperative pain control as subjects with chest wall postoperative pain commonly splint with respiration. Splinting is associated with atelectasis and pneumonia.

- Liposomal Bupivacaine and Stand Bupivacaine Adverse Events (y/n):
  - Gastrointestinal- nausea, emesis, constipation
  - Hypersensitivity- pruritis, urticaria, anaphylaxis
  - Cardiac- atrioventricular heart block, cardiac arrest

- Neurologic- dizziness, altered mental status, seizure
- Miscellaneous

To assess if there are differences in the complications between the study groups.

- Length of Stay (days)

Length of stay in the hospital can be used as downstream marker of overall postoperative course. It is limited by attending practice patterns.

- Total Opioid Prescription at Discharge (morphine equivalents in mg)

To assess if there are differences in the amount of opioid prescribed at discharge.

- Total Opioid Use as Outpatient (morphine equivalents in mg)

To assess if there are differences in the amount of opioid used after discharge.

- Direct Costs of Hospital Encounter (dollars)

The interventions in the study add costs over standard of care. It is important to evaluate the burden on the health care system in addition to subject outcomes.

- Quality of Life: Short-Form-8 Health Survey (Rand Health)

A change in quality of life before and after surgery will assessed. This survey is limited by subject adherence to completion.

5.3 Safety Evaluations

All subjects will be monitored for cardiac arrhythmias with continuous cardiac telemetry throughout the entirety of their hospitalization per standard postoperative care. If cardiac arrhythmias occur, they will be managed by the surgery inpatient team and cardiology consultation if deemed necessary.

The mental status of each subject will be assessed daily by the surgery inpatient team and each shift (every 12 hours) by the nursing staff. Workup and management of altered mental status is at the discretion of the surgery team.

Surgical wounds will be monitored daily by the surgery inpatient team and each shift (every 12 hours) by the nursing staff. Evidence of hypersensitivity reaction will be treated with observation, antihistamines, and/or epinephrine depending upon the severity of reaction.

The minimum duration of inpatient monitoring is 24 hours. For subjects that are discharged on POD1 after 24 hours of monitoring, a safety assessment will be performed by telephone on POD2. If subject answers "Yes" to any of the questions, the subject will be brought into clinic for further evaluation. See *POD2 Safety Assessment* below for more information.

Adverse events will be assessed continuously, starting with the first patient enrollment and until study completion, and will be immediately reported to the Medical Monitor. Serious and severe adverse events, regardless of causality, will be followed until resolution or stabilization per Section 11 below.

Subjects will be discharged with specialized discharge instructions to alert them of potential adverse effects and instruct them when to call the clinic.

POD2 Safety Assessment

The safety assessment will be conducted over the phone on POD2 for subjects that were discharged on POD1. If the subject answers "yes" to any of these questions, the event will be recorded as an AE and the patient will be brought into clinic for further evaluation.

- Is the subject oriented?

  _ Yes _ No _ Not Assessable

- Since your last assessment have you had numbness of the lips, the tongue, or around the mouth?

  _ Yes _ No

- Since your last assessment have you had a metallic taste in your mouth?

  _ Yes _ No

- Since your last assessment, have you had problems with your hearing not related to the use of a hearing aid?

  _ Yes _ No

- Since your last assessment, have you had problems with your vision not related to the use of eye glasses?

  _ Yes _ No

- Since your last assessment, have your muscles been twitching?

_ Yes _ No

- Since your last assessment, have you had heart palpitations in which you can feel your heart beating irregularly?

  _ Yes _ No

6 SUBJECT SELECTION

6.1 Study Population

Subjects who are planned to undergo minimally invasive lung resection and meet the inclusion and exclusion criteria will be eligible for participation in this study. Of note, subjects with non-English proficiency will be eligible for participation in this study: Spanish, Cantonese, Mandarin, Russian. These subjects will be provided written Consent, Experimental Subject's Bill of Rights, and HIPAA Authorization in their preferred language with use of a Qualified Interpreter.

6.2 Inclusion Criteria

1. Robot or video-assisted lung resection for all indications

   Robotic or video-assisted techniques both use three to four incisions that are <15mm and there are no expected differences between the techniques. The indication for surgery is not expected to influence the primary outcome.

2. Surgeons: David M. Jablons MD, Melissa H. Coleman MD, or Johannes R. Kratz MD
3. Written informed consent obtained from subject or subject's legal representative and ability for subject to comply with the requirements of the study.

6.3 Exclusion Criteria

1. Additional thoracic procedures performed beyond lung resection and mediastinal lymphadenectomy (such as chest wall resection, rib resection, muscle flap, etc) and/or extra-thoracic procedures (such as abdominal surgery, neck surgery, etc).

   Additional procedures will alter postoperative course and postoperative pain.

2. Reported hypersensitivity to amide local analgesia (such as lidocaine, bupivacaine, ropivacaine).
3. Reported Cardiac Conduction Abnormalities (Wolf-Parkinson-White, second degree Mobitz II or third degree atrioventricular heart block).

   Amide local analgesia can cause heart block and/or cardiac arrest.

4. Hepatic Dysfunction defined as cirrhosis complicated by ascites, esophageal varices, or hepatic encephalopathy determined by preoperative history and physical.

   Amide local analgesia is metabolized by the liver.

5. Renal Dysfunction requiring hemodialysis or peritoneal dialysis determined by preoperative history and physical.

   Amide local analgesia excreted by the kidneys.

6. Preoperative Neuropathic Pain requiring tricyclic antidepressants or calcium channel alpha 2-delta ligands (gabapentin, pregabalin).

   To compare subjects without preoperative neuropathic pain.

7. Preoperative Daily Opioid Usage.

   To compare subjects without preoperative pain requiring opioids.

8. Pregnant or breastfeeding during participation in the study.

   Subjects not eligible for surgery or the study.

9. <18 years of age.

10. Presence of a condition or abnormality that in the opinion of the investigator would compromise the safety of the patient or the quality of the data.

7 CONCURRENT MEDICATIONS

Intraoperative analgesia provided by the anesthesia team will not be altered and will be performed per standard care. All subjects will be started on the same postoperative pain medications in the hospital and when discharged as outlined in Section 7.1.

7.1 Allowed Medications and Treatments

Standardized Hospital Pain Medication Regimen:

Medication will not be given if there is known allergy. Goal pain management is to allow the subject to ambulate and perform incentive spirometry per standard of care. Escalation of opioid dosing if needed will be at the discretion of the inpatient surgery team.

- PO Tylenol 1000mg every 6 hours
- PO Gabapentin 300mg twice a day
- IV Ketorolac 15mg every 6 hours for 24 hours, then PO Diclofenac 50mg BID (if <75 years old and normal renal function)
- PO Oxycodone 5-10mg every 4 hours as needed for moderate pain
- IV Hydromorphone 0.2-0.4mg every 2 hours as needed for severe pain

Standardized Discharge Pain Medication Regimen:

All subjects to be discharged on the following pain regimen outlined below. Medication will not be given if there is known allergy.

- PO Acetaminophen 1000mg every 6 hours for 2 weeks
- PO Gabapentin 300mg twice a day for 2 weeks
- PO Diclofenac 50mg BID for 2 weeks
- PO Oxycodone as needed for pain – 20 Pills in Total

8 STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

80 eligible subjects will be randomly assigned to intraoperative intercostal nerve blocks and wound infiltration by Standard Bupivacaine or Liposomal Bupivacaine in a 1:1 ratio with varying block size (4-8) using Stata 15.1 (College Station, TX) ralloc.ado package. When the subject arrives in the operating room, the surgeon/study doctor will contact the pharmacy who will determine treatment assignment and prepare the medication as outlined in Sections 8.3-8.4.

8.2 Blinding

All patients will be blinded to the treatment groups as they will receive the one-time treatment while under general anesthesia in the operating room.

All study staff will be blinded to the treatment groups, except those staff involved in assigning treatment groups. Access to the randomization code will be strictly controlled. The study blind will be broken on completion of the clinical study and after the study database has been locked.

Investigators will be blinded to the medical treatment groups - Standard Bupivacaine and Liposomal Bupivacaine. As Standard Bupivacaine is clear and Liposomal Bupivacaine is milky white, obscuring over-wraps will be placed over syringe. See Section 8.3-8.3.2 for more information.

During the study, the blind may be broken only in emergencies when knowledge of the patient's treatment group is necessary for further patient management. If this occurs, the investigator will contact the study staff involved in assigning treatment groups, and the blind will be broken. When possible, the investigator should discuss the emergency with the Medical Monitor prior to unblinding.

8.3 Formulation of Test and Control Products

Study Treatment

Liposomal Bupivacaine - Exparel®

- Manufacturer: Pacira Pharmaceuticals Inc - Parsippany, NJ
- Formulation: Suspension, Injection
- Preparation: See Section 8.3.1

Active Comparator

Standard Bupivacaine - Marcaine®

- Manufacturer: Hospira Inc - Lake Forest, IL
- Formulation: Suspension, Injection
- Preparation: See Section 8.3.2

The study treatment and active comparator will be prepared by the Investigational Pharmacy under aseptic conditions and used within 24 hours.

8.3.1 Formulation of Test Product (See Table 1 in Section 8.3.2)

Liposomal Bupivacaine

- Drug Preparation: 266mg (20cc) Liposomal Bupivacaine admixed with 0.25% (2.5mg/cc) Standard Bupivacaine* and varied 0.9% normal saline volume for total volume of 60cc.
    - 266mg (20cc) Liposomal Bupivacaine is the FDA-approved dose for wound infiltration.
    - Standard Bupivacaine is added to bridge the time to efficacy of Liposomal Bupivacaine, which occurs in 6-8 hours. This is standard clinical practice.
    - Normal saline is used to the dilute the drug in order to have sufficient volume to perform the intervention.
    - As Standard Bupivacaine is clear and Liposomal Bupivacaine is milky white, obscuring over-wraps will be placed over syringe.

  *If subject weight ≥35kg, 30cc Standard Bupivacaine will be used. If subject weight <35kg, maximum dose of 2mg/kg Standard Bupivacaine will be used.

8.3.2 Formulation of Control Product

Standard Bupivacaine

- Drug Preparation: 0.25% (2.5mg/cc) Standard Bupivacaine* admixed with varied 0.9% normal saline volume for total volume of 60cc.
    - Normal saline is used to the dilute the drug in order to have sufficient volume to perform the intervention.
    - As Standard Bupivacaine is clear and Liposomal Bupivacaine is milky white, obscuring over-wraps will be placed over syringe.

  *If subject weight ≥35kg, 30cc Standard Bupivacaine will be used. If subject weight <35kg, maximum dose of 2mg/kg Standard Bupivacaine will be used.

Table 1: Drug Preparation

	Liposomal Bupivacaine	**0.25% Standard Bupivacaine**
Active Ingredient: cc (mg)	20 (266)	30 (75)*
0.9 % Normal Saline: cc	10	30
0.25% Standard Bupivacaine: cc (mg)	30 (75)*	n/a

* If subject weight <35kg, maximum dose of 2mg/kg will be used.

8.3.3 Packaging and Labeling

Study drugs (Liposomal Bupivacaine and Standard Bupivacaine) will be labeled with the required FDA warning statement, the protocol number, the subject number, and directions for use. As Standard Bupivacaine is clear and Liposomal Bupivacaine is milky white, obscuring over-wraps will be placed over syringe. The inpatient pharmacy will prepare and deliver the drug to the operating room.

8.4 Supply of Study Drug at the Site

Study drugs (Liposomal Bupivacaine and Standard Bupivacaine) are already stocked and available at the inpatient pharmacy for use in the operating room.

8.4.1 Dosage/Dosage Regimen

See Sections 8.3.1 and 8.3.2 for Drug Preparation.

Liposomal Bupivacaine

- 5cc of drug preparation will be injected into each intercostal space 3-10 and subcutaneously into each wound.

Standard Bupivacaine

- 5cc of drug preparation will be injected into each intercostal space 3-10 and subcutaneously into each wound.

8.4.2 Dispensing

The inpatient investigational pharmacist will dispense the drugs to the operating room.

8.4.3 Administration Instructions

Liposomal Bupivacaine

- 5cc of prepared drug will be percutaneously injected into each intercostal space 3-10 with a 22-gauge spinal needle under direct intrathoracic vision and subcutaneously into each wound at the conclusion of the surgery.

Standard Bupivacaine

- 5cc of prepared drug will be percutaneously injected into each intercostal space 3-10 with a 22-gauge spinal needle under direct intrathoracic vision and subcutaneously into each wound at the conclusion of the surgery.

Prior to injection, the investigator will aspirate to ensure that the tip of the needle is not in the intravascular space.

8.4.4 Storage

Study drugs will be stored per inpatient pharmacy standards.

8.5 Study Drug Accountability

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The number of study drug dispensed and returned by the subject will be recorded on the Investigational Drug Accountability Record. The study monitor will verify these documents throughout the course of the study.

8.6 Measures of Treatment Compliance

Subject compliance is not an issue with this study as the treatment is given in a single episode by the investigators at the conclusion of surgery. A standardized approach will be

used by all investigators as outlined in Section 8.4.3. To ensure that each subject receives the same postoperative pain management, a standardized electronic orderset will be utilized.

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication will be documented at the preoperative and postoperative clinic visits. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at the preoperative clinic visit.

9.1.3 Medical History

Relevant medical history, including history of current disease and information regarding underlying diseases will be recorded at the preoperative clinic visit.

9.1.4 Physical Examination

A complete physical examination will be performed by either the investigator or a subinvestigator who is a physician within the Department of Surgery, Division of Cardiothoracic Surgery. Qualified staff (MD, NP, RN, and PA) may complete the abbreviated physical exam at all other visits. New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

9.1.5 Vital Signs

Body temperature, blood pressure, pulse and respirations will be performed after resting for 5 minutes at the preoperative and postoperative clinic visits.

9.1.6 Other Clinical Procedures

Subjects will be given the Short Form-8-Health Survey at the preoperative and postoperative clinic visits. In addition, subjects will be given a Pain Medication Survey at the postoperative clinic visit to capture what medications are still being used to control pain.

9.1.7 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates), severity, outcome, treatment, and relation to study drug will be recorded on the case report form (CRF).

9.2 Clinical Laboratory Measurements

9.2.1 Pregnancy Test

A urine pregnancy test will be obtained from female subjects who are of childbearing age on the day of their surgery.

10 EVALUATIONS BY VISIT

10.1 Visit 1 – Preoperative Clinic Visit

1. Review the study with the subject and obtain written informed consent and HIPAA authorization.
2. Assign the subject a unique screening number.
3. Record demographics data.
4. Record medical history, including indication for surgery and prior thoracic surgeries.
5. Record concomitant medications.
6. Perform a complete physical examination.
7. Perform and record vital signs.
8. Obtain routine preoperative studies as clinically indicated, including pulmonary function tests, cardiology evaluation, chest imaging (CT, PET-CT, MRI), bronchoscopy with endoscopic ultrasound, and lung biopsy.
9. Administer Short Form-8-Health Survey
10. Schedule subject for surgery.

10.2 Visit 2 – Surgery with Hospitalization

1. Collect urine pregnancy test in female patients of childbearing age in the preoperative suite.
2. Randomize to Liposomal Bupivacaine or Standard Bupivacaine during surgery.
3. Administer intervention during surgery.
4. Record any Adverse Experiences and/or Review subject diary for adverse experiences and exclusionary medication use daily.
5. Concomitant medications administration.
6. Perform abbreviated physical examination daily.
7. Perform and record vital signs every 4 hours.
8. Monitor with Continuous Pulse Oximetry and Continuous Cardiac Monitoring throughout hospitalization.

10.3 Visit 3 – Postoperative Clinic Visit

1. Record any Adverse Experiences.
2. Record changes to concomitant medications.
3. Perform abbreviated physical examination.
4. Perform and record vital signs.
5. Administer Short Form-8-Health Survey and Pain Medication Survey.

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 will be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.2 Serious Adverse Experiences (SAE)

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

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity

- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

11.2.1 Serious Adverse Experience Reporting

The study site will document all SAEs that occur (whether or not related to study drug) per UCSF CHR Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

11.3 Protocol Defined Important Medical Findings Requiring Real Time Reporting

The following medical findings that occur will require real time reporting by the inpatient surgical team to the medical monitoring team:

- Cardiovascular: Bradycardia, Heart Block, Ventricular Arrhythmia, and/or Cardiac Arrest requiring intervention
- Neurologic: Seizure
- Hypersensitivity: Anaphylaxis
- Death

11.4 Medical Monitoring

Lundy Campbell MD, should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone/Pager: (415) 443-3692
Fax: (415) 476-8444

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation of Study Drug

Early discontinuation of study drug is not applicable as study drug is given in a single episode.

12.3 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject or the investigator feel that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in

the subject's source documents. Subjects who withdraw after Visit 2 but prior to Visit 3 will be encouraged to come in for a final visit.

12.4 Replacement of Subjects

Subjects who withdraw from the study treatment will be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject or investigator fail to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

Failure to meet inclusion/exclusion criteria

Did not receive specified intervention

Use of a prohibited concomitant medication

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The sponsor will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

14 DATA SAFETY MONITORING

A Data Monitoring Committee (DMC) comprised of the Medical Monitor, External Investigator, and Clinical Pharmacist will review data relating to safety and efficacy, conduct and review interim analyses, and ensure the continued scientific validity and merit of the study, according to the UCSF Data Safety Monitoring Board Operations Manual and a DMC Charter to be established for this protocol. There will be an interim review conducted at 1/3 and 2/3 goal enrollment by the DMC for the purpose of monitoring study conduct and assessing patient safety. Further details regarding the timing and content of the interim reviews is included in the statistical section below.

14.1 DMC Charter

Introduction

The purpose of this charter is to define the responsibilities of the DMC, detail membership requirements, describe the data to be reviewed, delineate the meeting process, and outline the considerations and policies of the DMC. The DMC will act in an expert, independent advisory capacity to monitor participant safety, and evaluate the efficacy and conduct of the study.

Study Overview

- Study title: Minimally Invasive Thoracic Surgery Intercostal Nerve Block Trial
- Study design: Randomized, double-blind, active-comparator controlled clinical trial to assess the analgesic efficacy of intercostal nerve block by Liposomal Bupivacaine versus Standard Bupivacaine in subjects undergoing minimally invasive lung resection.
- Phase: III
- Number of participants: 80
- Number of sites: 1

DMC Responsibilities

- Review the research protocol, informed consent documents, and plans for data safety and monitoring prior to initiation of study, periodically during the study, and at the conclusion of the study;
- Conduct interim and final evaluation of the study, including safety data, quality and timeliness of data submission, participant recruitment, accrual and retention, risk versus benefit, including unanticipated problems and protocol violations, efficacy, statistical outcomes, and other factors that can affect study outcome, including aggregate and individual participant data related to safety, data integrity and overall conduct of the study;
- Protect the safety of the study participants;
- Review and evaluate ad hoc safety issues concerning the study at the request of the Investigator;
- Make recommendations to the Investigators concerning continuation, termination, or other modifications of the study based on the observed beneficial or adverse effects of the study;
- Operate according to the procedures described in this charter.

DMC Membership

The DMC will be comprised of an External Investigator, Clinical Pharmacist, and the Medical Monitor who will also serve as the Chairman of the DMC.

- External Investigator: Ankit Sarin, MD, Assistant Professor of Surgery at UCSF. Dr. Sarin is the Surgical Director of the Enhanced Recovery After Surgery Program in Colorectal Surgery and has expertise in postoperative analgesia.

- Clinical Pharmacist: Candy Tsourounis, PharmD at UCSF. Candy has expertise pertaining to the efficacy and risks associated with local amide analgesia.

- Medical Monitor / Chairman of the DMC: Lundy Campbell MD, Clinical Professor of Anesthesia at UCSF. Dr. Campbell was selected as he is an expert in local amide analgesia.

Although DMC members are expected to serve for the duration of the study, in the unlikely event that a member is unable to continue participation, the reason will be documented and a replacement member will be selected by the Investigator. The new member must have comparable expertise and qualifications to the DMC member he/she is

replacing. DMC members must not have any real or perceived scientific, financial, professional, personal, proprietary, or other conflict of interest related to the conduct, outcome, or impact of the study.

Review of Safety Data

The primary charge of the DMC is to monitor the study for participant safety. The safety and related data the DMC will review includes,

- Participant recruitment, accrual, retention, and withdrawal information
- Adverse events (AEs) and serious adverse events (SAEs)
    - Tabulated by body system, intensity, seriousness, duration, treatment given, and the relationship to the study drug and study procedure
    - Comparison of events that occur between treatment arms
    - Individual events of particular concern

In particular, the following are adverse events of special interest pertinent to Liposomal Bupivacaine and Standard Bupivacaine:

- Nausea, emesis, and/or constipation and are expected to occur in >10% of subjects.
- Less common adverse events include dizziness, altered mental status, and hypersensitivity reactions with urticaria and/or pruritis.
- Very rare, but serious adverse events include neurologic toxicity with seizures and apnea, cardiac toxicity with atrioventricular nodal conduction abnormalities and cardiac arrest, and hypersensitivity reaction with anaphylaxis.

SAEs must be reported by the Investigator to the DMC Chair.

Review of Other Data

- Effectiveness

The DMC monitors effectiveness outcomes to determine relative risk/benefit, futility, or for early termination due to overwhelming effectiveness.

- Study Conduct

The DMC reviews data related to study conduct. Data to be reviewed and listed in the DMC reports regarding study conduct includes: summary of protocol violations, completeness and timeliness of study visit data, enrollment eligibility and ineligibility information, noncompliance, unanticipated problems, information concerning withdrawal of participants. The DMC may issue recommendations regarding study conduct when concerns arise that aspects of study conduct may threaten participant safety or study integrity.

DMC Meetings

- Projected Schedule of Meetings

An initial meeting of the DMC will be held prior to any participant enrollment in order for the members to review the charter, form an understanding of the protocol and definitions being used, establish a distribution and meeting schedule, review the study modification and/or termination guidelines, and finalize format and protocol-specified statistical

methods to be used in reports to be considered by the DSMB. Subsequent DMC meetings will be held to review at 1/3 and 2/3 goal enrollment, and at the conclusion of the study.

- Ad Hoc Meetings

An ad hoc meeting of the DMC may be called at any time if immanent participant safety issues arise. If a significant safety concern arises during the study, the DMC Chair may convene a meeting to review safety and any other aspect of the study. Significant safety events may include, but are not limited to, the following:

- A death or life-threatening condition sustained by a participant, regardless of causality
- An unexpected serious safety issue newly identified during the development program that could expose participants to unnecessary risks
- Any other concern regarding participant safety raised by any DMC member

- Meeting Format

DMC meetings will be conducted in person.

- Voting

DMC recommendations will be agreed upon by formal majority vote. In event of a split vote, the DMC Chair will cast the deciding vote.

- Stopping Rules

The DMC will determine whether the study should continue as planned, proceed with modifications, or be terminated. The justification to terminate the study may be due to the DMC's analysis that there is overwhelming effectiveness, futility, or safety issues. If the DMC votes to terminate the study, a final study report will be made.

15 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

15.1 Data Sets Analyzed

All eligible patients who are randomized into the study and receive the intervention will be included in the analysis.

15.2 Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized: age, gender, race and ethnicity, height, weight, comorbid conditions, smoking history, lung function, indication for surgery, prior thoracic surgery.

15.3 Analysis of Primary Endpoint

Null Hypothesis: There is no difference in cumulative in-hospital use of opioids in subjects who receive intercostal nerve block and wound infiltration Liposomal Bupivacaine or Standard Bupivacaine during minimally invasive lung resection.

Student's t-test will be used to assess the means of the cumulative total of in-hospital oral morphine equivalents. It is presumed that the data will be normally distributed. If this assumption is not met, transformation or nonparametric tests (Mann-Whitney U test) will be used. Moreover, as there are only 40 subjects per group, it is possible that we do not achieve effective randomization. If this occurs, we will utilize linear regression adjusting for age, sex, race, comorbidity, diagnosis, and procedure performed. A power of 0.8 and 2-sided alpha error set at 0.05 will be used to assess for statistical significance.

15.4 Analysis of Secondary Endpoints

- Cumulative Daily In-Hospital Pain Score (0-10)
- Mean Time to First Opioid Use (hours)
- Mean Time to Ambulation (hours)
- Pulmonary Complications: Pneumonia and Atelectasis requiring Bronchoscopy (y/n)
- Liposomal Bupivacaine and Stand Bupivacaine Adverse Events (y/n):
  - Gastrointestinal- nausea, emesis, constipation
  - Hypersensitivity- pruritis, urticaria, anaphylaxis
  - Cardiac- atrioventricular heart block, cardiac arrest
  - Neurologic- dizziness, altered mental status, seizure
  - Miscellaneous

  Safety and tolerability data will be summarized by treatment group. Adverse event rates will be coded by body system and will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to study drug.
- Length of Stay (days)
- Total Opioid Prescription at Discharge (morphine equivalents in mg)
- Total Opioid Use as Outpatient (morphine equivalents in mg)
- Direct Costs of hospital encounter (dollars)
- Quality of life – Short-Form-8 Health Survey (Optum Health)

Student's t-test, Pearson's chi-squared test, and Kaplan-Meier survival estimate will be used. A 2-sided alpha error set at 0.05 will be used to assess for statistical significance.

15.5 Interim Analysis

There will be interim reviews conducted by the DMC for the purpose of monitoring study conduct and assessing patient safety at 1/3 and 2/3 goal enrollment. Blinding will be maintained. An O'Brien-Fleming alpha spending function with symmetric stopping boundaries for benefit and harm will be utilized. If the stopping boundaries have been reached (absolute value of z-value >3), the data will be unblinded for review and the trial will be terminated. Finally, there also will be consideration of terminating trial if there is consensus of futility.

15.6 Sample Size and Randomization

80 Subjects will be randomized to 1:1 to Liposomal Bupivacaine or Standard Bupivacaine by varying block size (4-8). 80 subjects will provide 80% power to detect a statistically significant effect with 2-sided alpha error set at 0.05 if the measured effect is 19% absolute reduction in cumulative daily in-hospital use of opioids.

The mean daily in-hospital usage of opioids is 35mg morphine equivalents with standard deviation of 12mg. This was estimated by review of previously published studies and corroboration with UCSF clinical practice patterns [12]. A 19% absolute reduction in cumulative daily in-hospital use of opioids corresponds to 1 fewer oxycodone dose per day, which was considered the minimum clinically significant effect.

16 DATA COLLECTION, RETENTION AND MONITORING

16.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) in REDCap when the information corresponding to that visit is available. If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. The Short Form 8 Health Survey and Pain Medication Survey will be administered and recorded as a REDCap survey.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

16.2 Data Management Procedures

The data will be entered into REDCap. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

16.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked, and resolved through the EDC system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

16.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures. Appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

16.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the IRB/IEC and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

16.6 Monitoring

By signing this protocol, the Investigator grants permission to the appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

16.7 Subject Confidentiality

In order to maintain subject confidentiality, all protected health information is stored in REDCap.

17 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

All study records will be stored on REDCap that contains a firewall with a secure server that is backed up regularly off-site. Clinical information will not be released without written permission of the subject, except as necessary for monitoring. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

17.1 Protocol Amendments

Any amendment to the protocol will be written by the Investigator. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to

eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

17.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to the Sponsor. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

17.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form and HIPAA authorization and provide the documents to the Sponsor for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written

form and subjects must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC from the subject will also be obtained. A copy of the signed consent form will be given to the subject and the original will be maintained with the subject's records.

17.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

17.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol, except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the DMC any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

APPENDIX 1. SCHEDULE OF STUDY VISITS

	VISIT 1 PREOPERATIVE	VISIT 2 SURGERY/ADMISSION	VISIT 3 POSTOPERATIVE
Informed Consent	**X**		
Medical History	**X**		
Complete Physical Exam	**X**		
Abbreviated Physical Exam		**X**	**X**
Height/Weight	**X**	**X**	**X**
Vital Signs	**X**	**X**	**X**
Pregnancy Test (Urine)		**X**	
Randomization		**X**	
Administration of Study Drug		**X**	
Concomitant Medication Review	**X**	**X**	**X**
Adverse Experiences		**X**	**X**

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