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CLINICAL STUDY PROTOCOL: BUPI-502

Protocol Title:	A Phase 4, Randomized, Open-Label Study of the Pharmacokinetics and Tolerability of Bupivacaine HCl Following One of Two Routes of Administration in Subjects Undergoing Augmentation Mammoplasty
Brief Title:	Bupivacaine HCl PK and Safety in Augmentation Mammoplasty
Investigational Product:	None
Phase of Development:	4
Sponsor:	Heron Therapeutics, Inc. 4242 Campus Point Court, Suite 200 San Diego, CA 92121 USA 1-858-251-4400
Medical Monitor(s):	[redacted]
Medical Project Leader:	[redacted]
Protocol Version:	Version 1 20 August 2018

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SPONSOR SIGNATURE

Protocol Title:	A Phase 4, Randomized, Open-Label Study of the Pharmacokinetics and Tolerability of Bupivacaine HCl Following One of Two Routes of Administration in Subjects Undergoing Augmentation Mammoplasty
Protocol Number:	BUPI-502

This protocol Version 1 has been reviewed and approved by the Sponsor.

The electronic signature is appended.

[redacted]
Heron Therapeutics, Inc.

INVESTIGATOR AGREEMENT

CLINICAL STUDY PROTOCOL: BUPI-502

TITLE: A Phase 4, Randomized, Open-Label Study of the Pharmacokinetics and Tolerability of Bupivacaine HCl Following One of Two Routes of Administration in Subjects Undergoing Augmentation Mammoplasty

I have read the protocol and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. I will conduct the study as outlined herein.

I will provide copies of the protocol, the Investigator's Brochure, and all other information on the investigational product that were furnished to me by the Sponsor to all physicians and other study personnel responsible to me who participate in this study, and will discuss this material with them to ensure that they are fully informed regarding the investigational product and the conduct of the study.

I agree to keep records on all subject information (ie, medical records, Case Report Forms, and informed consent statements), study drug shipment and return forms, and all other information collected during the study in accordance with local and national Good Clinical Practice (GCP) guidelines.

Principal Investigator: _____

Address: _____

Signature: _____

Date: _____

PROTOCOL SYNOPSIS

NAME OF SPONSOR:	Heron Therapeutics, Inc.
NAME OF FINISHED PRODUCT:	Bupivacaine HCl without epinephrine
NAME OF ACTIVE INGREDIENT:	Bupivacaine
PROTOCOL NUMBER:	BUPI-502
PHASE OF DEVELOPMENT:	4
PROTOCOL TITLE: A Phase 4, Randomized, Open-Label Study of the Pharmacokinetics and Tolerability of Bupivacaine HCl Following One of Two Routes of Administration in Subjects Undergoing Augmentation Mammoplasty	
NUMBER OF PLANNED SUBJECTS: Approximately 30 subjects will be randomized and dosed.	
STUDY SITES: Approximately 2 study sites in the United States (US).	
STUDY OBJECTIVES: Primary: To characterize the bupivacaine pharmacokinetic (PK) profiles of bupivacaine HCl in this study population. Secondary: To assess the safety and tolerability of bupivacaine HCl in this study population.	
METHODOLOGY: This is a Phase 4, randomized, open-label study of bupivacaine HCl administered either by instillation into the surgical site or by injection into the surgical site in approximately 30 subjects undergoing bilateral submuscular augmentation mammoplasty under general anesthesia. Subjects will be screened within 28 days prior to study drug administration. Subjects who meet the Screening eligibility criteria will be randomized in a 1:1 ratio to receive a single dose of bupivacaine HCl without epinephrine 0.25% (75 mg, 30 mL) either by instillation into each pectoral pocket or by injection into each pectoral pocket (total dose of 150 mg, 60 mL). Randomization may be done up to 1 business day prior to study drug administration. On the day of surgery (Day 1), subjects who continue to meet the eligibility criteria will undergo augmentation mammoplasty under general anesthesia. Spinal, epidural, or regional anesthesia is not allowed. Dexamethasone cannot be administered prophylactically before surgery. During surgery, the use of fentanyl up to 4 µg/kg will be permitted. In order to decrease the inherent variability of intraoperative pain control on immediate postoperative pain, subjects will receive fentanyl 50 µg intravenously (IV) just prior to the end of the surgery. Intraoperative administration of other opioids or any other analgesics (including ketamine), local anesthetics, or anti-inflammatory agents (except as specified by the protocol) is prohibited, unless needed to treat an adverse event (AE) that occurs after signing the informed consent form (ICF), for pretreatment prior to a needle placement, or to decrease venous irritation (eg, caused by propofol, in which case no more than a single administration of lidocaine 20 mg IV may be administered). Bupivacaine HCl without epinephrine 0.25% (75 mg, 30 mL) will be administered prior to the end of surgery, either by instillation into each pectoral pocket or by injection into each pectoral pocket based on randomization (total dose of 150 mg, 60 mL). The surgeon should administer 5 mL of ropivacaine 0.5% via injection into each of the pectoral surgical incision lines at closure (total of 10 mL). Following surgery and immediate postoperative recovery, subjects will be transferred to the postanesthesia care unit (PACU). Subjects will remain in the hospital/research facility for a minimum of 72 hours after the end of surgery to undergo postoperative assessments. After the 72-hour assessments have been completed, subjects may be discharged. Subjects will return to the study site on Day 10 and	

Day 28 to complete follow-up assessments.

STUDY POPULATION:

Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study:

1. Is able to provide written informed consent.
2. Is able to adhere to the study visit schedule and complete all study assessments.
3. Is female ≥18 years of age at screening.
4. Is scheduled to undergo primary bilateral submuscular augmentation mammoplasty with saline or silicone smooth implants with a volume of 300 to 500 mL, inclusive. Note: textured implants are not allowed.
5. Has an American Society of Anesthesiologists Physical Status of I, II, or III.
6. Subjects are eligible only if all of the following apply:
    a. Not pregnant (subjects of childbearing potential must have a negative urine pregnancy test at screening and on Day 1 before study drug administration).
    b. Not lactating.
    c. Not planning to become pregnant during the study.
    d. Surgically sterile; or at least 2 years post-menopausal; or have a monogamous partner who is surgically sterile; or is practicing double-barrier contraception; or practicing abstinence (must agree to use double-barrier contraception in the event of sexual activity); or using an insertable, injectable, transdermal, or combination oral contraceptive approved by the US Food and Drug Administration (FDA) for greater than 2 months prior to screening and commits to the use of an acceptable form of birth control for the duration of the study and for 30 days after study drug administration. Note: women in only a same-sex relationship do not need to meet this criterion.

Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the study:

1. Has a planned concurrent surgical procedure (eg, mastopexy).
2. Has a planned concurrent reconstructive procedure status post breast cancer therapy.
3. Has a pre-existing concurrent acute or chronic painful physical/restrictive condition expected to require analgesic treatment in the postoperative period for pain that is not strictly related to the augmentation mammoplasty.
4. Has a contraindication or a known or suspected history of hypersensitivity or clinically significant idiosyncratic reaction to bupivacaine, ropivacaine (or other local anesthetics), oxycodone, morphine, or fentanyl.
5. Has been administered a bupivacaine-containing product within 5 days prior to the scheduled surgery.
6. Has been administered bupivacaine or ropivacaine within 72 hours prior to the scheduled surgery.
7. Has a medical condition such that, in the opinion of the Investigator, participating in the study would pose a health risk to the subject or confound the postoperative assessments. Conditions may include, but are not limited to, any of the following:
    a. History of clinically significant cardiac abnormality such as myocardial infarction within 6 months prior to signing the informed consent, New York Heart Association class III or IV, or clinically significant abnormalities of electrocardiogram (ECG) or cardiac function.
    b. History of coronary artery bypass graft surgery within 12 months of signing the ICF.
    c. History of severe liver function impairment, as defined by Child-Pugh Class C, having an aspartate aminotransferase >3 × the upper limit of normal (ULN), or having an alanine aminotransferase >3 × ULN.

d. History of severe kidney function impairment as defined by creatinine clearance (Cockcroft Gault) <30 mL/min, being on dialysis, and/or having a serum creatinine >2 × ULN.
e. History of known or suspected coagulopathy or uncontrolled anticoagulation.
f. History of platelet counts <100,000/μL, hemoglobin<10 g/dL, or absolute neutrophil count (ANC) <1500/mm^3.

8. As per subject history and/or medical records, has active infection or is currently undergoing treatment for Hepatitis B, Hepatitis C, or human immunodeficiency virus (HIV).
9. Has uncontrolled anxiety, psychiatric, or neurological disorder that might interfere with study assessments.
10. Had a malignancy in the last year, with the exception of nonmetastatic basal cell or squamous cell carcinoma of the skin or localized carcinoma in situ of the cervix.
11. Has a known or suspected history of drug abuse, a positive drug screen on the day of surgery, or a recent history of alcohol abuse. Note: Subjects with a positive drug screen who are taking an allowed, prescribed medication that is known to result in a positive drug test (eg, amphetamine and dextroamphetamine for attention-deficit/hyperactivity disorder, benzodiazepine for anxiety disorder) may be eligible for participation in the study. Subjects taking medical marijuana are not allowed to participate in the study.
12. Previous participation in an investigational product or device clinical trial within 30 days or within 5 elimination half-lives (whichever is longer) prior to surgery, or is planning to take part in another clinical trial while participating in this study.
13. Has undergone 3 or more surgeries in 12 months prior to signing the ICF, other than for diagnostic procedures (eg, colonoscopy).
14. Has a body mass index (BMI) >35 kg/m^2.

STUDY DRUG, DOSE, AND MODE OF ADMINISTRATION:

Bupivacaine HCl without epinephrine for injection has been approved by the US FDA.

Bupivacaine HCl without epinephrine 0.25% (75 mg per pectoral pocket, 30 mL; total of 150mg, 60 mL) will be administered by either instillation into the pectoral pocket or injection into the pectoral pocket. Bupivacaine HCl will be supplied by the sites. MARCAINE is preferred if available to the study sites.

Ropivacaine 0.5% (5 mL) will be administered via injection into each of the pectoral surgical incision lines (total of 10 mL). Ropivacaine will be supplied by the sites.

REFERENCE THERAPY, DOSE, AND MODE OF ADMINISTRATION:

None.

DURATION OF TREATMENT:

Subjects will receive a single dose of study drug. The overall duration of the study is anticipated to be approximately 3 months. The total duration of study participation for each subject (from Screening through Day 28) will be up to 60 days.

STUDY ASSESSMENTS:

PK and safety assessments will be performed. The start of study drug administration will be considered as Time 0 for all safety and PK timepoints.

Safety Assessments

- AEs from the time the subject signs the ICF through Day 28.
- Local anesthetic systemic toxicity (LAST) assessments at 30 minutes, 1 hour, 2 hours, 4 hours, 12 hours, 24 hours, and 72 hours after the start of study drug administration. If early neurologic and cardiac signs and symptoms of LAST are observed, unscheduled vital sign measurements, 12-lead

ECG, and blood sample collection for PK must be performed.

- Clinical safety laboratory tests (hematology and serum chemistry) at the Screening Visit, at 24 hours (hematology only), and at 72 hours, and Day 10.
- Physical examination at Screening Visit and 72 hours; the Screening Visit will also include height, weight, and BMI calculation.
- Wound healing assessment via Southampton Scale at 72 hours and on Day 10 and Day 28.
- Vital signs (resting heart rate, blood pressure, respiration rate, and body temperature) at the Screening Visit, on Day 1 before surgery, and post-treatment at 30, 60, 90 minutes and at 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours and on Day 10 and Day 28.

Pharmacokinetics Assessments

Blood samples for bupivacaine PK analysis will be collected prior to surgery, and post-treatment at 15, 30, 45, 60, 75, and 90 minutes, and at 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours after start of study drug administration.

STUDY ENDPOINTS:

Safety Endpoints

- Incidence of treatment-emergent AEs (TEAEs), serious TEAEs (SAEs), opioid-related TEAEs (ORAEs) through Day 28, and potential LAST-related TEAEs.
- Changes from baseline in clinical laboratory results.
- Changes from baseline in vital signs at each assessed timepoint.
- Rate of potential LAST symptoms based on questionnaire assessments.
- Wound healing assessment at 72 hours and on Day 10 and Day 28.

Pharmacokinetic Endpoints

- Maximum observed plasma concentration (C_{max}).
- Area under the curve (AUC) from Time 0 to the last collection time after study drug administration ($AUC_{0\text{-}last}$).
- AUC from Time 0 extrapolated to infinity ($AUC_{0\text{-}\infty}$).
- Time to maximum plasma concentration (T_{max}).
- Apparent terminal elimination rate constant (λ_z).
- Apparent terminal elimination half-life ($t_{½el}$).

STATISTICAL METHODS:

Safety Analyses

All safety data will be listed and summarized by treatment group, and no statistical hypothesis testing will be performed. All TEAEs will be coded and tabulated by System Organ Class and Preferred Term. Incidence of TEAEs, SAEs, ORAEs, and potential LAST-related TEAEs will be summarized. Associated clinical laboratory parameters such as hepatic enzymes, renal function, and hematology values will be grouped and presented together in summary tables. Individual subject values will be listed and values outside of the standard reference range will be flagged. Changes in vital sign parameters will be

summarized. Potential LAST assessment questionnaire results and wound healing questionnaire results will be summarized.

Pharmacokinetic Analyses

The plasma PK parameters for bupivacaine will be derived by noncompartmental analysis of the plasma concentration-time profiles. Data will be summarized by treatment group.

Determination of Sample Size

The sample size was selected empirically without formal statistical assumptions.

SCHEDULE OF EVENTS

Assessments	Time window	Screening		Day 1		15 m	30 m	45 m	60 m	75 m	90 m	2h	3h	4h	6h	8h	12h	24h	48h	72h	D 10	D 28	
		≤28 D	≤1 D	Pre-op	OR	±5 m	±5 m	±5 m	±5 m	±5 m	±5 m	±15 m	±15 m	±15 m	±30 m	±30 m	±30 m	±1h	±2h	±2h	±2d	±4d	ET[a]
Obtain informed consent		X																					
Assess/confirm eligibility		X		X																			
Medical history		X																					
Demographics		X																					
Urine pregnancy test (WOCBP only)		X		X[b]																			
Urine drug screen		X		X[b]																			
Physical examination		X[c]																		X			X[d]
Vital signs		X		X			X		X		X	X	X	X	X	X	X	X	X	X			X
12-lead ECG (triplicate)		X																					
Randomize subject			X																				
*PK blood sample				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Clinical safety laboratory tests		X																X[e]		X	X		X[f]
Surgery					X[g]																		
Administer study drug					X																		
Potential LAST symptom assessment[h]							X		X			X		X			X	X		X			
Southampton wound healing assessment																				X	X	X	X[i]
Concomitant medications[j]		←																				→	X
Adverse events[k]		←																				→	X

Abbreviations: AE, adverse event; D, day(s); D10, Day 10; D28, Day 28; ECG, electrocardiogram; ET, Early Termination; h, hour; m, minutes; LAST, Local Anesthetic Systemic Toxicity; OR, operating room; PK, pharmacokinetic; Preop, preoperative assessments; WOCBP, women of childbearing potential.

* Time 0 for all assessments will be start of study drug administration. Assessments at timepoints when the subject is asleep should be obtained if possible to do so without waking the subject (eg, blood collection for PK) or marked "Not Done" if not possible.

[a] Subjects who withdraw from the study before their Day 28 Visit will be asked to complete ET procedures.

[b] The urine drug screen and urine pregnancy test should be performed first. Results should be confirmed negative prior to performing any additional assessments and prior to initiation of surgery. A subject who fails the drug test may be rescreened at the discretion of the Investigator. Subjects with a positive drug screen who are taking an allowed, prescribed medication that is known to result in a positive drug test (eg, amphetamine and dextroamphetamine for attention-deficit/hyperactivity disorder, benzodiazepine for anxiety disorder) may be eligible for participation in the study. Subjects taking medical marijuana are not allowed to participate in the study.

[c] Includes height, weight, and body mass index calculation.

[d] Only if the subject withdraws prior to 72 hours.

[e] Hematology only.

[f] Only if the subject withdraws prior to Day 10.

[g] The length of the surgical incision should be recorded.

[h] If a cardiac or neurological treatment-emergent adverse event occurs during the study, a blood sample should be collected (unscheduled if not already specified) at the time that the event is noted to determine the plasma bupivacaine concentration; vital sign measurements and a 12-lead ECG must be performed (unscheduled if necessary).

[i] Only if the subject withdraws at 72 hours or after.

[j] At the Screening Visit, ensure subject is not taking any prohibited medications. Record all medications taken from the time the subject signs the Informed Consent Form (ICF) through Day 28.

[k] Adverse events will be collected from the time the subject signs the ICF through Day 28.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
λ_z	Apparent terminal elimination rate constant
AE	Adverse event
AUC	Area under the curve
$AUC_{0\text{-last}}$	AUC from Time 0 to the last collection time after study drug administration
$AUC_{0\text{-}\infty}$	AUC from Time 0 extrapolated to infinity
BMI	Body mass index
CFR	Code of Federal Regulations
C_{max}	Maximum observed plasma concentration
CV	Cardiovascular
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council for Harmonisation
IV	Intravenous(ly)
LAST	Local anesthetic systemic toxicity
NSAID	Nonsteroidal anti-inflammatory drugs
ORAE	Opioid-related treatment-emergent adverse event
PACU	Postanesthesia care unit
PK	Pharmacokinetic(s)
SAE	Serious treatment-emergent adverse event
TEAE	Treatment-emergent adverse event
$t_{½el}$	Apparent terminal elimination half-life
T_{max}	Time to maximum plasma concentration

ULN	Upper limit of normal
US	United States

Note: Abbreviations used only in tables, figures, or an appendix are defined in the table or figure footnotes or the appendix.

1. INTRODUCTION

1.1. Background Information and Study Rationale

Up to 70% of patients have moderate to severe pain after surgery, and the most severe pain occurs within the first 72 hours (Lynch, 1997; Svensson, 2000; Apfelbaum, 2003; Gan, 2014; Misiolek, 2014; Singla, 2014; Meissner, 2015). Standard clinical practice for managing postoperative pain includes local anesthetics administered in the perioperative setting, and opioids following surgery for patients with inadequate pain control. Bupivacaine is the most common long-acting local anesthetic used in surgery and is considered the standard of care (Cox, 2003; ASA Guidelines, 2012). However, this agent has the potential for serious complications associated with local anesthetic systemic toxicity (LAST) (eg, cardiovascular [CV] and neurological toxicity), most notably after unintentional intravascular injection or injection into highly vascular areas (Covino, 1986; Kehlet, 2011; MARCAINE USPI, 2011; MARCAIN SmPC, 2016).

The rationale for this Phase 4 study is to characterize the safety and pharmacokinetics (PK) of bupivacaine HCl following either injection or instillation into the pectoral pockets for subjects undergoing augmentation mammoplasty.

1.2. Rationale for Study Design, Doses, and Control Groups

Augmentation mammoplasty is one of the most common cosmetic surgical procedures worldwide (International Society of Aesthetic Plastic Surgery, Global Statistics, 2016); however, there are limited PK and safety data on the use of bupivacaine in augmentation mammoplasty by infiltration (Mahabir, 2004; McCarthy, 2009; Smoot, 2012). Therefore, augmentation mammoplasty was selected as the surgical model for this study that is designed to characterize the PK and safety of bupivacaine HCl administered by injection or instillation.

The bupivacaine HCl PK profiles will be characterized during the 72-hour postoperative assessment period, and safety evaluation will continue through the 28-day follow-up period.

Although postoperative pain is not being assessed in this study, the choice of rescue medication has been prespecified during the 72-hour postoperative observation period in order to minimize variability for the safety evaluation. All subjects with inadequately controlled pain will have access to prespecified rescue medication, including oral immediate-release oxycodone (no more than 10 mg in a 4-hour period as needed) and/or intravenous (IV) morphine (no more than 10 mg in a 2-hour period as needed).

Bupivacaine is approved by the United States (US) Food and Drug Administration (FDA) and in many countries outside the US for surgical anesthesia and for acute pain management (nerve block) in adults and children (MARCAINE™, SENSORCAINE®, and VIVACAINE™) (MARCAINE USPI, 2011). According to the US label, the maximum dose of bupivacaine without epinephrine 0.25% administered by infiltration is 175 mg. The infiltration administration technique includes injection and/or instillation. In this study, bupivacaine HCl without epinephrine 0.25% (75 mg, 30 mL) will be administered by either instillation into each pectoral pocket or injection into each pectoral pocket for a total dose of 150 mg (60 mL). The dose and

administration methods, which are consistent with bupivacaine labeling, were chosen based on feedback from experts regarding the standard dose used in clinical practice (Mahabir 2004; McCarthy 2009).

1.3. Potential Risks and Benefits

While bupivacaine HCl is considered the standard of care for surgical analgesia, it has potential risks that include dose-related CV and central nervous system toxicity (MARCAINE USPI, 2011). Therefore, close attention should be given to conditions that may represent reported toxicities associated with bupivacaine including, but not limited to, perioral tingling, metallic taste, visual and auditory disturbances, muscle twitching, seizure, acidosis, shortness of breath, bradycardia (heart rate <50 beats per minute with symptoms), hypotension (systolic blood pressure <90 mmHg or symptomatic decrease from baseline), low oxygen saturation (≤90% for ≥1 minute), and cardiac arrest.

Bupivacaine HCl is indicated for the production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures. The duration of anesthesia with MARCAINE is such that for most indications, a single dose is sufficient. The onset of action with MARCAINE is rapid and anesthesia is long lasting. The duration of anesthesia is significantly longer with MARCAINE than with any other commonly used local anesthetic. It has also been noted that there is a period of analgesia that persists after the return of sensation, during which time the need for strong analgesics is reduced.

For more information about bupivacaine HCl, refer to the prescribing information (MARCAINE USPI, 2011).

The potential risks of ropivacaine are characteristic of those associated with other amide-type local anesthetics and may be associated with excessive plasma levels, which may be due to overdosage, unintentional intravascular injection, or slow metabolic degradation. High doses may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, and possibly cardiac arrest. Neurological reactions are characterized by excitation and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, and constriction of the pupils.

Ropivacaine is indicated for the production of local or regional anesthesia for surgery and for acute pain management (NAROPIN USPI, 2015). A total of 7 clinical studies were performed to evaluate the local infiltration of ropivacaine to produce anesthesia for surgery and analgesia in postoperative pain management. In these studies, 297 patients who received ropivacaine in doses up to 200 mg (concentrations up to 5 mg/mL, 0.5%) were evaluable for efficacy. When compared to placebo, ropivacaine produced lower pain scores and a reduction of analgesic consumption.

For more information about ropivacaine, refer to the prescribing information (NAROPIN USPI, 2015).

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to characterize the bupivacaine PK profiles of bupivacaine HCl in this study population.

2.2. Secondary Objectives

The secondary objective is to assess the safety and tolerability of bupivacaine HCl in this study population.

3. INVESTIGATIONAL PLAN AND ENDPOINTS

3.1. Description of the Study Design

3.1.1. Overall Study Design

This is a Phase 4, randomized, open-label study of bupivacaine HCl administered either by instillation into the surgical site or by injection into the surgical site in approximately 30 subjects undergoing bilateral submuscular augmentation mammoplasty under general anesthesia.

Subjects will be screened within 28 days prior to study drug administration. Subjects who meet the Screening eligibility criteria will be randomized in a 1:1 ratio to receive bupivacaine HCl without epinephrine 0.25% (75 mg, 30 mL; total of 150 mg, 60 mL) either by instillation into each pectoral pocket or by injection into each pectoral pocket. Randomization may be done up to 1 business day prior to study drug administration. On the day of surgery (Day 1), subjects who continue to meet the eligibility criteria will undergo augmentation mammoplasty under general anesthesia. Spinal, epidural, or regional anesthesia is not allowed.

Dexamethasone cannot be administered prophylactically before surgery. During surgery, the use of fentanyl up to 4 µg/kg will be permitted. In order to decrease the inherent variability of intraoperative pain control on immediate postoperative pain, subjects will receive fentanyl 50 µg IV just prior to the end of the surgery. Intraoperative administration of other opioids or any other analgesics (including ketamine), local anesthetics, or anti-inflammatory agents (except as specified by the protocol) is prohibited, unless needed to treat an adverse event (AE) that occurs after signing the informed consent form (ICF), for pretreatment prior to a needle placement, or to decrease venous irritation (eg, caused by propofol, in which case no more than a single administration of lidocaine 20 mg IV may be administered).

Bupivacaine HCl without epinephrine 0.25% (75 mg, 30 mL) will be administered prior to the end of surgery, either by instillation into each pectoral pocket or by injection into each pectoral pocket (total dose of 150 mg, 60 mL). The surgeon should then administer 5 mL of 0.5% ropivacaine via injection into each of the pectoral surgical incision lines at closure (total of 10 mL).

Following surgery and immediate postoperative recovery, subjects will be transferred to the postanesthesia care unit (PACU). Subjects will remain in the hospital/research facility for a minimum of 72 hours after the end of surgery to undergo postoperative assessments. After the 72-hour assessments have been completed, subjects may be discharged. Subjects will return to the study site on Day 10 and Day 28 to complete follow up assessments.

3.1.2. Treatment Groups

Approximately 30 subjects will be randomized to 1 of the following 2 treatment groups in a 1:1 ratio:

- Bupivacaine HCl without epinephrine 0.25% (75 mg, 30 mL; total of 150 mg, 60 mL) via injection into each pectoral pocket (15 subjects).

- Bupivacaine HCl without epinephrine 0.25% (75 mg, 30 mL; total of 150mg, 60 mL) via instillation into each pectoral pocket (15 subjects).

3.1.3. Postoperative Analgesia Rescue Medications

Subjects should only receive rescue medication upon request for pain control, as needed, during the 72-hour postoperative observation period.

Postoperative rescue medication will consist of oral immediate-release oxycodone (no more than 10 mg in a 4-hour period as needed) and/or IV morphine (no more than 10 mg in a 2-hour period as needed). No other analgesic agents, including nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, are permitted during the 72-hour postoperative observation period.

After 72 hours, the analgesic regimen may be adjusted for each subject individually as deemed appropriate by the physician responsible for the postoperative care.

3.1.4. Postoperative Assessments

Safety assessments will include AE recording, LAST assessments, physical examinations, vital signs, 12-lead electrocardiograms (ECGs), wound healing assessment, and clinical safety laboratory tests (hematology and serum chemistry).

PK assessments will include the collection of blood samples to evaluate the PK profile of bupivacaine HCl. See Section 7.2.2 for instructions regarding unscheduled PK blood sample collection for signs and symptoms associated with potential LAST

See Section 6 for more information on the study procedures and assessments, and Section 7 and the SCHEDULE OF EVENTS table for the timing of procedures and assessments.

3.2. Study Endpoints

3.2.1. Safety Endpoints

The safety endpoints of this study are as follows:

- Incidence of treatment-emergent AEs (TEAEs), serious TEAEs (SAEs), and opioid-related TEAEs (ORAEs) through Day 28, and potential LAST-related TEAEs.
- Changes from baseline in clinical laboratory results.
- Changes from baseline in vital signs at each assessed timepoint.
- Rate of potential LAST symptoms based on questionnaire assessments.
- Wound healing assessment at 72 hours and on Day 10 and Day 28.

3.2.2. Pharmacokinetic Endpoints

The PK endpoints for this study are as follows:

- Maximum observed plasma concentration (C_{max}).
- Area under the curve (AUC) from Time 0 to the last collection time after study drug administration ($AUC_{0\text{-last}}$).

- AUC from Time 0 extrapolated to infinity ($AUC_{0-\infty}$).
- Time to maximum plasma concentration (T_{max}).
- Apparent terminal elimination rate constant (λ_z).
- Apparent terminal elimination half-life ($t_{½el}$).

3.3. Study Duration

The overall duration of the study is anticipated to be approximately 3 months. The total duration of study participation for each subject (from Screening through Day 28) will be up to 60 days.

For regulatory reporting purposes, the end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1. Study Population

Approximately 30 subjects will be randomized and dosed in this study in approximately 2 study sites in the US.

4.1.1. Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study:

1. Is able to provide written informed consent.
2. Is able to adhere to the study visit schedule, and complete all study assessments.
3. Is female ≥18 years of age at screening.
4. Is scheduled to undergo primary bilateral submuscular augmentation mammoplasty with saline or silicone smooth implants with a volume of 300 to 500 mL, inclusive. Note: textured implants are not allowed.
5. Has an American Society of Anesthesiologists Physical Status of I, II, or III.
6. Subjects are eligible only if all of the following apply:
    a. Not pregnant (subjects of childbearing potential must have a negative urine pregnancy test at screening and on Day 1 before study drug administration).
    b. Not lactating.
    c. Not planning to become pregnant during the study.
    d. Is surgically sterile; or is at least 2 years post-menopausal; or have a monogamous partner who is surgically sterile; or is practicing double-barrier contraception; or practicing abstinence (must agree to use double-barrier contraception in the event of sexual activity); or using an insertable, injectable, transdermal, or combination oral contraceptive approved by the US FDA for greater than 2 months prior to screening and commits to the use of an acceptable form of birth control for the duration of the study and for 30 days after study drug administration. Note: women in only a same-sex relationship do not need to meet this criterion.

4.1.2. Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the study:

1. Has a planned concurrent surgical procedure (eg, mastopexy).
2. Has a planned concurrent reconstructive procedure status post breast cancer therapy.
3. Has a pre-existing concurrent acute or chronic painful physical/restrictive condition expected to require analgesic treatment in the postoperative period for pain that is not strictly related to the augmentation mammoplasty.
4. Has a contraindication or a known or suspected history of hypersensitivity or clinically significant idiosyncratic reaction to bupivacaine, ropivacaine (or other local anesthetics), oxycodone, morphine, or fentanyl.

5. Has been administered a bupivacaine-containing product within 5 days prior to the scheduled surgery.
6. Has been administered bupivacaine or ropivacaine within 72 hours prior to the scheduled surgery.
7. Has a medical condition such that, in the opinion of the Investigator, participating in the study would pose a health risk to the subject or confound the postoperative assessments. Conditions may include, but are not limited to, any of the following:
    a. History of clinically significant cardiac abnormality such as myocardial infarction within 6 months prior to signing the informed consent, New York Heart Association class III or IV, or clinically significant abnormalities of ECG or cardiac function.
    b. History of coronary artery bypass graft surgery within 12 months of signing the ICF.
    c. History of severe liver function impairment, as defined by Child-Pugh Class C, having an aspartate aminotransferase >3 × the upper limit of normal (ULN), or having an alanine aminotransferase >3 × ULN.
    d. History of severe kidney function impairment as defined by creatinine clearance (Cockcroft Gault) <30 mL/min, being on dialysis, and/or having a serum creatinine >2 × ULN.
    e. History of known or suspected coagulopathy or uncontrolled anticoagulation.
    f. History of platelet count <100,000/μL, hemoglobin <10 g/dL, or absolute neutrophil count (ANC) <1500/mm^3.
8. As per subject history and/or medical records, has active infection or is currently undergoing treatment for Hepatitis B, Hepatitis C, or human immunodeficiency virus (HIV).
9. Has uncontrolled anxiety, psychiatric, or neurological disorder that might interfere with study assessments.
10. Had a malignancy in the last year, with the exception of nonmetastatic basal cell or squamous cell carcinoma of the skin or localized carcinoma in situ of the cervix.
11. Has a known or suspected history of drug abuse, a positive drug screen on the day of surgery, or a recent history of alcohol abuse. Note: Subjects with a positive drug screen who are taking an allowed, prescribed medication that is known to result in a positive drug test (eg, amphetamine and dextroamphetamine for attention-deficit/hyperactivity disorder, benzodiazepine for anxiety disorder) may be eligible for participation in the study. Subjects taking medical marijuana are not allowed to participate in the study.
12. Previous participation in an investigational product or device clinical trial within 30 days or within 5 elimination half-lives (whichever is longer) prior to surgery, or is planning to take part in another clinical trial while participating in this study.
13. Has undergone 3 or more surgeries in 12 months prior to signing the ICF, other than for diagnostic procedures (eg, colonoscopy).
14. Has a body mass index (BMI) >35 kg/m^2.

4.2. Method of Assigning Subjects to Treatment Groups

Subjects who meet the Screening eligibility criteria will be randomized. Randomization may be done up to 1 business day prior to study drug administration. Subjects will be randomized using a computer generated randomization scheme. All randomization information will be kept in a secure location accessible only by the randomization personnel. No subject may receive study drug prior to randomization.

4.2.1. Procedures for Handling Randomized Subjects Who Do Not Meet the Study Eligibility Criteria

Subjects who fail to meet the eligibility criteria should not, under any circumstances, receive study drug.

Subjects who meet the Screening eligibility criteria and are randomized, but who do not meet the eligibility criteria on Day 1 prior to study drug administration will be withdrawn from the study without receiving study drug. In the event a subject does not meet the eligibility criteria but is randomized and receives study drug, the Investigator should inform the Sponsor immediately. The Sponsor's Medical Monitor and the Investigator will discuss whether to allow the subject to continue on study.

4.3. Blinding

This is an open-label study.

4.4. Subject Withdrawal and Replacement

4.4.1. Subject Withdrawal

Subjects are free to withdraw from the study at any time without prejudice to further treatment. A subject may also be withdrawn from the study by the Investigator or the Sponsor at any time if either determines that it is not in the subject's best interest to continue participation.

Possible reasons for early withdrawal include the following:

- Adverse event.
- Withdrawal by subject.
- Death.
- Lost to follow-up.
- Pregnancy.
- Investigator's decision.
- Sponsor's decision.
- Failure to meet randomization criteria at Day 1.

The date and the primary reason for early withdrawal will be recorded on the electronic case report form (eCRF). At the time of withdrawal from the study, every attempt should be made to complete the Early Termination Visit assessments (see Section 7.4).

4.4.2. Subject Replacement

Randomized subjects who withdraw from study will not be replaced. To account for withdrawal of subjects who are ineligible at Day 1 or are otherwise randomized but not dosed, enrollment will continue until at least 30 subjects have been randomized and dosed.

5. STUDY TREATMENT

All subjects will receive a single dose of study drug. Study drug is defined as bupivacaine HCl without epinephrine.

5.1. Description of Study Drug

Bupivacaine HCl without epinephrine for injection is an amide-type, immediate-release formulation indicated for the production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures. It is a clear, colorless, and sterile isotonic solution containing sodium chloride (MARCAINE USPI, 2011).

5.2. Manufacturing, Packaging, and Labeling

Bupivacaine HCl has been approved by the FDA. The study drug will be provided by the study site.

5.3. Storage

Bupivacaine HCl will be stored as per the prescribing information (MARCAINE USPI, 2011).

5.4. Preparation

Study drug will be prepared at the study site according to the prescribing information.

5.5. Study Drug Administration

Bupivacaine HCl without epinephrine 0.25% (75 mg, 30 mL) will be administered either by instillation into each pectoral pocket or injection into each pectoral pocket (total dose of 150 mg, 60 mL) after the surgery is complete, but prior to completion of wound closure. Additional information about study drug administration will be specified by the Sponsor in the Pharmacy/Study Manual.

For the instillation group, bupivacaine will be administered in a standardized manner. After the implant is properly positioned, a standard red rubber catheter (10 Fr – 14 Fr) is placed within the incision at the lower border. After the subcutaneous tissue is closed, 30 mL is pushed through the catheter so that the injectate coats the surface of the musculature as the catheter is withdrawn. The remainder of the wound may then be closed. The same method is repeated for the contralateral side.

For the injection group, bupivacaine will be administered into all 4 quadrants of the musculature of the pectoral pocket. Taking care to inject shallow into the musculature, approximately 7.5 mL should be injected into the upper outer quadrant of the breast, followed by the upper medial quadrant, then the lower lateral, and finally the lower medial quadrant. Multiple injections will be needed, especially on the lateral side, to ensure complete coverage of the tissue. Care must be taken to aspirate prior to each injection; if blood is seen in the aspirate, the needle should be withdrawn and redirected to ensure there is no inadvertent intravascular exposure. The same method is repeated for the contralateral side.

The surgeon should administer 5 mL of ropivacaine 0.5% via injection into each of the pectoral surgical incision lines at closure (total of 10 mL).

5.6. Study Drug Compliance

All study drug must be administered in accordance with the treatment assignment. Because study drug is being administered as a component of the surgical procedure, a lack of treatment compliance is not expected.

5.7. Study Drug Accountability

The study drug for this study will be used only as directed in the study protocol. In accordance with Good Clinical Practice (GCP), Investigators are required to maintain accurate and up-to-date records of all study drug to permit reconciliation. The Investigator or designee must maintain adequate records of distribution, including the date received, number and units received, and lot numbers, dispensing, and return or destruction of all study drug (ie, accountability or dispensing logs).

All study drug records must be readily available for inspection by the site's clinical monitor and/or auditor. No study drug can be disposed of at the study site until the clinical monitor has verified the accuracy of the study drug records at the study site.

6. STUDY PROCEDURES AND ASSESSMENTS

The following sections describe the study procedures and assessments that will be performed during the study. Additional information about the timing of assessments is provided in Section 7 and the SCHEDULE OF EVENTS table.

6.1. Medical History and Demographics

6.1.1. Medical History

A complete medical history will be obtained before randomization to ensure subjects qualify for the study. Medical history will be obtained through subject interview. A review of the subject's medical records from their primary care physician is not required. Data collected will include medical and surgical history.

6.1.2. Demographics

Demographic information collected will include age, sex, race, and ethnicity.

6.2. Prior and Concomitant Therapy

All medications taken by subjects between the day of signing the ICF and Day 28 will be recorded. For subjects entering on a stable dose of permitted medication, any change in dose should also be recorded.

Medications include prescription or over-the-counter medications (including herbal products and vitamins).

6.2.1. Allowed Concomitant Medications

All treatments that the Investigator considers necessary for a subject's welfare may be administered at the discretion of the Investigator's in keeping with the standard of medical care.

Antiemetic medications may be given to treat nausea and/or vomiting, but should not be administered prophylactically (ie, as a routine preventative in the absence of signs or symptoms of nausea or vomiting).

During surgery, the use of fentanyl up to 4 µg/kg is permitted. In addition, subjects will receive protocol specified fentanyl 50 µg IV just prior to the end of the surgery. As clinically appropriate, the minimum possible fentanyl dose should be used.

See Section 3.1.3 for information about permitted rescue medications.

6.2.2. Prohibited Medications

6.2.2.1. Medications Prohibited Prior to Surgery

Refer to exclusion criteria 5, 6, 11, and 12 for medications that are prohibited prior to the scheduled surgery (Section 4.1.2).

Dexamethasone also cannot to be administered prophylactically before surgery.

6.2.2.2. Medications Prohibited During Surgery

Spinal, epidural, or regional anesthesia is not permitted.

Intraoperative administration of opioids or any other analgesics (including ketamine), local anesthetics, or anti-inflammatory agents (except as specified by the protocol) is prohibited, unless needed to treat an AE that occurs after signing the ICF, for pretreatment prior to a needle placement, or to decrease venous irritation (eg, caused by propofol, in which case no more than a single administration of lidocaine 20 mg IV may be administered).

6.2.2.3. Medications Prohibited From Time 0 Through 72 Hours

With the exception of the opioid rescue medications specified in Section 3.1.3, no other analgesic agents, including NSAIDs and acetaminophen, are permitted during the 72-hour postoperative observation period. After 72 hours, the analgesic regimen may be adjusted for each subject individually as deemed appropriate by the physician responsible for the postoperative care.

6.3. Safety Assessments

6.3.1. Adverse Events

All AEs regardless of causality or seriousness will be recorded from the time the subject signs the ICF through Day 28. See Section 8 for additional safety information.

6.3.2. Local Anesthetic Systemic Toxicity Assessment

A LAST assessment questionnaire is provided (Appendix B) to monitor for early neurologic and cardiac signs and symptoms of LAST (Vasques, 2015).

Subjects should be assessed with this questionnaire to identify early stages of toxicity to determine whether treatment should be initiated. If a subject has signs or symptoms that may be attributed to LAST, vital sign measurements, 12-lead ECG recorded in triplicate, and blood sample collection for PK must promptly be performed. If symptoms are present at a timepoint when these assessments are not scheduled, unscheduled assessments must be performed.

Signs and symptoms that are clinically significant and may be attributed to LAST should be recorded as AEs.

6.3.3. Physical Examinations

Scheduled physical examinations will include an evaluation of the following: head, eyes, ears, nose, and throat as well as CV, respiratory, gastrointestinal, neurological, dermatological, and musculoskeletal systems.

Baseline height and weight measurements, and calculation of BMI (BMI = weight [kg]/height [m^2]) will be conducted.

Unscheduled physical examinations may also be performed (the extent of which is to be determined by the Investigator) at any time during the study if indicated by a change in the subject's medical history or condition.

6.3.4. Vital Signs

Vital signs will include systolic and diastolic blood pressure, resting heart rate, and respiration rate. Subjects should be in a supine position (includes sitting in a recliner chair) for at least 5 minutes before taking vital signs. Clinically significant post-treatment vital sign results should be recorded as AEs.

6.3.5. 12-Lead Electrocardiograms

A Screening ECG will be obtained for all subjects. Standard digital 12-lead ECG results will be recorded in triplicate. Subjects should be in the supine position (includes sitting in a recliner chair) for at least 5 minutes before each ECG recording. The mean of the 3 ECGs will be used as the baseline result.

A 12-Lead ECG recorded in triplicate must promptly be performed for subjects who have signs or symptoms that may be attributed to LAST (see Section 6.3.2).

6.3.6. Wound Healing Evaluation

Surgical wound healing will be evaluated by the Investigator or other medically qualified clinical site personnel; every attempt should be made by the site to use the same assessor for individual subject assessments. The findings will be graded according to the Southampton Wound Scoring System (Bailey, 1992); see Appendix C.

6.3.7. Clinical Laboratory Tests

Blood and urine samples will be collected for diagnostic screening tests and for safety laboratory tests (hematology and serum chemistry). See Table 1 for a list of clinical laboratory tests and parameters. Blood samples will be tested by a central laboratory. Urine samples will be tested by local laboratories.

Laboratory results will be reviewed by the Investigator. Any laboratory values outside of the normal reference range will be evaluated for clinical significance. Clinically significant findings after study drug administration will be recorded as AEs.

Refer to the Laboratory Manual for detailed instructions on sample collection, processing, and shipping procedures.

Table 1: Clinical Laboratory Tests

Diagnostic Screening Tests (Local Laboratories):	
Urine Pregnancy test: Human chorionic gonadotropin test (female subjects of childbearing potential only) Drug screen: Amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates/opioids, phencyclidine, propoxyphene, and methadone	
Safety Laboratory Tests (Central Laboratory):	
Hematology	**Serum Chemistry**
Hematocrit	Alanine aminotransferase
Hemoglobin	Albumin
Platelet count	Alkaline phosphatase
Red blood cell count	Aspartate aminotransferase
White blood cell count (with automated differential)	Bicarbonate
	Blood urea nitrogen
	Calcium
	Chloride
	Creatinine
	Direct bilirubin
	Gamma-glutamyltransferase
	Glucose
	Lactate dehydrogenase
	Magnesium
	Phosphorus
	Potassium
	Sodium
	Total bilirubin
	Total protein
	Uric acid

6.4. Pharmacokinetic Assessments

Serial blood samples for bupivacaine PK analysis will be collected from subjects. Blood samples may be drawn using a properly maintained indwelling cannula. Samples will be sent to a central laboratory for analysis. Refer to the Laboratory Manual for detailed instructions on sample collection, processing, storage, and shipping procedures.

7. TIMING OF PROCEDURES AND ASSESSMENTS

This section lists the study procedures and assessments that will be performed at scheduled timepoints during the study. See Section 6 for information on study procedures and assessments

Unless there is a safety concern, every effort should be made to avoid protocol deviations. For pain assessments at timepoints when the subject is asleep, an attempt should be made to wake the subject. If there is no response, the assessments at these timepoints may be recorded as "Not Done." Assessments that can be done without waking the subject (eg, blood collection for PK) should be completed. Additional visits and/or assessments are permitted if clinically indicated in the opinion of the Investigator.

When the following assessments are scheduled at the same timepoint, it is recommended that they be performed in this order:

- Vital signs.
- 12-lead ECG.
- LAST assessment.
- Blood sample collection.
- Physical examination.
- Wound healing assessment.

7.1. Screening Period (Day -28 to Day-1)

After providing written informed consent, potential study subjects will undergo Screening procedures to confirm eligibility to participate in the study. Screening procedures must be performed within 28 days prior to study drug administration.

The Investigator must evaluate the subject's medical history and the results of all Screening assessments to determine study eligibility before the subject is randomized. Screening laboratory test results that do not meet the eligibility criteria may not be repeated without the Sponsor's approval.

Screening procedures and assessments will include the following:

- Medical history.
- Demographic recording.
- Physical examination including weight, height, and BMI calculation.
- Vital signs measurements.
- 12-lead ECG (triplicate).
- Urine collection for pregnancy test (female subjects of childbearing potential only).
- Urine collection for drug screen.
- Blood sample collection for the hematology and serum chemistry.

- AE recording (from signing the ICF).
- Prior and concomitant medication recording.

Subjects who meet the eligibility criteria may be randomized up to 1 business day prior to study drug administration. Subjects do not need to be present for randomization to occur.

7.2. Study Drug Administration, Surgery, and Observational Period

7.2.1. Day of Surgery (Day 1)

7.2.1.1. Prior to Surgery

On the day of surgery (Day 1), subjects will be reassessed for study eligibility. Subjects who continue to meet the eligibility criteria can continue on study and the following study procedures and assessments will be performed before surgery:

- Vital signs measurements.
- Urine sample collection for the following assessments:
  - Drug screen.
  - Pregnancy test (female subjects of childbearing potential only).
- Blood collection for PK.
- AE recording.
- Prior and concomitant medication assessment.

7.2.1.2. Surgery and Study Drug Administration

Subjects will be admitted to the surgical unit and will undergo a bilateral submuscular augmentation mammoplasty under general anesthesia. Sites should follow intraoperative safety monitoring in accordance with American Society of Anesthesiologists (ASA) Standards for Basic Anesthetic Monitoring (American Society of Anesthesiologists, 2015). The start and stop time of surgery and additional surgical details should be recorded in the eCRF. Concomitant medications used during surgery and AEs will be recorded.

Study drug will be administered via instillation or injection into the surgical site at the end of the surgical procedure, but prior to completion of wound closure. See Section 5.5 and the Pharmacy/Study manual for complete details on the method of study drug administration. The start and stop times of study drug dosing will be recorded in the eCRF. Details of administration will be recorded on a worksheet, which will be used in the dictation of the surgical notes and will become part of the source document. After wound closure, the surgeon should then administer 5 mL of 0.5% ropivacaine via injection into each of the pectoral surgical incision lines (total of 10 mL).

Note: The start of study drug administration will be considered as Time 0 for all safety and PK assessments.

After immediate postoperative recovery, subjects will be transferred to the PACU.

7.2.2. Postoperative Assessment Period (Up to 72 Hours)

Subjects will remain in the hospital/research facility for 72 hours after surgery. Study procedures and assessments that will be performed are listed below.

All timepoints are generally referenced to the end of surgery. Actual times will be recorded for all events, and any deviation outside the specified ranges must be clearly documented in the subject's study records.

- **Vital signs measurements**: 30 minutes (±5 min), 60 minutes (±5 min), 90 minutes (±15 min), 2 hours (±15 min), 3 hours (±15 min), 4 hours (±15 min), 6 hours (±30 min), 8 hours (±30 min), 12 hours (±30 min), 24 hours (±1 h), 48 hours (±2 h), and 72 hours (±2 h).
- **LAST assessments**: 30 minutes (±5 min), 60 minutes (±5 min), 2 hours (±15 min), 4 hours (±15 min), 12 hours (±30 min), 24 hours (±1 h), and 72 hours (±2 h). If symptoms are present at 30 minutes, 1 hour, or 2 hours, an unscheduled blood sample will be collected for PK and a 12-lead ECG will be performed. If symptoms are present at 72 hours, an unscheduled blood sample will be collected for PK.
- **PK sample collection**: 15 minutes (±5 min), 30 minutes (±5 min), 45 minutes (±5 min), 60 minutes (±5 min), 75 minutes (±5 min), 90 minutes (±5 min), 2 hours (±15 min), 3 hours (±15 min), 4 hours (±15 min), 6 hours (±30 min), 8 hours (±30 min), 12 hours (±30 min), 24 hours (±1 h), 48 hours (±2 h), and 72 hours (±2 h).
- **Physical examination**: 72 hours (±2 h; height and weight not required).
- **Blood sample for clinical safety laboratory tests**: 24 hours (±1 h; hematology only) and 72 hours (±2 h; hematology and serum chemistry).
- **Wound healing assessment**: 72 hours (±2 h).
- **AE recording**: Any time during the postoperative assessment period up to and including 72 hours.
- **Concomitant medication recording**: Any time during the postoperative assessment period up to and including 72 hours.

7.2.3. End of the Postoperative Assessment Period

After the 72 hour postoperative assessments have been completed, the subject may be discharged if medically ready. The time of discharge will be recorded. If a subject is not ready to be discharged due to an AE, it should be recorded on the AE eCRF as per Section 8.3.1. If a subject is ready for discharge but is not discharged for any reason other than AE, it should be recorded on the eCRF.

7.3. Follow-Up Period

7.3.1. Day 10 Visit (±2 Days)

All subjects will return to the study site and will have the following procedures and assessments.

- Wound healing assessment.
- Blood sample collection for the hematology and serum chemistry.
- Concomitant medication recording.
- AE recording.
  - Note: A blood sample to determine plasma bupivacaine concentration should be collected if the Investigator thinks the AE is potentially related to the cardiac or neurologic systems.

7.3.2. Day 28 Visit (±4 Days)

All subjects will return to the study site and will have the following procedures and assessments.

- Wound healing assessment.
- Concomitant medication recording.
- AE recording.
  - Note: A blood sample to determine plasma bupivacaine concentration should be collected if the Investigator thinks the AE is potentially related to the cardiac or neurologic systems.

7.4. Early Termination Visit

Subjects who withdraw from the study before their Day 28 Visit will be asked to complete Early Termination procedures, which will include the following:

- Vital signs.
- Blood sample collection for clinical safety laboratory tests (hematology and serum chemistry) (if withdrew prior to Day 10).
- Physical examination (if withdrew prior to 72 hours [height and weight not required]).
- Wound healing assessment.
- AE recording.
- Concomitant medication recording.

7.5. Unscheduled Visits and Assessments

Unscheduled visits and assessments should be performed if clinically indicated in the opinion of the Investigator. Except when urgent clinical evaluation is necessary, it is expected that the Investigator will have the subject return for an unscheduled visit rather than directing the subject to a hospital emergency room. The following procedures and assessments are examples of what may be performed at an unscheduled visit, depending on the clinical situation:

- Vital signs.
- Physical examination.

- ECG.
- Wound healing assessment.
- AE recording.
- Concomitant medication recording.
- Blood sample collection to determine plasma bupivacaine concentration (if the unscheduled visit is potentially related to a cardiac or neurological TEAE).
- Blood sample collection for clinical safety laboratory tests (hematology and chemistry).

8. SAFETY MONITORING AND REPORTING

Investigators are responsible for the detection and documentation of events that meet the definition of an AE, a serious adverse events/serious TEAE (SAE), suspected adverse reaction, serious suspected adverse reaction, or unanticipated problem, as provided in this protocol.

Investigators must review the local product label for bupivacaine HCl so as to be aware of the safety-related events, which may be anticipated with its use. Investigators will also be versed in the latest standard of care guidelines.

8.1. Definition of Safety Parameters

8.1.1. Definition of an Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE may be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not considered causally associated with the use of the study drug. Any abnormal laboratory value, vital sign result, or ECG finding deemed clinically significant by the Investigator, regardless of causal relationship, must be reported as an AE. LAST signs or symptoms, abnormal physical examination findings and wound healing abnormalities should also be recorded as AEs. A clinical diagnosis, rather than the changes in laboratory analyte or other assessment, should be recorded (eg, anemia rather than low hemoglobin value).

Examples of AEs include the following:

- Significant or unexpected worsening or exacerbation of the condition or indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency or intensity of the condition (eg, abnormal physical examination finding).
- Signs, symptoms, or clinical sequelae of a suspected interaction.
- Signs, symptoms, or clinical sequelae of a suspected overdose of the study drug or a concurrent medication (overdose per se should not be reported as an AE or SAE, unless nonserious or serious sequelae occur).
- The following abnormal laboratory results:
  - Any laboratory abnormality suggestive of a new disease/organ toxicity or a worsening of a pre-existing condition.
  - Any laboratory abnormality that required the subject to have investigational product interrupted or discontinued.
  - Any laboratory abnormality that required the subject to receive specific treatment for the lab abnormality.

- Any laboratory abnormality that required additional monitoring and follow-up visits.
- Any laboratory abnormality requiring further diagnostic investigation.

The following examples are not considered AEs:

- Medical or surgical procedure (eg, endoscopy, appendectomy), although the condition that leads to the procedure is an AE.
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) (including laboratory values) present or detected at the start of the study that do not worsen.
- The disease or disorder being studied, or expected progression, signs, or symptoms of the disease or disorder being studied, unless they become more severe or occur with a greater frequency than expected for the subject's condition.
- Transient paresthesia that is considered to be clinically normal (would be expected to occur as a long-acting local anesthetic wears off).

8.1.2. Definition of a Serious Adverse Event

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death.
- A life-threatening AE (ie, presented an immediate risk of death from the event as it occurred. This criterion is not intended to include an AE that, had it occurred in a more severe form, might have caused death.)
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or 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.

The following events do not meet the definition of an SAE: hospitalization for elective treatment of a pre-existing condition that does not worsen from baseline, hospitalizations for a standard procedure for study drug administration and routine monitoring of the studied indication not associated with any deterioration in condition, social or convenience admission to a hospital, prolongation of a hospitalization for social or convenience reasons not associated with the

occurrence of an AE, or hospitalization or an emergency room visit that lasts less than 24 hours that does not meet the criteria of an important medical or a life-threatening event.

According to 21 Code of Federal Regulations (CFR) 812.3(s), an unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

8.1.3. Definition of a Suspected Adverse Reaction

A suspected adverse reaction is defined as any AE for which there is a reasonable possibility that the AE was caused by the study drug.

8.1.4. Definition of a Serious Suspected Adverse Reaction

A serious suspected adverse reaction is any suspected adverse reaction that is determined to be serious, based on the outcomes of a SAE described in Section 8.1.2.

8.1.5. Definition of Unanticipated Problems

Unanticipated problems are incidents, experiences, or outcomes that meet all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the research protocol and informed consent document approved by the ethics committee (EC; includes Institutional Review Boards [IRBs], Independent Ethics Committees [IECs], and Research Ethics Boards [REBs]) and (b) the characteristics of the participant population being studied.
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggest that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

An unanticipated adverse device effect is defined in Section 8.1.2.

8.2. Classification of Adverse Events

8.2.1. Severity of Adverse Events

The Investigator will assess the severity of each AE based on his/her clinical judgment using one of the following categories:

- **Mild:** Event is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.

- **Moderate:** Event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe:** Event interrupts a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2. Relationship to Study Drug

The Investigator will assess the relationship of each AE to study drug based on his/her clinical judgment. The Investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study drug must always be suspect. The Sponsor's assessment of relationship may differ from the Investigator's assessment.

Relationship to study drug will be assessed according to the following guidelines:

- **Possibly related:** The AE is known to occur with the study drug, there is a reasonable possibility that the study drug caused the AE, or there is a temporal relationship between the study drug and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study drug and the AE.
- **Unlikely related:** There is not a reasonable possibility that the administration of the study drug caused the event, there is no temporal relationship between the study drug and event onset, or an alternate etiology has been established.

Even in situations in which minimal information is available for initially reporting an SAE, it is important that the Investigator always make an assessment of causality for every event before entering the information into the eCRF or completing the SAE reporting form, in the event electronic data capture (EDC) is not available. The causality assessment is one of the criteria used when determining regulatory reporting requirements. The Investigator may change his or her opinion of causality in light of follow-up information and amend the SAE information accordingly in the eCRF or the SAE reporting form, as applicable.

8.3. Time Period and Frequency for Event Assessment and Follow Up

8.3.1. Adverse Event and Serious Adverse Event Monitoring

All AEs regardless of causality or seriousness will be recorded from the time the subject signs the ICF through Day 28.

If an Investigator becomes aware of an SAE that occurs in a subject more than 28 days after study drug administration and the Investigator considers the event to be possibly related to the study drug, the Investigator should report the SAE to the Sponsor as outlined in Section 8.4.1.

8.3.2. Follow-Up of Events

After the occurrence of an AE or SAE, the Investigator is required to follow each subject proactively and provide further information on the subject's condition. All AEs and SAEs documented at a previous visit or contact and designated as ongoing will be reviewed at subsequent visits or contacts.

Nonserious AEs will be followed after the last scheduled study visit until the event resolves, the condition stabilizes, or until the event is otherwise explained or judged by the Investigator to be no longer clinically significant (unless the subject is lost to follow-up or withdraws consent).

The Investigator will assess the outcome of each AE using the following categories:

- **Resolved:** The event resolved or the subject recovered without sequelae. An event (either serious or nonserious) occurred and had an endpoint, and the subject experienced no restrictions. Examples include stent placement for coronary artery disease (a device implanted is not a sequela), an appendectomy (a scar is not a sequela), a postoperative wound infection, or an upper respiratory tract infection.
- **Resolved with sequelae:** The event has at least one secondary outcome that may result in permanent disability, functional limitation, or both. Such sequelae are usually limited to SAEs. Examples include hip replacement resulting in foot drop (foot drop is not the intended outcome but is a risk of surgery), stroke resulting in paralysis, or emboli formation after a bacterial infection resulting in a renal infarct and loss of renal function.
- **Not resolved:** At the end of the study, a nonserious event either has not changed in intensity or may not have recovered to baseline values, and the outcome is unknown. Examples include headache, low-grade fever, or nausea.
- **Unknown:** The subject has withdrawn from the study prematurely or is lost to follow-up, and the status of the event is unknown.
- **Death**

SAEs will be followed until the event resolves (ie, when the event no longer meets any of the seriousness criteria), the condition stabilizes, or until the event is otherwise explained or judged by the Investigator to be no longer clinically significant (unless the subject is lost to follow-up or withdraws consent). The Investigator will ensure that follow-up information provided to the Sponsor includes results of any additional laboratory tests or investigations, histopathologic examinations, or consultations with other healthcare professionals that serve to clarify the nature of the event, the cause of the event, or both. New or updated information will be recorded as outlined in Section 8.4.1.

8.4. Reporting Procedures

8.4.1. Reporting Serious Adverse Events to the Sponsor

If the Investigator determines that an event meets the protocol definition of an SAE due to any cause that occurs during the course of this study, regardless of relationship to study drug, he/she

must notify the Sponsor by entering the SAE information into the eCRF **within 24 hours of the Investigator becoming aware of the SAE**.

If EDC is not available, the Investigator must complete an SAE reporting form and email it to the Sponsor **within 24 hours of the Investigator becoming aware of the SAE**. The Investigator must also enter the SAE information into the eCRF as soon as possible thereafter.

Email Address: Heron_PV@ubc.com

In the initial email, the Investigator must provide to the Sponsor the following eCRF pages, completed to the greatest extent possible:

- AE record
- Medical history
- Prior and concomitant medications

Also, the following documents are to be forwarded: any laboratory results, diagnostic test results, or medical reports relevant to the SAE.

EDC is the primary method for notification of SAE information. In rare circumstances and in the absence of email capacity, notification by fax or telephone is acceptable, with a copy of the SAE reporting form sent by overnight mail. Initial notification via telephone does not replace the need for the Investigator to complete the SAE information in the eCRF within the time frames outlined.

If the Investigator does not have all information regarding an SAE, he/she must not wait to receive additional information before notifying the Sponsor of the event. The SAE must be updated when additional information is received. Follow-up information received on all SAEs must be forwarded to the Sponsor using the same timelines as for an initial report.

The Investigator must notify the Sponsor by reporting any unanticipated adverse device effect within 24 hours of the Investigator becoming aware of the effect.

8.4.2. Reporting Unanticipated Problems to the Sponsor

If the Investigator determines that an event meets the protocol definition of an unanticipated problem, he/she must notify the Sponsor by completing an Unanticipated Problem Form and emailing it to the Sponsor **within 24 hours of the Investigator becoming aware of the problem**.

Email Address: Heron_PV@ubc.com

The following information will be included with unanticipated problem reporting:

- Protocol identifying information: protocol title, protocol number, and Investigator's name.
- A detailed description of the event, incident, experience, or outcome.
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an unanticipated problem.

It is the Investigator's responsibility to report unanticipated problem to the Sponsor and their EC, as required by local regulations.

8.4.3. Regulatory Reporting Requirements

The Investigator must promptly report all SAEs and unanticipated adverse device effects to the Sponsor in accordance with the procedures detailed in Section 8.4.1. The Sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the Investigator to the appropriate project contact for SAE receipt is essential so that serious suspected adverse reactions that are either unexpected or observed with increasing occurrence be reported and legal obligations and ethical responsibilities regarding the safety of other subjects are met.

Investigator letters are prepared according to Sponsor policy and are forwarded to the Investigators as necessary. An Investigator letter is prepared for any suspected adverse reaction that is attributable to study drug, serious, and unexpected. The purpose of the Investigator letter is to fulfill specific regulatory and GCP requirements regarding the product under investigation.

The Investigator, or responsible person according to local requirements, must comply with requirements related to the reporting of SAEs to the EC.

The Sponsor is responsible for informing ECs, Investigators, and regulatory authorities of finding that could adversely affect the safety of subjects or affect the conduct of the study. Events will be reported to regulatory authorities in accordance with expedited and period reporting requirements.

8.4.4. Pregnancy Reporting

Any subject who becomes pregnant during the study must be withdrawn from the study immediately. Female subjects who become pregnant within 28 days after receiving study drug should also notify the Investigator. The Investigator must attempt to follow the pregnancy to term or termination in order to report on outcome and health status of mother and child.

The Investigator must notify the Sponsor of any pregnancy by completing a Pregnancy Form and emailing it to the Sponsor **within 24 hours after the Investigator becomes aware of the pregnancy**.

Email Address: Heron_PV@ubc.com

8.5. Safety Oversight

Because this is a study evaluating approved products used in accordance with the product information, there will be no additional safety oversight.

The stopping criteria, enrollment suspension or study termination for safety issues, are provided in Section 13.5.

9. OTHER STUDY RESTRICTIONS

9.1. Contraception

Female subjects of childbearing potential must use an acceptable form of contraception in the event of sexual activity during the study and for 30 days after study drug administration. Acceptable forms of contraception include double-barrier contraception or an insertable, injectable, transdermal, or combination oral contraceptive approved by applicable regulatory authorities. Note: The does not apply to women in only a same-sex relationship or women in a monogamous relationship with a surgically sterile partner.

10. STATISTICAL CONSIDERATIONS

10.1. General Considerations

All safety data will be listed by subject. Unless otherwise specified, Baseline is defined as the last observed measurement, whether scheduled or unscheduled, prior to the start of study drug administration. All data will be summarized by treatment group. Continuous variables will be summarized using the number of subjects with data (n), mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

10.2. Determination of Sample Size

The sample size in this study was selected empirically without formal statistical assumptions.

10.3. Analysis Populations

Safety Population: All subjects who receive study drug will be included in the Safety Population. This population will be used for all summaries of safety data. The actual treatment received will be used for analysis in this population.

PK Population: All subjects who received at least 1 dose of study medication and had sufficient data to calculate PK parameters and do not have protocol deviations or AEs thought to significantly affect the PK of bupivacaine were included in the PK Population.

10.4. Statistical Analysis Methods

10.4.1. Disposition and Demographics

The number and percentage of subjects in the Safety Population will be summarized. Subject disposition, including the number of subjects screened, randomized, dosed, completing the 72-hour postoperative observation period, completing Day 28, and not completing Day 28 by reason for withdrawal will be summarized. Subject demographics and baseline characteristics will be summarized and will include age, age category, sex, race, ethnicity, height, weight, and BMI.

10.4.2. Safety Analyses

All safety data will be listed and summarized by treatment group.

AEs that occur between the time the subject signs the ICF and the start of study drug administration will be considered pretreatment AEs. AEs that start during or after study drug administration, or AEs with an onset prior to study drug administration that worsen during or after study drug administration will be considered TEAEs. All TEAEs will be coded and tabulated by System Organ Class and Preferred Term. Incidence of TEAEs, SAEs, and ORAEs will be summarized. AEs leading to study withdrawal, if any, will be listed separately.

Associated laboratory parameters such as hepatic profile, renal function, and hematology values will be grouped and presented together in summary tables. For each laboratory test, individual

subject values outside the standard reference range will be flagged. Shift tables will be produced showing the frequency of shifts from Baseline to the lowest and to the highest on study value in and out of the normal range as well as by visit. Laboratory parameters will also be summarized by visit.

The change from Baseline to each visit for each of the vital sign variables will be summarized. Abnormal vital sign values will be flagged and listed.

Wound healing assessment will be summarized. LAST assessment questionnaire results will be summarized.

10.4.3. Pharmacokinetic Analyses

Plasma bupivacaine concentrations will be determined using validated liquid chromatography tandem-mass spectrometry assays. Concentrations will be calculated by interpolation from a calibration curve. PK parameter estimates will be calculated using noncompartmental analysis.

10.5. Interim Analysis

No formal interim analyses are planned.

11. QUALITY ASSURANCE AND QUALITY CONTROL

Quality assurance and quality control systems will be implemented and maintained with standard operating procedures (SOPs) by the Sponsor and its designee(s), as appropriate, to ensure that the clinical study is conducted and the data are generated, documented (recorded), and reported in compliance with the protocol, International Council for Harmonisation (ICH) Guideline for Good Clinical Practice E6 guidelines, and applicable regulatory requirements. The accuracy, completeness, and reliability of the study data presented to the Sponsor, however, are the responsibility of the Investigator. The Investigator or designee must record all required data using the prespecified data collection method defined by the Sponsor or its designee.

The study will be monitored regularly by the Sponsor (Section 13.1) and may be audited or inspected by the Sponsor (or designee), EC, and/or regulatory authorities at any time during the study or after study completion. In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, the competent authority, or other regulatory agencies direct access to all study records. The Investigator will immediately notify the Sponsor of all audits or inspections scheduled by any regulatory authority and promptly forward copies of any audit or inspection reports received to the Sponsor.

12. REGULATORY AND ETHICAL CONSIDERATIONS

12.1. Regulatory Authority Approval

The Sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country specific regulatory requirements before any site may initiate the study in that country.

12.2. Ethical Conduct of the Study

This study will be conducted in compliance with the protocol and all applicable regulatory requirements in accordance with ICH/GCP and in general conformity with the most recent version of the Declaration of Helsinki.

12.3. Ethics Committee Approval

The Investigator or the Sponsor is responsible for submitting the following documents to the ECs for review and, if applicable, approval: study protocol, ICF(s), Investigator's Brochure, recruitment materials, information about study compensation to subjects, and any information for presentation to potential subjects by ECs.

The Investigator is responsible for providing the Sponsor with the written EC approval prior to commencing the study (ie, before shipment of study drug to the site). All amendments to the protocol require review and approval by the EC before the changes are implemented to the study. All changes to the ICF will be approved by the EC; a determination will be made regarding whether previously consented participants need to be re-consented. If any other information approved by the EC for presentation to potential subjects is amended during the study, the Investigator is also responsible for ensuring EC review and approval.

Study sites must adhere to all requirements stipulated by their respective ECs. This may include, but not be limited to, notifying the EC of serious and unexpected AEs or other local safety reporting requirements, submitting a final status report, or providing a synopsis of the study report upon study completion.

12.4. Informed Consent Process

Note: All references to "subject" in this section refer to the study subject or his/her legally authorized representative.

The Sponsor (or its designee) will provide Investigators with a multicenter ICF for this study. Investigators may adapt the information to suit the needs of their institution, if necessary (although it must reflect the required elements of informed consent specified in 21 CFR Part 50.25). The final ICF must be accepted by the Sponsor and approved by the EC. Investigators must provide the Sponsor with an unsigned copy of the final ICF before and after it is approved by the EC. If any new information becomes available that might affect subjects' willingness to participate in the study, or if any amendments to the protocol require changes to the ICF, the Sponsor will provide Investigators with a revised ICF.

Prior to participating in any study-related procedure, each subject must sign and date an EC-approved ICF written in a language the subject can understand. The ICF should be as nontechnical as practical and understandable to the subject. The ICF must provide the subject with all the information necessary to make an informed decision about their participation in the study, including the nature and intended purpose of the study, possible benefits, possible risks, disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF details the requirements of the participant and the fact that he/she is free to withdraw at any time without giving a reason and without prejudice to his/her further medical care. Before informed consent is obtained, the subject should be given ample time and opportunity to inquire about the details of the study. All questions must be answered to the satisfaction of the subject.

Once signed, the original ICF will be stored in the Investigator's site file and made available for review by the Sponsor. Documentation of the informed consent discussion must be noted in the subject's case history. All subjects will receive a copy of their signed and dated ICF.

If the ICF is revised during the study and requires the subject to be re-consented, informed consent will be obtained in the same manner as for the original ICF.

12.5. Confidentiality

All information provided by Heron Therapeutics, Inc. and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the Investigator and site staff. This information and data will not be used by the Investigator or other site personnel for any purpose other than conducting the study and will not be released to any unauthorized third party without prior written approval of the Sponsor. These restrictions do not apply to the following: 1) information that becomes publicly available through no fault of the Investigator or site staff, 2) information that must be disclosed in confidence to an EC solely for the evaluation of the study results, 3) information that must be disclosed in order to provide appropriate medical care to a study subject, or 4) study results that may be published as described in Section 13.6. If a written contract for the conduct of the study is executed and that contract includes confidentiality provisions inconsistent with this statement; that contract's confidentiality provisions shall apply rather than this statement; provided, however, that the confidentiality provisions in any written contract shall not be less restrictive than this statement.

The Investigator agrees to comply with all applicable national, state, and local laws and regulations relating to the privacy of subjects' health information. The Investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with the privacy regulations of the Health Insurance Portability and Accountability Act (HIPAA) and in a form satisfactory to the Sponsor.

The subject's contact information will be securely stored at each clinical site for internal use during the study. Throughout the study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected in the subject's eCRF). At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the EC and institutional regulations.

To comply with ICH guidelines for GCP and to verify compliance with this protocol, the Sponsor requires that the Investigator permit its monitor or designee's monitor, representatives from any regulatory authority, the Sponsor's designated auditors, and the appropriate ECs to review the subject's original medical records (source data or documents), including, but not limited to, clinical laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization by the subject as part of the informed consent process (Section 12.4).

13. STUDY ADMINISTRATION

13.1. Clinical Monitoring

The Sponsor (or its designee) is responsible for ensuring the proper conduct of the study. This includes ensuring the subjects' rights and well-being are protected, the conduct of the study is within compliance of an approved protocol and GCPs, and the integrity of the data are accurate, complete and verifiable from source documentation. At regular intervals during the study, the Sponsor's study monitors will contact the study site via site visits, telephone calls, emails, and letters in order to review study progress and the eCRF completion and to address any concerns or questions regarding the study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: subjects' informed consent documents, subject recruitment procedures, subjects' compliance with the study procedures, source-data verification, drug accountability, use of concomitant therapy by subjects, AE and SAE documentation and reporting, and the quality of data.

13.2. Source Documents and Record Retention

Each study site will maintain study documents and records as specified in *ICH E6, Section 8 (Essential Documents for the Conduct of a Clinical Trial)* and as required by regulatory and institutional requirements. These include, but are not limited to the following: the study protocol, eCRF, delegation of authority log, pharmacy dispensing records, drug accountability logs, AE reports, subject source data (original or certified copies), correspondence with health authorities and ECs, ICFs, monitoring visit logs, laboratory certification or quality control procedures, and laboratory reference ranges. Access to study documents and records will be strictly controlled (Section 12.5).

Study records must be retained for 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 until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by applicable regulatory requirements or if agreed to in the Clinical Trial Agreement. It is the responsibility of the Sponsor to inform the site as to when these documents no longer need to be retained.

13.3. Management of Protocol Amendments and Deviations

13.3.1. Protocol Modification

The protocol cannot be modified except in a formal protocol amendment by the Sponsor.

13.3.2. Protocol Deviations

Protocol deviations are a change, divergence, or departure from the study design or procedures defined in this protocol. An Important Protocol Deviation is a deviation that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. The Investigator will notify the EC of any protocol deviations as required by EC guidelines and site requirements. Protocol deviations will be

documented at the site and in the Sponsor files. In the event of an Important Protocol Deviation, the site will notify the Sponsor or designee. The Sponsor is responsible for notifying the regulatory authorities of any protocol deviations, if required.

13.4. Financial Disclosure

Investigators are required to inform the Sponsor of all disclosable financial interests or arrangements (including those of their spouse and dependent children), prior to study initiation at the site, at study completion, and 1 year after study completion in accordance with 21 CFR Part 54. In addition, the Investigator or subinvestigators must promptly notify the Sponsor if there are any reportable changes that occur during the above-described period.

Disclosable financial interests or arrangements, or the absence thereof will be recorded on the Financial Disclosure for Clinical Investigators Form.

Any Investigator(s) added as investigational staff to the FDA 1572 form must complete the Financial Disclosure for Clinical Investigators Form at the start of his/her participation in the study. The Financial Disclosure for Clinical Investigators Form for any Investigator(s) leaving the study prior to completion will also be obtained.

13.5. Stopping Criteria: Suspension or Termination of Study or Investigational Site

13.5.1. Suspension of Study

Enrollment will be suspended if the Sponsor discovers the occurrence of either of the following:

- Any death for which a clear alternative cause (unrelated to study drug) is not readily apparent.
- Three (3) non-fatal SAEs that are considered by the Sponsor to be possibly related to study drug, and that are either unexpected or for which a clear alternative cause is not readily apparent.

13.5.2. Termination of Study or Investigational Site

If the Sponsor, Investigator, or officials from regulatory agencies discover conditions arising during the study that indicate that the study should be halted or that a study site should be closed, this action may be taken after appropriate consultation between the Sponsor and Investigator(s). Reasons for terminating the study early or closing a site include, but are not limited to, the following:

- If there is a suspension of the study and further investigation shows that any death or 3 non-fatal SAEs are determined by the Sponsor to be related to study drug and pose an unacceptable risk to the study subjects, the study will be terminated.
- Discovery of an unexpected, significant, or unacceptable risk to the subjects.
- Failure of the Investigator to comply with the protocol, GCP regulations and guidelines, or local requirements.

- Insufficient adherence to protocol requirements or an unacceptably high rate of missing, erroneous, or improperly collected data.
- Data are not sufficiently complete and/or evaluable.
- Inadequate recruitment of subjects by the Investigator.
- Sponsor decision.

If the study is terminated early by the Sponsor, written notification documenting the reason for study termination will be provided to the Investigator and regulatory authorities. The Investigator will promptly inform the EC and provide the reason(s) for study termination.

13.6. Publication and Information Disclosure Policy

All information provided by the Sponsor and all data and information generated by the site as part of the study (other than a subject's medical records) are the sole property of Heron Therapeutics, Inc.

For clinical interventional studies in patients, Heron will post study results on websites such as https://clinicaltrials.gov/ and https://eudract.ema.europa.eu/ in accordance with FDA and European Union reporting rules. Regardless of study outcome, Heron commits to submit for publication results of its interventional clinical studies according to the prespecified plans for data analysis. Wherever possible, Heron also plans to submit for publication the results of any nonclinical or technology studies while protecting any proprietary information.

Any publication or presentation of the results of this study may only be made in compliance with the provisions outlined in the executed Clinical Trial Agreement. Heron has developed a policy for the publication of scientific and clinical data that follows the recommendations of the International Committee of Medical Journal Editors (ICMJE), the CONSORT (Consolidated Standards of Reporting Trials) group and Good Publication Practice (GPP). A copy of this policy will be made available to the Investigator upon request.

When the study is completed or prematurely terminated, the Sponsor or designee will ensure a Clinical Study Report is written in compliance with ICH E3 (Structure and Content of Clinical Study Reports) and submitted to the regulatory authorities, as required by the applicable regulatory requirement(s). Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical study report. The Investigator will be provided reasonable access to statistical tables, listings, and figures, as well as relevant reports, and will have the opportunity to review the complete study results.

14. REFERENCE LIST

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APPENDIX A. AMERICAN SOCIETY OF ANESTHESIOLOGISTS PHYSICAL STATUS CLASSIFICATION SYSTEM

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 substantial functional limitations. Examples include, but not limited to: 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	Substantial functional limitations; one or more of moderate to severe diseases. Examples include, but not limited to: 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 PCA <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 include, but not limited to: recent (<3 months) of 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 include, but not limited to: 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, acute renal disease; ASA, American Society of Anesthesiologists; 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; PCA, postconceptional age; PS, physical status; TIA, transient ischemic attack.

Note: 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 Physical Status Classification System approved by the ASA House of Delegates on October 15, 2014.

APPENDIX B. LOCAL ANESTHETIC SYSTEMIC TOXICITY ASSESSMENT

This Local Anesthetic Systemic Toxicity (LAST) questionnaire is provided to monitor for neurologic and cardiac signs and symptoms of LAST. Subjects should be assessed with this questionnaire at the following timepoints: 30 minutes (±5 min), 60 minutes (±5 min), 2 hours (±15 min), 4 hours (±15 min), 12 hours (±30 min), 24 hours (±1 h), and 72 hours (±2 h) following the start of study drug administration, and at the Early Termination Visit if the subject withdraws before 72 hours.

If a subject has signs or symptoms that may be attributed to LAST, vital sign measurements, 12-lead ECG, and blood sample collection for PK must be performed.

Instructions for completing the LAST questionnaire are provided on the following page.

Local Anesthetic Systemic Toxicity (LAST) Questionnaire

Record "Present" or "Absent" for each of the following symptoms. Clinically significant signs and symptoms that are present should be entered on the electronic case report form (eCRF) as adverse events. Note that if an event qualifies as an SAE (Section 8.4.1), the Sponsor must be notified within 24 hours of when the Investigator is first aware of the event.

Metallic/strange taste	Present ☐	Absent ☐
Perioral tingling	Present ☐	Absent ☐
Ringing in ears	Present ☐	Absent ☐
Visual disturbance	Present ☐	Absent ☐
Tremors	Present ☐	Absent ☐
Muscle twitching	Present ☐	Absent ☐
Dizziness/lightheadedness	Present ☐	Absent ☐
Convulsion/seizure	Present ☐	Absent ☐
Bradycardia	Present ☐	Absent ☐
Arrhythmia	Present ☐	Absent ☐
Hypotension	Present ☐	Absent ☐
Cardiac arrest	Present ☐	Absent ☐
Respiratory arrest	Present ☐	Absent ☐

Reference: Vasques, F., A.U. Behr, G. Weinberg, C. Ori, G. Di Gregorio (2015). "A Review of Local Anesthetic Systemic Toxicity Cases Since Publication of the American Society of Regional Anesthesia Recommendations: To Whom It May Concern." Reg Anesth Pain Med 40(6): 698-705.

APPENDIX C. WOUND HEALING ASSESSMENT - SOUTHAMPTON WOUND SCORING SYSTEM

Grade		Appearance
0		Normal healing
I.	**Normal healing with mild bruising or erythema:**	
a		Some bruising
b		Considerable bruising
c		Mild erythema
II.	**Erythema plus other signs of inflammation:**	
a		At 1 point
b		Around sutures
c		Along wound
d		Around wound
III.	**Clear or haemoserous discharge:**	
a		At 1 point only (≤2cm)
b		Along wound (>2 cm)
c		Large volume
d		Prolonged (>3 days)
	Major complication	
IV.	**Pus:**	
a		At 1 point only (≤2cm)
b		Along wound (>2 cm)
V.	**Deep or severe wound infection with or without tissue breakdown; haematoma requiring aspiration**	

Reference: Bailey, I. (1992). "Community surveillance of complications after hernia surgery." BMJ 304: 469-471.

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