Document Type:	Study Protocol
Official Title:	A Phase 2B, Randomized, Controlled Study of HTX-011 Administered Via Pectoral Nerve Block in Subjects Undergoing Upper Extremity Surgery for Augmentation Mammoplasty
NCT Number:	NCT03011333
Document Date:	15-Nov-2017

CLINICAL STUDY PROTOCOL: HTX-011-211

Protocol Title:	A Phase 2B, Randomized, Controlled Study of HTX-011 Administered Via Pectoral Nerve Block in Subjects Undergoing Upper Extremity Surgery for Augmentation Mammoplasty
Brief Title:	Phase 2B upper extremity nerve block study
Investigational Product:	HTX-011 (extended-release 2.5% bupivacaine and 0.075% meloxicam)
Phase of Development:	2B
Sponsor:	Heron Therapeutics, Inc. 4242 Campus Point Court, Suite 200 San Diego, CA 92121 1-858-251-4400
Medical Monitor:	[redacted]
Medical Project Leader:	[redacted]
Protocol Version:	Version 6 — 15 November 2017 Version 5 — 07 August 2017 Version 4 — 04 April 2017 Version 3 — 02 February 2017 Version 2 — 16 December 2016 Version 1 — 20 September 2016

INVESTIGATOR AGREEMENT

CLINICAL STUDY PROTOCOL: HTX-011-211

TITLE: A Phase 2B, Randomized, Controlled Study of HTX-011 Administered Via Pectoral Nerve Block in Subjects Undergoing Upper Extremity Surgery for 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, 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

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Name of Active Ingredients: Bupivacaine and meloxicam	**Phase of Development:** 2B

Study Objectives:

Primary Objective:

- To compare the efficacy and duration of analgesia following bilateral ultrasound-guided lateral and medial pectoral nerve block with HTX-011 to bupivacaine HCl without epinephrine and saline placebo in subjects undergoing upper extremity surgery.

Secondary Objectives:

- To evaluate the efficacy and duration of analgesia for HTX-011 administered using different techniques in this study population.
- To evaluate additional efficacy parameters in this study population.
- To characterize the bupivacaine and meloxicam pharmacokinetic (PK) profiles of HTX-011 in this study population.
- To determine the optimal administration technique of HTX-011 in this surgical model.
- To further assess the safety and tolerability of HTX-011 in this study population.

Methodology: This is a Phase 2B, randomized, double-blind, active- and saline placebo-controlled multicenter study in subjects undergoing bilateral submuscular augmentation mammoplasty under general anesthesia.

Subjects will be screened within 21 days prior to study drug administration. 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 administered a single dose of study drug (HTX-011, bupivacaine HCl without epinephrine, or saline placebo) via bilateral ultrasound-guided lateral and medial pectoral nerve block and/or instillation into the surgical site. For subjects receiving study drug via ultrasound-guided lateral and medial pectoral nerve block, study drug will be administered within 4 hours prior to undergoing mammoplasty. For subjects receiving study drug via instillation, study drug will be administered prior to the end of surgery.

Dexamethasone cannot to 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 in pain control on postoperative pain perception, subjects in Cohorts 2 and 4 will receive protocol-specified 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 (except for ropivacaine HCl), 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) or for pretreatment prior to a needle placement.

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 at 120 ±6 hours, and on Day 10 and Day 28 to complete follow-up assessments.

An internal Interim Review Committee (IRC) will review unblinded, summary-level efficacy, safety, and PK data from each cohort to determine if enrollment should be initiated in the next cohort and to guide Phase 3 study design. Each interim analysis will be performed after at least 80% of the planned number of subjects have all of their pain intensity and opioid use data through the 72-hour postoperative assessments entered into the electronic clinical

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database for that cohort. The IRC will operate under a written, detailed IRC Charter.

The study will include up to 4 cohorts.

Cohort 1

Approximately 24 subjects will be randomized to 1 of the following 3 treatment groups in a 2:1:1 ratio:

- HTX-011 60 mg (2.1 mL) via bilateral ultrasound-guided lateral and medial pectoral nerve block (12 subjects)
- Bupivacaine HCl without epinephrine 0.25% (50 mg, 20 mL) via bilateral ultrasound-guided lateral and medial pectoral nerve block (6 subjects)
- Saline placebo (2.1 mL) via bilateral ultrasound-guided lateral and medial pectoral nerve block (6 subjects)

Cohort 2

Cohort 2 was planned as an optional cohort. Following a review of the results from Cohort 1, the IRC recommended initiating enrollment in Cohort 2 and randomizing approximately 48 subjects to 1 of the following 3 treatment groups in a 2:1:1 ratio:

- HTX-011 (a single dose recommended by IRC of 120 mg/3.6 mg [bupivacaine/meloxicam doses], 4.1 mL) via bilateral ultrasound-guided lateral and medial pectoral nerve block (24 subjects)
- Bupivacaine HCl without epinephrine 0.25% (50 mg, 20 mL) via bilateral ultrasound-guided lateral and medial pectoral nerve block (12 subjects)
- Saline placebo (volume matching HTX-011 in Cohort 2) via bilateral ultrasound-guided lateral and medial pectoral nerve block (12 subjects)

Cohort 3

Cohort 3 was planned as an optional cohort. Following a review of the results from Cohort 2, the IRC recommended initiating enrollment in Cohort 3 and randomizing approximately 48 subjects to 1 of the following 3 treatment groups in a 2:1:1 ratio:

- HTX-011 (a single dose recommended by IRC of 240 mg/7.2 mg [bupivacaine/meloxicam doses], 8.2 mL) via bilateral ultrasound-guided lateral and medial pectoral nerve block (24 subjects)
- Bupivacaine HCl without epinephrine 0.25% (50 mg, 20 mL) via bilateral ultrasound-guided lateral and medial pectoral nerve block (12 subjects)
- Saline placebo (volume matching HTX-011 in Cohort 3) via bilateral ultrasound-guided lateral and medial pectoral nerve block (12 subjects)

Cohort 4

Cohort 4 was planned as an optional cohort. Following a review of the results from Cohort 3, the IRC recommended initiating enrollment in Cohort 4 and randomizing approximately 120 subjects to 1 of the following 4 treatment groups in a 4:4:1:1 ratio:

- HTX-011 (a single dose recommended by IRC of 400 mg/12 mg [bupivacaine/meloxicam doses], 13.7 mL) via bilateral ultrasound-guided lateral and medial pectoral nerve block (48 subjects)
- HTX-011 (a single dose recommended by IRC of 400 mg/12 mg [bupivacaine/meloxicam doses], 13.7 mL) via instillation into the intended space for the implant, with 200 mg/6 mg, 6.8 mL per side, and saline placebo (volume matching HTX-011 in Cohort 4) via bilateral ultrasound-guided lateral and medial pectoral nerve block for masking (48 subjects)
- Bupivacaine HCl without epinephrine 0.25% (50 mg, 20 mL) via bilateral ultrasound-guided lateral and medial

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pectoral nerve block (12 subjects)

- Saline placebo (volume matching HTX-011 in Cohort 4) via bilateral ultrasound-guided lateral and medial pectoral nerve block (12 subjects)

Postoperative Opioid Rescue Medications

Subjects should only receive rescue medication upon request for pain control as needed during the 72-hour postoperative observation period. Prior to the administration of the first dose of rescue medication, if the subject has not already had at least 1 postoperative pain score assessed, then a Numeric Rating Scale (NRS) score at rest (NRS-R) and a Numeric Rating Scale score with activity (NRS-A) pain score must be obtained.

Postoperative rescue medication will consist of oral (PO) immediate-release oxycodone (no more than 10 mg within a 4-hour period as needed) and/or intravenous morphine (no more than 10 mg within 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. Subjects will complete a daily diary to record if they take an opioid medication between 72 hours and Day 28.

Number of Planned Subjects: Up to approximately 240 subjects will be randomized and dosed

Study Sites: Approximately 5 study sites in the United States (US)

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, adhere to the study visit schedule, and complete all study assessments.
2. Is female ≥18 years of age at screening.
3. Is scheduled to undergo primary bilateral submuscular augmentation mammoplasty with saline or silicone smooth implants with a volume of 300 to 500 cc, inclusive. Note: textured implants are not allowed.
4. Has an American Society of Anesthesiologists Physical Status of I, II, or III.
5. Is suitable for a nerve block procedure.
6. Is able to demonstrate motor function by raising both arms above the head unassisted.
7. Is able to assess sensory function by exhibiting sensitivity to cold in the pectoral area (upper outer quadrant).
8. Subjects are eligible only if all of the following apply:
    a. Not pregnant (subjects of child-bearing potential must have a negative urine pregnancy test at screening and on Day 0 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.

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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 and which may confound the postoperative assessments.
4. Has a contraindication or a known or suspected history of hypersensitivity or clinically significant idiosyncratic reaction to bupivacaine (or other local anesthetics), meloxicam (or other NSAIDs), oxycodone, morphine, or fentanyl.
5. Has known or suspected daily use of opioids for 7 or more consecutive days within the previous 6 months.
6. Has taken NSAIDs (including meloxicam) within at least 10 days prior to surgery with the exception of subjects on low-dose (<100 mg) daily acetylsalicylic acid for cardioprotection.
7. Has taken long-acting opioids within 3 days prior to surgery.
8. Has taken any opioids within 24 hours prior to the scheduled surgery.
9. Has been administered bupivacaine within 5 days prior to the scheduled surgery.
10. Has been administered any local anesthetic within 72 hours prior to the scheduled surgery other than to treat an AE that occurs after signing the ICF and prior to study drug administration or for pretreatment prior to a needle placement.
11. Has initiated treatment with any of the following medications within 1 month prior to study drug administration or is taking any of these medications to control pain: selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin, duloxetine, or cyclooxygenase-2 (COX-2) inhibitors. (Note: If a subject is taking one of these medications for a reason other than pain control, she must be on a stable scheduled dose [ie, not "as needed"] for at least 1 month prior to study drug administration.) Anxiolytics prior to surgery are permitted, if necessary.
12. 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. Loss of sensation in extremities or significant peripheral neuropathy.
13. 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).
14. Has uncontrolled anxiety, psychiatric, or neurological disorder that might interfere with study assessments.
15. Has any chronic neuromuscular deficit of either pectoral nerve function or arm/shoulder/truncal musculature.
16. Has any chronic condition or disease that would compromise neurological or vascular assessments.
17. Had a malignancy in the last year, with the exception of non-metastatic basal cell or squamous cell carcinoma

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of the skin or localized carcinoma in situ of the cervix.

18. 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.
19. Previous participation in an HTX-011 study or received an investigational product or device in a 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.
20. Has undergone 3 or more surgeries in 12 months prior to signing the ICF, other than for diagnostic procedures (eg, colonoscopy).
21. Has a body mass index (BMI) >35 kg/m^2.

Investigational Product, Dose, and Mode of Administration:

HTX-011 is an extended-release, fixed-ratio combination product that contains bupivacaine (a local anesthetic as the free base) and low-dose meloxicam (an NSAID) incorporated in a bioerodible polymer (termed Biochronomer®). HTX-011 will be supplied by the Sponsor as a sterile, viscous liquid.

A single dose of HTX-011 will be administered by bilateral ultrasound-guided lateral and medial pectoral nerve block and/or instillation within the pectoral pocket. Doses between 60 and 400 mg, inclusive, may be evaluated in this study.

Reference Therapy, Dose, and Mode of Administration:

Bupivacaine HCl without epinephrine 0.25% (50 mg) and saline placebo (0.9% sodium chloride solution) will be administered by bilateral ultrasound-guided lateral and medial pectoral nerve block.

Bupivacaine HCl and saline placebo will be supplied by sites.

Duration of Treatment: Subjects will receive a single dose of study drug. The overall duration of the study is anticipated to be approximately 18 months. The total duration of study participation for each subject (from Screening through Day 28) will be up to 53 days.

Criteria for Evaluation:

Efficacy, safety, and PK assessments will be performed. The end of surgery will be considered as Time 0 for all efficacy and safety assessments, except where otherwise specified. The start of study drug administration will be considered as Time 0 for all PK timepoints.

Efficacy Assessments:

- Pain intensity scores using the Numeric Rating Scale at rest (NRS-R) on Day 0 before study drug administration; at 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours; and on Day 10 and Day 28.
- Pain intensity scores using the NRS-A (with the elbows at the side and against the body, raise hands in front of abdomen, clasp hands together, and hold that position for at least 5 seconds) on Day 0 before study drug administration; at 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours; and on Day 10 and Day 28.
- Date, time of administration, and amount of all opioid rescue medication taken through 72 hours.
- Subject daily diary to record if any opioids were taken from 72 hours through Day 28.
- Patient Global Assessment (PGA) of pain control at 24, 48, and 72 hours, and on Day 28.
- Discharge readiness assessment per the Modified Postanaesthetic Discharge Scoring System (MPADSS) criteria

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at 2, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours. (Note: This study instrument assesses a subject's potential readiness to be discharged and should be repeated at all scheduled timepoints. It is not meant to be used to decide on whether or not to discharge a subject from the study, as subjects are required to remain in the hospital/research facility for 72 hours.)

- Subject's satisfaction with postoperative pain control at 24, 48, and 72 hours, and on Day 10 using a 5-point Likert scale.
- Overall benefit of analgesia score (OBAS) at 24, 48, and 72 hours, and on Day 28.

Safety Assessments:

- AEs from the time the subject signs the Informed Consent Form through Day 28.
- Clinical laboratory tests at the Screening visit (hematology and serum chemistry), 24 hours (hematology only), and at 72 hours and Day 10 (hematology and serum chemistry).
- Physical examination at the Screening visit and 72 hours; the Screening visit should include height, weight, and BMI calculation.
- Wound healing assessment at 72 hours and on Day 10 and Day 28.
- Vital signs (resting heart rate, blood pressure, and respiration rate) at the Screening visit, on Day 0 before study drug administration, and post-treatment at 24, 48, and 72 hours.
- ECG at the Screening visit.
- Continuous Holter monitoring beginning at least 24 hours prior to surgery through 72 hours.
- Motor function assessment (ie, with the elbows at the side and against the body, raise hands in front of abdomen, clasp hands together, and hold that position for at least 5 seconds) at the Screening visit; 6, 12, 24, 48, and 72 hours; and on Day 10.
- Sensory function assessment (ie, cold alcohol swab test on the upper outer quadrant of the breast on the side of the dominant hand) at the Screening visit; at 15, 30, and 60 minutes after the start of ultrasound-guided study drug administration; at 6, 12, 24, 48, and 72 hours after the end of surgery; and on Day 10.
- Blinded assessor's satisfaction with return of sensory and motor function at 24, 48, and 72 hours and on Day 10 using a 5-point Likert scale.

Pharmacokinetic Assessments:

Blood samples for bupivacaine and meloxicam PK analysis will be collected at the following timepoints: prior to study drug administration and at 30 minutes and 1, 2, 4, 6, 8, 12, 20, 22, 24, 26, 28, 36, 48, 60, 72, and 120 hours after the start of study drug administration. (Note: when PK and NRS pain intensity assessments coincide, the NRS pain intensity assessments should be conducted before the blood draw.)

Study Endpoints:

Primary Efficacy Endpoint

- Mean area under the curve (AUC) of the NRS-A pain intensity scores through 24 hours (AUC_{0-24}).

Secondary Efficacy Endpoints

- Mean total postoperative opioid consumption (in morphine equivalents) through 24, 48, and 72 hours.
- Median time in hours to first opioid rescue administration through 72 hours.
- Mean AUC of the NRS-A pain intensity scores at the following intervals: 0-6, 0-12, 12-24, 24-48, 0-48, 48-72,

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and 0-72 hours.

- Mean AUC of the NRS-R pain intensity scores at the following intervals: 0-6, 0-12, 12-24, 0-24, 24-48, 0-48, 48-72, and 0-72 hours.
- Mean NRS-R pain intensity scores at each assessed timepoint.
- Mean NRS-A pain intensity scores at each assessed timepoint.
- Integrated Rank Analysis of Silverman using the NRS-A pain intensity AUC scores and total opioid consumption through 24, 48, and 72 hours.
- Proportion of subjects achieving a score of "good" or better (>1) pain control based on PGA at 24, 48, and 72 hours, and on Day 28.
- Proportion of subjects who are pain-free at rest (defined as an NRS-R pain intensity score of 0 or 1) at each assessed timepoint.
- Proportion of subjects who are pain-free with activity (defined as an NRS-A pain intensity score of 0 or 1) at each assessed timepoint.
- Proportion of subjects who are opioid-free through 24, 48, and 72 hours.
- Proportion of subjects who are opioid-free from 72 hours through Day 10 and Day 28.
- Proportion of subjects who first achieve an MPADSS score ≥9 at 2, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours.
- Mean subject's satisfaction with postoperative pain control at 24, 48, and 72 hours and on Day 10.
- Mean OBAS at 24, 48, and 72 hours, and on Day 28.

Safety Endpoints

- Incidence of treatment-emergent AEs (TEAEs), serious TEAEs (SAEs), and opioid-related AEs (ORAEs) through Day 28.
- Change from baseline in clinical laboratory results.
- Change from baseline in vital signs at each assessed timepoint.
- Change from baseline in Holter data.
- Wound healing assessment at 72 hours and on Day 10 and Day 28.
- Time to return of motor function.
- Loss of sensation in the breast at 15, 30, and 60 minutes after the start of ultrasound-guided study drug administration.
- Time to return of sensory function.
- Blinded assessor's satisfaction with return of sensory and motor function at 24, 48, and 72 hours, and on Day 10.

Pharmacokinetic Endpoints

- Maximum observed plasma concentration (C_{max}).
- 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).

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- Apparent terminal elimination half-life ($t_{½el}$).

Statistical Methods:

Efficacy Analyses:

For the purposes of statistical hypothesis testing, data for saline placebo subjects will be pooled across cohorts into a single saline placebo treatment group, and data for bupivacaine HCl subjects will be pooled across cohorts into a single bupivacaine HCl treatment group. The primary endpoint of mean AUC_{0-24} of the NRS-A pain intensity scores will be analyzed using an analysis of variance (ANOVA) model with treatment as the main effect. Each dose of HTX-011 will be tested against each of the pooled control arms. Results will be expressed as mean AUCs and standard deviations (SDs), least-squares mean differences and standard errors (SEs) with associated 95% confidence intervals (CIs), and p-values. Other continuous efficacy endpoints will be analyzed similarly to the primary endpoint.

Categorical endpoints will be analyzed using Fisher's exact test. Results will be expressed as the number and percentage of subjects meeting the relevant endpoint, differences in proportions with 95% CIs, and p-values. Median time in hours to first opioid rescue administration will be analyzed using Kaplan-Meier methods.

Safety Analyses:

All safety data will be listed and summarized by treatment group, with data for each control group pooled across cohorts, 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, and ORAEs will be summarized and presented in descending order of frequency according to the highest dose of HTX-011 studied. 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.

Interim Analysis:

Up to 4 interim analyses are planned. An internal IRC will review unblinded, summary-level data from each cohort to make study design decisions. Each interim analysis will be performed after at least 80% of the planned number of subjects have all of their pain intensity and opioid use data through the 72-hour postoperative assessments entered into the electronic clinical database for that cohort. The internal IRC will be composed of 1 Sponsor representative from the Clinical Research, Biometrics, Pharmacovigilance, Regulatory, and Pharmaceutical and Translational Sciences functions. The IRC will operate under a written, detailed IRC Charter.

Determination of Sample Size:

The sample size of up to approximately 240 subjects in this study was selected empirically without formal statistical assumptions.

SCHEDULE OF EVENTS

Assessments*	Time Window	Screening		Day 0		1h	2h	4h	6h	8h	12h	20h	22h	24h	26h	28h	36h	48h	60h	72h	120h	D10	D28	ET[a]
		≤21 days	≤1 day	Preop	OR	±5 min	±15 min	±15 min	±30 min	±30 min	±30 min	±1h	±1h	±1h	±1h	±1h	±2h	±2h	±2h	±2h	±6h	±2d	±4d	
Obtain informed consent		X																						
Assess/confirm eligibility		X		X[b]																				
Medical history		X																						
Demographics		X																						
Urine pregnancy test (WOCBP only)[c]		X		X[b]																				
Urine drug screen[c]		X		X[b]																				
Physical examination		X[d]																		X				X[e]
Vital signs		X		X[b]										X				X		X				X[e]
12-lead ECG (triplicate)		X																						
Sensory function test (cold test)		X		X[g]					X		X			X				X		X		X		X[h]
Motor function test[i]		X							X		X			X				X		X		X		X[h]
Subject training for pain assessments		X		X[b]																				
Randomize subject[j]			X																					
Holter monitoring[k]			◄	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	►				
Clinical safety laboratory tests[l]		X												X						X		X		X[h]
Administer study drug[m]				X	X																			
Surgery					X																			
Record any opioid rescue medication						◄	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	►					
Pain intensity assessment (NRS-R)[n]				X[b]		X	X	X	X	X	X			X			X	X	X	X		X	X	X[e]
Pain intensity assessment (NRS-A)[n]				X[b]		X	X	X	X	X	X			X			X	X	X	X		X	X	X[e]
Discharge readiness per MPADSS[o]							X	X	X	X	X			X			X	X	X	X				
Wound healing assessment																				X		X	X	X
Subject's satisfaction with pain control														X				X		X		X		
Blinded assessor satisfaction with return of sensory and motor function														X				X		X		X		
PGA of pain control														X				X		X			X	X[f]
OBAS assessment														X				X		X			X	
Subject daily diary[p]																				◄	- - -	- - -	►	
Concomitant medications[q]		◄	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	►	X
Adverse events[r,s]		◄	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	►	X
*PK blood sample[s,t]				X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

Abbreviations: d, day; ECG, electrocardiogram; ET, Early Termination; h, hour; min, minutes; MPADSS, Modified Postanaesthetic Discharge Scoring System; NRS-A, Numeric Rating Scale with activity; NRS-R, Numeric Rating Scale at rest; OBAS, overall benefit of analgesia score; OR, operating room; PGA, Patient

Global Assessment; PK, pharmacokinetic; Preop, preoperative assessments; WOCBP, women of childbearing potential; D10, Day 10; D28, Day 28.

* The start of study drug administration will be considered as Time 0 for all PK timepoints. The end of surgery (defined as placement of last suture) will be considered as Time 0 for all efficacy and safety timepoints. For 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 awakening the subject (eg, blood collection for PK sample) should be completed. See Section 6 for more information on study procedures and assessments.

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

[b] Before study drug administration.

[c] Result must be negative and confirmed prior to study drug administration. 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.

[d] Includes height, weight, and body mass index (BMI) calculation.

[e] Only if subject withdraws prior to 72 hours.

[f] Only if subject withdraws prior to Day 28.

[g] A sensory function test (cold alcohol swab test on the upper outer quadrant of the breast on the side of the dominant hand) should be performed at 15, 30, and 60 minutes after the start of ultrasound-guided study drug administration. Assessments do not need to be performed if the subject is in or on the way to the operating room.

[h] Only if subject withdraws prior to Day 10.

[i] Having the subject keep her elbows at her side and against her body and then raise her hands in front of her abdomen, clasp hands together, and hold that position for at least 5 seconds.

[j] Subjects who meet the Screening eligibility criteria will be randomized. Randomization may be done up to 1 business day prior to study drug administration. Subject does not need to be present for randomization to occur.

[k] Subjects will be required to have continuous reading of the Holter monitor at least 24 hours before surgery.

[l] Hematology at 24 hours; hematology and serum chemistry at all other timepoints.

[m] For subjects receiving study drug via ultrasound-guided lateral and medial pectoral nerve block, study drug will be administered within 4 hours prior to undergoing mammoplasty. For subjects receiving study drug via instillation into the surgical site, study drug will be administered prior to the end of surgery.

[n] NRS-R pain intensity scores will be assessed in a dependent position. NRS-A pain intensity scores will be assessed by having the subject keep her elbows at her side and against her body and then raise her hands in front of her abdomen, clasp hands together, and hold that position for at least 5 seconds.

[o] This study instrument assesses a subject's potential readiness to be discharged and should be repeated at all scheduled timepoints. It is not meant to be used to decide on whether or not to discharge a subject from the study.

[p] Subjects will complete a daily diary to record the use of opioids from 72 hours through Day 28.

[q] At the Screening Visit, ensure subject is not taking any prohibited medications. Record all medications taken between the day of signing the Informed Consent Form and Day 28.

[r] Adverse events will be collected from the time the subject signs the Informed Consent Form through Day 28.

[s] If a cardiac or neurological treatment-emergent adverse event occurs during the study, a blood sample should be collected at the time that the event is noted to determine the plasma bupivacaine concentration.

[t] A PK sample should be collected 30 minutes (±5 min) after the start of study drug administration.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ANOVA	Analysis of variance
ASA	American Society of Anesthesiologists
AUC	Area under the curve
BMI	Body mass index
CFR	Code of Federal Regulations
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
CTM	Clinical trial material
CV	Cardiovascular
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
ET	Early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPP	Good Publication Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
hr(s)	Hour(s)
IB	Investigator's Brochure
ICF	Informed Consent Form
IEC	Independent Ethics Committee
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IP	Investigational product
IRB	Institutional Review Board
IRC	Interim Review Committee
ITT	Intent-to-Treat
LAST	Local anesthetic systemic toxicity
LOCF	Last observation carried forward
min	Minute

mITT	Modified Intent-to-Treat
MPADSS	Modified Postanaesthetic Discharge Scoring System
NRS	Numeric Rating Scale
NRS-A	NRS scores with activity
NRS-R	NRS scores at rest (in a dependent position)
NSAID	Nonsteroidal anti-inflammatory drug
OBAS	Overall benefit of analgesia score
ORAE	Opioid-related adverse event
PACU	Postanesthesia care unit
PGA	Patient Global Assessment
PK	Pharmacokinetic(s)
PO	By mouth, orally
Preop	Preoperative
PRN	As needed
REB	Research Ethics Board
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SNRI	Selective norepinephrine reuptake inhibitors
SOP	Standard Operating Procedures
SPI	Summed pain intensity
SSRI	Selective serotonin reuptake inhibitors
$t_{½el}$	Apparent terminal elimination half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum plasma concentration
ULN	Upper limit of normal
US	United States
WOCBP	Women of child-bearing potential
wWOCF	Windowed worst observation carried forward
λz	Apparent terminal elimination rate constant

1. INTRODUCTION

1.1. Background Information and Study Rationale

It is estimated that up to 80% of patients suffer from moderate to severe pain during the first 24 to 48 hours after surgery (Gan 2014). Consequently, many are given narcotic analgesics for pain management. Administering a local anesthetic is a relatively simple and safe means of providing postoperative pain relief and promoting a quicker recovery; however, a major limitation of local anesthetics is their short duration of effect (6 to 12 hours following surgery) (Kehlet 2011). The development of an extended release local anesthetic that would provide pain relief during this critical postoperative timeframe and reduce the need for narcotics would be of clinical significance.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have long been used in the treatment of postoperative pain (Moote 1992), and there is evidence that there may be a synergistic interaction between local anesthetics and NSAIDs when locally administered together (Ortiz 2011).

In the past decade, the use of regional anesthesia in general, in particular peripheral nerve blocks, has increased dramatically. These techniques may allow for more rapid discharge from the hospital and decrease opioid load. Developing a long-acting agent that can be used in nerve block would help to further facilitate this trend.

Heron is developing HTX-011 for the management of postoperative pain. HTX-011 is an extended-release, fixed-ratio combination product that contains bupivacaine (a local anesthetic as the free base) and low-dose meloxicam (an NSAID) incorporated in a bioerodible polymer (termed Biochronomer®). When HTX-011 is administered, the polymer undergoes controlled hydrolysis in the tissue, resulting in the extended release of bupivacaine and meloxicam. The extended release is achieved using a proprietary vehicle formulation consisting of the novel tri[ethylene glycol]-based poly[orthoester] polymer (AP135) in combination with different excipients approved for human use (dimethyl sulfoxide, glycerol triacetate [triacetin], and maleic acid).

This is a Phase 2B, randomized, double-blind, active- and saline placebo-controlled, multicenter study in subjects undergoing augmentation mammoplasty to evaluate the analgesic efficacy, safety, and pharmacokinetics (PK) of HTX-011 when administered via bilateral ultrasound-guided lateral and medial pectoral nerve block before surgery and/or instillation into the surgical site.

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

Augmentation mammoplasty is an accepted model of postoperative pain. Augmentation mammoplasty produces generally reliable and persistent pain symptoms for a period typically lasting longer than 72 hours from the surgery, which allows for analysis of acute analgesia over an extended period of time.

HTX-011 will be administered by bilateral ultrasound-guided lateral and medial pectoral nerve block. A pectoral nerve block is commonly used for surgical anesthesia and the management of postoperative pain for upper extremity surgeries and is associated with a low risk of complications. HTX-011 may also be administered via instillation within the pectoral pocket. Nonclinical studies demonstrated that HTX-011 is compatible with the silicone membranes used to fabricate implants, and does not significantly affect the tensile properties of the membrane or extract significant amounts of silicone or other leachables. Bupivacaine HCl without epinephrine and saline placebo will be used as active control and placebo control, respectively, for efficacy and safety evaluations.

Initially, single doses of HTX-011 from 60 to 300 mg, inclusive, were to be evaluated in this study. Doses up to 600 mg have been evaluated in previous HTX-011 Phase 2 clinical studies. A Phase 1, saline placebo-controlled study evaluated single doses of 100, 200, and 400 mg of HTX-011 administered to healthy volunteers via subcutaneous injection. All doses were well tolerated, and demonstrated therapeutically relevant plasma bupivacaine levels were sustained for 2 to 3 days in the absence of the large initial peak observed with commercially available formulations of the drug (bupivacaine HCl). The analgesic effects of HTX-011 persisted through 96 hours, which closely correlated with plasma bupivacaine concentrations. HTX-011 doses up to 600 mg have also been administered in concluded and ongoing Phase 2 studies; current data show that they have been generally well tolerated.

Nonclinical and clinical data support a dose of HTX-011 400 mg/12 mg (bupivacaine/meloxicam doses) administered as a 100 mg dose to each of the lateral and medial pectoral nerves bilaterally. These data include results from a femoral nerve block toxicity study in the dog with HTX-011 doses of 60 mg and 120 mg via ultrasound guided administration that showed no gross or microscopic changes related to HTX-011. Moreover, the summary PK results from the HTX-011 doses of 120 mg/3.6 mg and 240 mg/7.2 mg in Cohorts 2 and 3 reviewed by the IRC in the present clinical study showed that the bupivacaine C_{max} was relatively linear with dose. Thus, extrapolation to a dose of 400 mg/12 mg is reasonable and yields a projected mean bupivacaine C_{max} of approximately 700 ng/mL. Further, mean bupivacaine C_{max} values for the 120 mg/3.6 mg and 240 mg/7.2 mg dose groups in the present study are consistent with dose-adjusted C_{max} values observed in the HTX-011 Phase 2 program following local administration of HTX-011.

The 28-day duration of postoperative assessments is considered appropriate for determining the analgesic effect-time curve, safety, and PK profiles for HTX-011.

Interim analyses will be performed after at least 80% of the planned number of subjects have all of their pain intensity and opioid use data through the 72-hour postoperative assessments entered into the electronic clinical database for that cohort. The choice of 72 hours was based on results from all HTX-011 clinical studies to date, which showed that the time to maximum plasma concentration for bupivacaine is less than 24 hours. An interim analysis after the 72-hour assessments will therefore include maximal exposure to study drug.

The study will employ a randomized and double-blind design to minimize potential bias in subject selection as well as efficacy and safety assessments. Specific members of the site's pharmacy staff and surgical staff will not be blinded to the treatment assignments because

HTX-011 is colored and viscous whereas bupivacaine HCl and saline placebo are not, and the volume of study drug to be administered varies by treatment group. However, subjects will also not be aware of the study drug they are receiving, and once surgery is complete and the subject is transferred to the postanesthesia care unit (PACU), the Investigator and all staff involved in efficacy and safety assessments will be blinded to treatment assignments until after database lock.

As a postoperative pain study, the primary endpoint is the area under the curve (AUC) of the Numeric Rating Scale (NRS) pain intensity scores with activity (NRS-A) from the start of study drug administration through 24 hours. Secondary efficacy endpoints will be assessed through 72 hours and beyond and will include assessments of opioid use, including the time to first use of opioid rescue medication, as recommended by draft Food and Drug Administration (FDA) guidelines (FDA Draft Guidance for Industry, *Analgesic Indications: Developing Drug and Biological Products* [February 2014]).

1.3. Potential Risks and Benefits

As of 28 February 2017, more than 600 subjects have been exposed to 1 of 3 different formulations of HTX-011 in 6 clinical studies. Studies included healthy volunteers and subjects undergoing elective surgery (bunionectomy, herniorrhaphy, and abdominoplasty). In healthy volunteer studies, the 2 most common adverse events (AEs) when HTX-011 was administered subcutaneously were contusion and erythema at the site of administration.

All subjects undergoing surgery received a single dose of an HTX-011 formulation ranging from 30 mg to 600 mg (based on bupivacaine dose) via local administration into the surgical site (injection, instillation, a combination of injection and instillation, or injection using a Mayo block). HTX-011 was generally well tolerated. Most of the treatment-related AEs (TEAEs) were mild or moderate in severity and resolved without sequelae. When administered to subjects undergoing surgery, the 2 most common TEAEs were nausea and constipation. [redacted] In a bunionectomy study with the current formulation at doses up to 200 mg, 1 SAE of non-healing postoperative wound was reported in a subject who received the 200 mg dose.

An identified risk for HTX-011 is incision site erythema, which was observed primarily in bunionectomy. Most events were self-limiting, mild or moderate in severity, and resolved without intervention or sequelae.

Potential risks for bupivacaine include dose-related cardiovascular (CV) and central nervous system toxicity (MARCAINE USPI 2011; MARCAIN SmPC 2016). 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.

Potential risks for meloxicam include CV adverse reactions and gastrointestinal bleeding (MOBIC SmPC 2015; MOBIC USPI 2016). NSAIDs may cause an increased risk of serious CV thrombotic events, myocardial infarction, and stroke, which can be fatal, and this risk may increase with duration of use. Patients with CV disease or risk factors for CV disease may be at greater risk. NSAIDs may also cause an increased risk of serious gastrointestinal AEs including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. Elderly patients are at greater risk for serious gastrointestinal events. It is unclear how applicable these potential risks are for meloxicam when given as a single local administration (a novel administration method for meloxicam) for postoperative pain as part of a fixed-ratio combination (eg, HTX-011).

The analgesic efficacy with the current HTX-011 formulation is being evaluated in ongoing Phase 2 studies. In one Phase 2 study in subjects undergoing unilateral open inguinal herniorrhaphy, single-dose administration of the current HTX-011 formulation at doses of 200 mg to 400 mg resulted in a significant reduction in mean AUC of pain intensity scores through 72 hours compared with saline placebo. Similar efficacy results were observed in a second Phase 2 study in subjects undergoing simple unilateral bunionectomy, where single-dose administration of the current HTX-011 formulation at doses ranging from 60 mg to 200 mg also significantly decreased the mean AUC of pain intensity scores through 72 hours. HTX-011 was also associated with decreased total opioid consumption, and resulted in more subjects who were opioid-free and a longer time to first opioid use compared with saline placebo.

For more information on HTX-011, refer to the HTX-011 Investigator's Brochure (IB). For more information on the active pharmaceutical ingredients, bupivacaine and meloxicam, refer to the local product labels.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to compare the efficacy and duration of analgesia following bilateral ultrasound-guided lateral and medial pectoral nerve block with HTX-011 to bupivacaine HCl without epinephrine and saline placebo in subjects undergoing upper extremity surgery.

2.2. Secondary Objectives

The secondary objectives are as follows:

- To evaluate the efficacy and duration of analgesia for HTX-011 administered using different techniques in this study population.
- To evaluate additional efficacy parameters in this study population.
- To characterize the bupivacaine and meloxicam PK profiles of HTX-011 in this study population.
- To determine the optimal administration technique of HTX-011 in this surgical model.
- To further assess the safety and tolerability of HTX-011 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 2B, randomized, double-blind, active- and saline placebo-controlled, multicenter study to evaluate the analgesic efficacy, safety, and PK of HTX-011 administered by pectoral nerve block and/or instillation into the surgical site in subjects undergoing bilateral submuscular augmentation mammoplasty under general anesthesia.

Subjects will be screened within 21 days prior to study drug administration. 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 administered a single dose of study drug (HTX-011, bupivacaine HCl without epinephrine, or saline placebo) via bilateral ultrasound-guided lateral and medial pectoral nerve block and/or instillation into the surgical site. For subjects receiving study drug via ultrasound-guided lateral and medial pectoral nerve block, study drug will be administered within 4 hours prior to undergoing mammoplasty. For subjects receiving study drug via instillation, study drug will be administered prior to the end of surgery (see Section 5.5 for details on study drug administration).

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 in pain control on postoperative pain perception, subjects in Cohorts 2 and 4 will receive protocol-specified 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 (except for ropivacaine HCl), or anti-inflammatory agents (except as specified by the protocol) is prohibited, unless needed to treat an AE that occurs after signing the Informed Consent Form (ICF) or for pretreatment prior to a needle placement.

Following surgery and immediate postoperative recovery, subjects will be transferred to the 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 at 120 ±6 hours, and on Day 10 and Day 28 to complete follow-up assessments.

An internal Interim Review Committee (IRC) will review unblinded, summary level efficacy, safety, and PK data from each cohort to determine if enrollment should be initiated in the next cohort and to guide Phase 3 study design. Each interim analysis will be performed after at least 80% of the planned number of subjects have all of their pain intensity and opioid use data through the 72-hour postoperative assessments entered into the electronic clinical database for that cohort. The IRC will operate under a written, detailed IRC Charter.

3.1.2. Treatment Groups

The study will include up to 4 cohorts.

Cohort 1

Approximately 24 subjects will be randomized to 1 of the following 3 treatment groups in a 2:1:1 ratio:

- HTX-011 60 mg (2.1 mL) via bilateral ultrasound-guided lateral and medial pectoral nerve block (12 subjects)
- Bupivacaine HCl without epinephrine 0.25% (50 mg, 20 mL) via bilateral ultrasound-guided lateral and medial pectoral nerve block (6 subjects)
- Saline placebo (2.1 mL) via bilateral ultrasound-guided lateral and medial pectoral nerve block (6 subjects)

Cohort 2

Cohort 2 was planned as an optional cohort. Following a review of the results from Cohort 1, the IRC recommended initiating enrollment in Cohort 2 and randomizing approximately 48 subjects to 1 of the following 3 treatment groups in a 2:1:1 ratio:

- HTX-011 (a single dose recommended by IRC of 120 mg/3.6 mg [bupivacaine/meloxicam doses], 4.1 mL) via bilateral ultrasound-guided lateral and medial pectoral nerve block (24 subjects)
- Bupivacaine HCl without epinephrine 0.25% (50 mg, 20 mL) via bilateral ultrasound-guided lateral and medial pectoral nerve block (12 subjects)
- Saline placebo (volume matching HTX-011 in Cohort 2) via bilateral ultrasound-guided lateral and medial pectoral nerve block (12 subjects).

Cohort 3

Cohort 3 was planned as an optional cohort. Following a review of the results from Cohort 2, the IRC recommended initiating enrollment in Cohort 3 and randomizing approximately 48 subjects to 1 of the following 3 treatment groups in a 2:1:1 ratio:

- HTX-011 (a single dose recommended by IRC of 240 mg/7.2 mg [bupivacaine/meloxicam doses], 8.2 mL) via bilateral ultrasound-guided lateral and medial pectoral nerve block (24 subjects)
- Bupivacaine HCl without epinephrine 0.25% (50 mg, 20 mL) via bilateral ultrasound-guided lateral and medial pectoral nerve block (12 subjects)
- Saline placebo (volume matching HTX-011 in Cohort 3) via bilateral ultrasound-guided lateral and medial pectoral nerve block (12 subjects)

Cohort 4

Cohort 4 was planned as an optional cohort. Following a review of the results from Cohort 3, the IRC recommended initiating enrollment in Cohort 4 and randomizing approximately 120 subjects to 1 of the following 4 treatment groups in a 4:4:1:1 ratio:

- HTX-011 (a single dose recommended by IRC of 400 mg/12 mg [bupivacaine/meloxicam doses], 13.7 mL) via bilateral ultrasound-guided lateral and medial pectoral nerve block (48 subjects)

- HTX-011 (a single dose recommended by IRC of 400 mg/12 mg [bupivacaine/meloxicam doses], 13.7 mL) via instillation into the intended space for the implant, with 200 mg/6 mg, 6.8 mL per side, and saline placebo (volume matching HTX-011 in Cohort 4) via bilateral ultrasound-guided lateral and medial pectoral nerve block for masking (48 subjects)

- Bupivacaine HCl without epinephrine 0.25% (50 mg, 20 mL) via bilateral ultrasound-guided lateral and medial pectoral nerve block (12 subjects)

- Saline placebo (volume matching HTX-011 in Cohort 4) via bilateral ultrasound-guided lateral and medial pectoral nerve block (12 subjects)

3.1.3. Postoperative Opioid Rescue Medications

Subjects should only receive rescue medication upon request for pain control, as needed, during the 72-hour postoperative observation period. Prior to the administration of the first dose of rescue medication, if the subject has not already had at least 1 postoperative pain score assessed, then NRS scores at rest (NRS-R) and with activity (NRS-A) must be obtained.

Postoperative rescue medication will consist of oral (PO) immediate-release oxycodone (no more than 10 mg in a 4-hour period as needed) and/or intravenous morphine (no more than 10 mg in a 2-hour period as needed). 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. Subjects will complete a daily diary to record if they take an opioid medication between 72 hours and Day 28.

3.1.4. Postoperative Assessments

Efficacy assessments will include pain intensity scores using the NRS-R and NRS-A; use of opioid recue medication; Patient Global Assessment (PGA) of pain control; assessments of discharge readiness; assessment of persistent postsurgical pain; subject's satisfaction with postoperative pain control; and the subject's assessment of overall benefit of analgesia.

Safety assessments will include AE recording, physical examinations, vital signs, motor function assessment, sensory function assessment, clinical safety laboratory tests (hematology and serum chemistry), wound healing assessment, and blinded assessor's satisfaction with return of sensory and motor function. Holter monitoring will also be assessed.

PK assessments will include the collection of blood samples to evaluate the bupivacaine PK profile for HTX-011 and bupivacaine HCl, and the meloxicam PK profile of HTX-011.

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. Efficacy Endpoints

Primary Efficacy Endpoint:

- Mean area under the curve (AUC) of the NRS-A pain intensity scores through 24 hours (AUC_{0-24}).

Secondary Efficacy Endpoints:

- Mean total postoperative opioid consumption (in morphine equivalents) through 24, 48, and 72 hours.
- Median time in hours to first opioid rescue administration through 72 hours.
- Mean AUC of the NRS-A pain intensity scores at the following intervals: 0-6, 0-12, 12-24, 24-48, 0-48, 48-72, and 0-72 hours.
- Mean AUC of the NRS-R pain intensity scores at the following intervals: 0-6, 0-12, 12-24, 0-24, 24-48, 0-48, 48-72, and 0-72 hours.
- Mean NRS-R pain intensity scores at each assessed timepoint.
- Mean NRS-A pain intensity scores at each assessed timepoint.
- Integrated Rank Analysis of Silverman using the NRS-A pain intensity AUC scores and total opioid consumption through 24, 48, and 72 hours.
- Proportion of subjects achieving a score of "good" or better (>1) pain control based on PGA at 24, 48, and 72 hours and on Day 28.
- Proportion of subjects who are pain-free (defined as an NRS-R pain intensity score of 0 or 1) at each assessed timepoint.
- Proportion of subjects who are pain-free (defined as an NRS-A pain intensity score of 0 or 1) at each assessed timepoint.
- Proportion of subjects who are opioid-free through 24, 48, and 72 hours.
- Proportion of subjects who are opioid-free from 72 hours through Day 10 and Day 28.
- Proportion of subjects who first achieve a Modified Postanaesthetic Discharge Scoring System (MPADSS) score ≥9 at 2, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours.
- Mean subject's satisfaction with postoperative pain control at 24, 48, and 72 hours, and on Day 10.
- Mean overall benefit of analgesia score (OBAS) at 24, 48, and 72 hours, and on Day 28.

3.2.2. Safety Endpoints

- Incidence of TEAEs, SAEs, and opioid-related AEs (ORAEs) through Day 28.
- Change from baseline in clinical laboratory results.
- Change from baseline in vital signs at each assessed timepoint.
- Change from baseline in Holter data.

- Wound healing assessment at 72 hours and on Day 10 and Day 28.
- Time to return of motor function.
- Loss of sensation in the breast at 15, 30, and 60 minutes after the start of ultrasound-guided study drug administration.
- Time to return of sensory function.
- Blinded assessor's satisfaction with return of sensory and motor function at 24, 48, and 72 hours, and on Day 10.

3.2.3. Pharmacokinetic Endpoints

- Maximum observed plasma concentration (C_{max}).
- 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 ($t_{½el}$).

3.3. Study Duration

The overall duration of the study is anticipated to be approximately 18 months. The total duration of study participation for each subject (from Screening through Day 28) will be up to 53 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

Up to approximately 240 subjects will be enrolled in this study in approximately 5 study sites in the United States (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, adhere to the study visit schedule, and complete all study assessments.
2. Is female ≥18 years of age at screening.
3. Is scheduled to undergo bilateral submuscular augmentation mammoplasty with saline or silicone smooth implants with a volume of 300 to 500 cc, inclusive. Note: textured implants are not allowed.
4. Has an American Society of Anesthesiologists Physical Status of I, II, or III.
5. Is suitable for a nerve block procedure.
6. Is able to demonstrate motor function by raising both arms above the head unassisted.
7. Is able to assess sensory function by exhibiting sensitivity to cold in the pectoral area (upper outer quadrant).
8. Subjects are eligible only if all of the following apply:

    a. Not pregnant (subjects of child-bearing potential must have a negative urine pregnancy test at screening and on Day 0 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.

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 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 and which may confound the postoperative assessments.

4. Has a contraindication or a known or suspected history of hypersensitivity or clinically significant idiosyncratic reaction to bupivacaine (or other local anesthetics), meloxicam (or other NSAIDs), oxycodone, morphine, or fentanyl.
5. Has known or suspected daily use of opioids for 7 or more consecutive days within the previous 6 months.
6. Has taken NSAIDs (including meloxicam) within at least 10 days prior to surgery with the exception of subjects on low-dose (<100 mg) daily acetylsalicylic acid for cardioprotection.
7. Has taken long-acting opioids within 3 days prior to surgery.
8. Has taken any opioids within 24 hours prior to the scheduled surgery.
9. Has been administered bupivacaine within 5 days prior to the scheduled surgery.
10. Has been administered any local anesthetic within 72 hours prior to the scheduled surgery other than to treat an AE that occurs after signing the ICF or for pretreatment prior to a needle placement.
11. Has initiated treatment with any of the following medications within 1 month prior to study drug administration or is taking any of these medications to control pain: selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin, duloxetine, or cyclooxygenase-2 (COX-2) inhibitors. (Note: If a subject is taking one of these medications for a reason other than pain control, she must be on a stable scheduled dose [ie, not "as needed"] for at least 1 month prior to study drug administration.) Anxiolytics prior to surgery are permitted, if necessary.
12. Has a medical condition 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. Loss of sensation in extremities or significant peripheral neuropathy.

13. 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).
14. Has uncontrolled anxiety, psychiatric, or neurological disorder that might interfere with study assessments

15. Has any chronic neuromuscular deficit of either pectoral nerve function or arm/shoulder/truncal musculature.
16. Has any chronic condition or disease that would compromise neurological or vascular assessments.
17. Had a malignancy in the last year, with the exception of non-metastatic basal cell or squamous cell carcinoma of the skin or localized carcinoma in situ of the cervix.
18. 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.
19. Previous participation in an HTX-011 study or received an investigational product or device in a 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.
20. Has undergone 3 or more surgeries in 12 months prior to signing the ICF, other than for diagnostic procedures (eg, colonoscopy).
21. 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, the assigned Pharmacist(s) and his/her verifier, and the unblinded clinical monitor. 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 0 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

The study will use a double-blind design. Specific members of the site's pharmacy and surgical staff will not be blinded to the treatment assignments because HTX-011 is colored and viscous in contrast to bupivacaine HCl and saline placebo, and the volume of study drug to be administered

varies by treatment group. However, the subject will not be told of her treatment assignment. In order to maintain the blind for the subject, the subject must not be allowed to see the color of the injectate, and the anesthesiologist must ensure he/she does not impress upon the subjects any visual or verbalized cues as to the treatment. Once surgery is completed and the subject is transferred to the PACU, the Investigator and all site staff involved in safety and efficacy assessments will be blinded to the treatment assignments until after database lock. The Sponsor's study team will also be blinded to the treatment assignments with the exception of the clinical trial material (CTM) staff, the clinical observers, the bioanalytical staff, and an unblinded statistician who will perform the randomization and interim analysis data reviews, but will otherwise be uninvolved in the conduct of the study. In addition, an internal IRC will be unblinded during the interim reviews of summary-level efficacy, safety, and PK data from the study.

4.3.1. Breaking the Blind

The study blind should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the study drug she received. An attempt should be made to contact the Sponsor before breaking the blind. If the Sponsor cannot be reached and the blind is broken by the Investigator, the reason for unblinding must be documented and the Sponsor must be contacted within 24 hours.

The Sponsor retains the right to break the treatment code for SAEs that are unexpected and are suspected to be causally related to an investigational product (IP) and that potentially require expedited reporting to regulatory authorities.

All circumstances leading to the premature unblinding must be clearly documented.

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
- Consent withdrawal
- Death
- Lost to follow up
- Investigator's decision
- Sponsor's decision
- Screen fail on Day 0

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

Any subject who is randomized but withdraws from the study prior to study drug administration will be replaced by the next eligible study subject. The replacement subject will be assigned to the same treatment group as the subject who withdrew.

5. STUDY TREATMENT

All subjects will receive a single dose of study drug. Study drug is defined as HTX-011 (IP), bupivacaine HCl without epinephrine (active control), or saline placebo (control).

HTX-011 will be supplied by the Sponsor. Bupivacaine HCl and saline placebo will be supplied by study sites.

5.1. Description of Investigational Product

HTX-011 is a slightly yellow, viscous, semi-solid gel liquid. HTX-011 is supplied in prefilled sterile syringes and/or vials. The prefilled syringe and vials serve only as a closed container for the drug product. For administration of study drug, the formulation in the prefilled syringes and/or vials will be aseptically transferred to sterile syringes.

5.2. Manufacturing, Packaging, and Labeling

HTX-011 will be manufactured according to Good Manufacturing Practices, and packaged and labeled by the Sponsor or designee. HTX-011 will be packed and dispatched to comply with shipping and storage conditions. HTX-011 labeling will comply with all applicable federal and local laws and regulations.

5.3. Storage

HTX-011 should be stored at the study site in a refrigerator at 2ºC to 8ºC. The refrigerator should be in a locked area with restricted access. A temperature log should be maintained to monitor the refrigerator's temperature.

Saline placebo and bupivacaine HCl will be stored as per the prescribing information

5.4. Preparation

Study drug will be prepared at the study site by unblinded study personnel. Refer to the Pharmacy Manual for details on study drug preparation.

5.5. Study Drug Administration

Study drug should be prepared and study drug administration equipment should be assembled and primed as outlined in the Pharmacy Manual.

Study personnel who are present during the administration of study drug are unblinded and cannot perform postoperative assessments.

5.5.1. Nerve Block

For bilateral ultrasound-guided lateral and medial pectoral nerve block, approximately half the total volume of study drug should be administered to each side and equal amounts should be administered per nerve.

Investigators will use ultrasound guidance to locate the lateral pectoral and medial pectoral nerves. The ultrasound machine may have capacity for color and needle localization software, if needed for ease of needle placement. With a linear array transducer in a sterile sleeve, the nerve will be identified in a transverse (short-axis) view below where it comes off at the brachial plexus; the internal appearance of the peripheral nerve bundle should appear to be a mixture of hypoechoic neural tissue (fascicles) and hyperechoic connective tissue (perineurium and epineurium). Once the optimal image of the nerve is obtained, a local anesthetic skin wheal (1% lidocaine) may be raised near the ultrasound transducer. A needle will be inserted through the skin wheal and directed medially in plane beneath the ultrasound transducer toward the nerves; the study drug will be injected around the nerves.

The surgeon should administer 5 mL of 0.5% ropivacaine HCl in each of the surgical incision lines at closure.

5.5.2. HTX-011 Instillation and Saline Placebo Nerve Block

To maintain the study blind for instillation only administration, a nerve block will be performed as described in Section 5.5.1 using saline placebo. In addition, the Investigator will instill HTX-011 into the surgical site in a manner to be specified by the Sponsor in the Pharmacy/Study Manual. Note: HTX-011 is to be instilled, not injected, into the tissue.

The surgeon should administer 5 mL of 0.5% ropivacaine HCl in each of the surgical incision lines at closure.

5.6. Study Drug Compliance

All study drug must be administered in accordance with the treatment assignment.

5.7. Study Drug Accountability

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

All study drug records must be readily available for inspection by the site's unblinded clinical monitor and/or auditor. No IP can be returned to the Sponsor or designee or disposed of at the study site until the unblinded clinical monitor has verified the accuracy of the study drug records at the study site. All returns, disposal, or destruction must be approved by the Sponsor in writing.

6. STUDY PROCEDURES AND ASSESSMENTS

The following sections describe the study procedures and assessments that will be performed during the study. See 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 in the subject's eCRF. 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).

During surgery, the use of fentanyl up to 4 µg/kg is permitted. In addition, subjects in Cohorts 2 and 4 will receive protocol-specified fentanyl 50 µg intravenously (IV) just prior to the end of the surgery. As the prescribing information for fentanyl citrate (Fentanyl Citrate USPI 2012) specifies that for intraoperative use a "moderate dose" of 2 to 20 µg/kg IV is necessary in order to allow the anesthesiologist to respond to any signal that the surgical stress is increasing or anesthesia lightening, this dose was chosen to be in the lowermost portion of that range and therefore not interfere with assessment of postoperative opioid load. As clinically appropriate, the minimum possible fentanyl dose should be used.

Medications that are prohibited during the study are described in Section 9.1.

6.3. Efficacy Assessments

6.3.1. Pain Intensity Assessment

Subjects will be asked to evaluate their current pain level at scheduled timepoints after surgery. Subjects will receive training by the site on how to provide pain intensity assessments.

Pain intensity scores will be assessed using an 11-point NRS (0–10) where 0 represents "no pain" and 10 represents "worst pain imaginable." NRS scores will be recorded at rest (NRS-R; in a dependent position) and with activity (NRS-A). For the prescribed activity, the subject will

keep her elbows at her side and against her body and will then raise her hands in front of her abdomen, clasp hands together, and hold that position for at least 5 seconds (Smoot 2012).

If a subject withdraws from the study before 72 hours, NRS-R and NRS-A pain intensity scores will be recorded at the time of withdrawal.

6.3.2. Use of Opioid Rescue Medications

The name, dose, and route as well as the date and time of administration of any opioid rescue medication taken must be recorded in the subject's eCRF from Time 0 through 72 hours. For more information on opioid rescue medications permitted, see Section 3.1.3.

6.3.3. Subject Daily Diary

Subjects will be provided a diary to record if they took any opioid medication that day. Subjects will be required to record their use of opioids on a daily basis from 72 hours through Day 28.

6.3.4. Patient Global Assessment of Pain Control

Subjects will be asked to evaluate the performance of study drug as a pain treatment at different intervals using a 4-point rating scale where 0 represents "poor" and 3 represents "excellent" (Rothman 2009). See Appendix D for the PGA scale.

6.3.5. Discharge Readiness

Discharge readiness will be assessed using the MPADSS criteria (Chung 1995). Refer to Appendix B.

Note: This study instrument assesses a subject's potential readiness to be discharged and should be repeated at all scheduled timepoints. It is not meant to be used to decide on whether or not to discharge a subject from the study. Subjects are required to remain in the hospital/research facility for 72 hours.

6.3.6. Satisfaction With Postoperative Pain Control and With Return of Sensory and Motor Function

The subject will be questioned about her satisfaction with postoperative pain control. The subject's response to the following statement "I am satisfied with postoperative pain control" will be recorded using a 5-point Likert scale where 1 represents "strongly disagree" and 5 represents "strongly agree."

The blinded assessor will also be questioned about his/her satisfaction with return of sensory and motor function using a 5-point Likert scale.

6.3.7. Overall Benefit of Analgesia Assessment

The subject will be questioned about their overall benefit of analgesia using a 7-item, multidimensional, quality assessment questionnaire (Lehmann 2010). The 7 items address pain,

vomiting, itching, sweating, freezing, dizziness, and overall satisfaction with postoperative pain and make up the OBAS. See Appendix E for the OBAS scale.

6.4. Safety Assessments

6.4.1. 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 details.

6.4.2. Local Anesthetic Systemic Toxicity Assessment

Subjects should be assessed on a regular basis to identify early neurologic and cardiac signs and symptoms that may be attributed to local anesthetic systemic toxicity (LAST; eg, metallic/strange taste, perioral tingling, ringing in ears, visual disturbance, tremors, muscle twitching, dizziness/lightheadedness, convulsion/seizure, bradycardia, arrhythmia, hypotension) (Vasques 2015). Additional monitoring of subjects for safety should be performed as needed (eg, vital signs, ECGs).

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

6.4.3. 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.

6.4.4. 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.

6.4.5. 12-Lead Electrocardiograms and Holter Monitoring

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.

Continuous Holter monitoring will be performed. Subjects will be required to have a continuous reading at least 24 hours before surgery and will wear the monitor for 72 hours after the start of study drug administration. While the limb leads will be kept on until the 72-hour timepoint, the chest leads may be removed just prior to the operation and replaced immediately after the operation, if needed. The limb leads should not be removed during the operation.

The ECG and Holter monitor results will be reviewed by a central reader and the information provided to the sites. Refer to the Cardiac Manual for instructions on collecting and transmitting results. Clinically significant findings after study drug administration will be recorded as TEAEs.

6.4.6. Wound Healing Assessment

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.

6.4.7. Motor Function Assessment

Motor function will be assessed by having the subject keep her elbows at her side and against her body and then raise her hands in front of her abdomen, clasp hands together, and hold that position for at least 5 seconds. The results will be recorded on the eCRF.

6.4.8. Sensory Function Assessment

Sensory function will be evaluated using a cold alcohol swab test. An alcohol pad will be placed on the upper outer quadrant of the breast on the side of the dominant hand. The subject will not see when the pad is applied. The subject will be asked “Can you detect cold?” The results (Yes or No) will be recorded on the eCRF.

6.4.9. 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 child bearing 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

6.5. Pharmacokinetic Assessments

Serial blood samples for bupivacaine and meloxicam 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 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 awakening the subject (eg, blood collection for PK sample) 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:

- NRS-R pain intensity assessment (assessed in a dependent position)
- PGA of pain control
- OBAS assessment
- Vital signs
- 12-lead ECG
- NRS-A pain intensity assessment (assessed by having the subject keep her elbows at her side and against her body and then raise her hands in front of her abdomen, clasp hands together, and hold that position for at least 5 seconds)
- Blood sample collection
- Physical examination
- Wound healing assessment
- Subject's satisfaction with postoperative pain control

7.1. Screening Period

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 21 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 child bearing potential only)

- Urine collection for drug screen
- Blood sample collection for the hematology and serum chemistry
- Sensory function assessment
- Motor function assessment
- Subject training for pain intensity assessments
- AE recording (from signing the ICF)
- Prior and concomitant medication recording

Subjects will be required to have a continuous reading of the Holter monitor at least 24 hours before surgery (Day 0).

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 0, Prior to Surgery

On the day of surgery (Day 0), 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 study drug administration:

- Vital signs measurements
- Urine sample collection for the following assessments:
    - Drug screen
    - Pregnancy test (female subjects of childbearing potential only)
- Subject training for pain intensity assessments (refresher training)
- NRS-R pain intensity assessment
- Blood collection for PK
- NRS-A pain intensity assessment
- AE recording
- Prior and concomitant medication assessment

After all assessments have been completed, study drug will be administered within 4 hours prior to surgery for subjects receiving study drug via ultrasound-guided lateral and medial pectoral nerve block. See Section 5.5 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.

A sensory function assessment (cold test) will be performed on the upper outer quadrant of the breast on the side of the dominant hand at 15, 30, and 60 minutes after the start of ultrasound-guided study drug administration. If the subject is already on her way to or in the operating room, the assessment may be avoided and “Not Done” recorded on the eCRF.

7.2.2. Pharmacokinetic Sampling After Study Drug Administration

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

Blood samples for PK analysis will be collected at the following timepoints: 30 minutes (±5 min); 1 hour (±5 min); 2 and 4 hours (±15 min); 6, 8, and 12 hours (±30 min); 20, 22, 24, 26, and 28 hours (±1 hr); 36, 48, 60, 72 hours (±2 hr); and 120 hours (±6 hr) after the start of study drug administration.

PK blood sample should be collected according to the above schedule even if the subject is still in the operating room.

7.2.3. Surgery (Day 0)

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.

For subjects receiving study drug via instillation, study drug will be administered prior to the end of surgery. See Section 5.5 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.

Note: The end of surgery (defined as placement of last suture) will be considered as Time 0 for all efficacy and safety assessments.

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

7.2.4. Postoperative Observation Period (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.

Timepoints are generally referenced to the end of surgery (with the exception of PK and the initial sensory assessments). 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.

- **NRS-R pain intensity assessment**: at 1 hour (±5 min); 2 and 4 hours (±15 min); 6, 8, and 12 hours (±30 min); 24 hours (±1 hr); and 36, 48, 60, and 72 (±2 hr)
- **NRS-A pain intensity assessment**: at 1 hour (±5 min); 2 and 4 hours (±15 min); 6, 8, and 12 hours (±30 min); 24 hours (±1 hr); and 36, 48, 60, and 72 hours (±2 hr)
- **PGA of pain control assessment**: 24 hours (±1 hr), 48 and 72 hours (±2 hr)
- **Vital signs measurements**: 24 hours (±1 hr), 48 and 72 hours (±2 hr)

- **Physical examination**: 72 hours (±2 hr; height and weight not required)
- **Blood sample for clinical safety laboratory tests**: 24 hours (±1 hr; hematology only) and 72 hours (±2 hr; hematology and serum chemistry)
- **Sensory function test:** 6 and 12 hours (±30 min); 24 hours (±1 hr); 48 and 72 hours (±2 hr)
- **Motor function test**: 6 and 12 hours (±30 min); 24 hours (±1 hr); 48 and 72 hours (±2 hr)
- **Discharge readiness assessment per the MPADSS criteria:** 2 and 4 hours (±15 min); 6, 8, and 12 hours (±30 min); 24 hours (±1 hr); and 36, 48, 60, and 72 hours (±2 hr)
- **Wound healing assessment:** 72 hours (±2 hr)
- **Subject's satisfaction with postoperative pain control:** 24 hours (±1 hr), 48 and 72 hours (±2 hr)
- **Blinded assessor's satisfaction with return of sensory and motor function:** 24 hours (±1 hr), 48 and 72 hours (±2 hr)
- **OBAS assessment:** 24 hours (±1 hr), 48 and 72 hours (±2 hr)
- **AE recording**: Any time between study drug administration and 72 hours
- **Concomitant medication recording**: Any time between study drug administration and 72 hours
- **Use of opioid rescue medication recording**: Any time between study drug administration and 72 hours

7.2.5. End of the Postoperative Assessment Period

After the 72-hour postoperative assessments have been completed, the Holter monitor will be removed if applicable, and the subject may be discharged. 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 6.4.1. If a subject is ready for discharge but is not discharged for any reason other than AE, it should be recorded on the eCRF.

Subjects will be given a diary to record their use of opioids on a daily basis from 72 hours through Day 28.

7.3. Follow-Up Period

7.3.1. 120 hours (±6 Hours) After Start of Study Drug Administration

Subjects will return to the study site and will have the following procedures and assessments:

- Blood sample collection for PK
- Review subject daily diary
- AE recording
- Concomitant medication recording

7.3.2. Day 10 Visit (±2 Days)

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

- NRS-R pain intensity assessment
- NRS-A pain intensity assessment

- Sensory function test
- Motor function assessment
- Wound healing assessment
- Blood sample collection for hematology and serum chemistry
- Subject's satisfaction with postoperative pain control
- Blinded assessor's satisfaction with return of sensory and motor function
- Review subject daily diary
- 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
- Concomitant medication recording

7.3.3. Day 28 Visit (±4 Days)

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

- NRS-R pain intensity assessment
- NRS-A pain intensity assessment
- PGA of pain control assessment
- OBAS assessment
- Wound healing assessment
- Return and review subject daily diary
- 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
- Concomitant medication recording

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:

- NRS-R pain intensity assessment (if withdrew prior to 72 hours)
- NRS-A pain intensity assessment (if withdrew prior to 72 hours)
- PGA of pain control assessment (if withdrew prior to Day 28)
- Return and review subject daily diary (if withdrew between 72 hours and Day 28)
- Vital signs (if withdrew prior to 72 hours)
- 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])
- Sensory function test (if withdrew prior to Day 10)
- Motor function assessment (if withdrew prior to Day 10)
- 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, SAE, suspected adverse reaction, serious suspected adverse reaction, unanticipated adverse device effect, or unanticipated problems, as provided in this protocol.

Investigators must review the HTX-011 IB so as to be aware of the safety-related events that 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. 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 preexisting 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 IP interrupted or discontinued
    - Any laboratory abnormality that required the subject to receive specific treatment for the 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 preexisting 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.

According to 21Code 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 an 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 and 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: htx011safety@herontx.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 preferred 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 entering the information into the eCRF within 24 hours of the Investigator becoming aware of the problem.

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

Email Address: htx011safety@herontx.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 problems 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 within 24 hours after the Investigator becomes aware of it using the SAE reporting procedures outlined in Section 8.4.1.

8.5. Safety Oversight

The internal, blinded Product Safety and Risk Management Committee will monitor safety data on a periodic basis throughout the study (ie, monthly unless more frequent monitoring is necessary due to high enrollment or safety concern), including regular review of ECG findings, AEs, and SAEs. ECGs and AEs will be reviewed to identify possible signs of LAST.

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

9. STUDY RESTRICTIONS

9.1. Prohibited Medications

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). Dexamethasone also cannot to be administered prophylactically before surgery.

Intraoperative administration of opioids or any other analgesics (including ketamine), local anesthetics, or anti-inflammatory agents except as specified by the protocol (ie, HTX-011, bupivacaine HCl, ropivacaine HCl, and fentanyl) is prohibited, unless needed to treat an AE that occurs after signing the ICF or for pretreatment prior to a needle placement.

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.

9.2. Contraception

Female subjects of child bearing potential with a non-surgically sterile partner 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 the FDA.

10. STATISTICAL CONSIDERATIONS

10.1. General Considerations

All efficacy and safety data will be listed by subject. Baseline is defined as the last observed measurement, whether scheduled or unscheduled, prior to the start of study drug administration. All safety and efficacy endpoints will be summarized by treatment group and/or cohort, as appropriate. Continuous variables will be summarized using the number of subjects with data (n), mean, standard deviation (SD), median, minimum, and maximum. Selected continuous variable summaries will also include the standard error (SE). Categorical variables will be summarized using frequency counts and percentages.

Unless otherwise specified, all statistical hypothesis testing will be two-sided using $\alpha = 0.05$.

10.2. Determination of Sample Size

The sample size of up to approximately 240 subjects in this study was selected empirically without formal statistical assumptions.

10.3. Analysis Populations

Intent-to-Treat (ITT) Population: All subjects who are randomized and do not screen fail on Day 0 will be included in the ITT Population. This population will be used in subject disposition analyses only.

Modified ITT (mITT) Population: All subjects in the ITT Population who have at least 1 post-treatment NRS-A pain intensity score will be included in the mITT Population. This population will be used as the primary analysis population for all efficacy endpoints.

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.

10.4. Statistical Analysis Methods

10.4.1. Disposition and Demographics

The number and percentage of subjects in each analysis 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 for the ITT Population. Subject demographics and baseline characteristics will be summarized for the mITT Population and will include age, age category, sex, race, ethnicity, height, weight, and BMI.

10.4.2. Efficacy Analysis

For the purposes of statistical hypothesis testing, data from subjects randomized to saline placebo will be pooled across cohorts into a single saline placebo treatment group, and data from subjects

randomized to bupivacaine HCl will be pooled across cohorts into a single bupivacaine HCl treatment group. Data from subjects randomized to HTX-011 will neither be pooled across dose levels nor pooled across methods of administration within a dose level.

10.4.2.1. Primary Efficacy Analysis

The primary analysis of mean AUC_{0-24} of the NRS-A pain intensity scores will be carried out on the mITT Population using an analysis of variance (ANOVA) model with treatment as the main effect. Each dose of HTX-011 will be tested against each of the pooled control arms. Results will be expressed as mean AUCs and SDs, least-squares mean differences and SEs with associated 95% confidence intervals (CIs), and p-values. To account for the duration effect of opioid rescue medication, the windowed worst observation carried forward (wWOCF) method will be implemented as the primary analysis method for endpoints involving NRS pain intensity scores. In this method, pain intensity scores observed during the analgesic window (duration of effect) of any opioid rescue medication will be replaced with the worst (highest) postdose nonmissing NRS pain intensity score observed prior to the rescue medication window, with the following exception: if the NRS pain intensity score for a windowed observation is higher than the worst pre-window score, then it will not be replaced. Sensitivity analyses for endpoints involving NRS pain intensity scores will analyze the data without adjustment for the effect of opioid rescue medications.

10.4.2.2. Secondary Efficacy Analyses

Continuous secondary efficacy endpoints will be analyzed in a manner similar to that specified for the primary endpoint.

Categorical endpoints will be analyzed using Fisher's exact test. Results will be expressed as the number and percentage of subjects meeting the relevant endpoint, differences in proportions with 95% CIs, and p-values.

Median time in hours to first opioid rescue administration will be analyzed using Kaplan-Meier methods.

10.4.2.3. Handling of Missing Data

Due to the required 72-hour inpatient post-surgery observation period, the amount of missing data is expected to be very low. For any missing data observed, NRS pain intensity scores will be imputed via last observation carried forward (LOCF), in which the most recent postdose nonmissing value is used for a subsequent missing value. For subjects who do not have a postdose value prior to their first missing value, the median of the postdose values at the relevant timepoint from subjects with observed data in the same randomized treatment group will be used. Predose values will not be carried forward to postdose timepoints. Analyses that adjust for the effect of opioid rescue medication will perform wWOCF following LOCF (ie, perform LOCF first, then apply wWOCF). Other continuous efficacy endpoints with missing data will be handled using LOCF. In general, subjects with missing categorical data at a timepoint will be assumed to have not met the endpoint at that timepoint. For the analysis of time to first opioid rescue medication, subjects who withdraw from the study prior to completing the 72-hour postoperative observation period or complete the 72-hour postoperative observation period

without having taken rescue medication will be censored at the time of study withdrawal or completion of the 72-hour postoperative observation period, whichever is earlier.

10.4.3. Safety Analysis

All safety analyses will be carried out on the Safety Population. All safety data will be listed and summarized by treatment group. Data from subjects treated with saline placebo will be pooled across cohorts into a single saline placebo treatment group, and data from subjects treated with bupivacaine HCl will be pooled across cohorts into a single bupivacaine HCl treatment group. Data from subjects treated with HTX-011 will neither be pooled across dose levels nor pooled across methods of administration within a dose level.

AEs will be monitored during the study and the data analyzed with respect to incidence within each treatment group as well as severity and potential relationship of the AEs to study drug. 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 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 and presented in descending order of frequency according to the highest dose of HTX-011 studied. 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 and listed. 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, time to return of motor function, and loss of sensation in the breast, time to return of sensory function, and blinded assessor's satisfaction with return of sensory and motor function will be summarized at each timepoint or overall, as appropriate.

10.4.4. Pharmacokinetic Analysis

Plasma bupivacaine and meloxicam 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

Up to 4 interim analyses will be performed. An internal IRC will review unblinded summary-level data from each cohort to make study design decisions, as outlined in Section 3.1.2. Each interim analysis will be performed after at least 80% of the planned number

of subjects have all of their pain intensity and opioid use data through the 72-hour postoperative assessments entered into the electronic clinical database for that cohort. The internal IRC will be composed of 1 Sponsor representative from the Clinical Research, Biometrics, Pharmacovigilance, Regulatory, and Pharmaceutical and Translational Sciences functions. The IRC will operate under a written, detailed IRC Charter.

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, GCP, International Conference on Harmonisation (ICH) E6 guidelines, and any other applicable regulatory requirement. 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), IB, recruitment materials, information about study compensation to subjects, 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 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 a subject’s 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 her 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 will include details the requirements of the participant and the fact that she is free to withdraw at any time without giving a reason and without prejudice to 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 her 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 (unblinded monitor only), 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 (see 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 Violations and Deviations

The Investigator will not implement any protocol deviation without agreement by the Sponsor except where necessary to eliminate an immediate hazard to study subjects.

Protocol deviations fall into 2 categories: those with approval prior to the event (protocol exemptions) and those occurring during the course of the study without prior approval (protocol violations). If an exemption from the protocol design (eg, a missed study visit or an unmet inclusion or exclusion criterion) is desired for an individual subject, other than those to eliminate immediate hazard, the Investigator must request an exemption from the Sponsor or designee. The Investigator will notify the EC of exemptions and deviations, as required by EC guidelines and site requirements. Exemptions (with rationale) will be documented at the site and in the Sponsor files. For any protocol violation, the site will document the protocol violation in the subject's source documents. In the event of a significant violation, the site will notify the Sponsor or designee. Significant violations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessments. The Sponsor is responsible for notifying the regulatory authorities, 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 our 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. Discharge Readiness Assessment - Modified Postanaesthetic Discharge Scoring System Criteria

The Modified Postanaesthetic Discharge Scoring System (MPADSS) will be used to assess the subject's discharge readiness. This assessment will be used for data collection only and is not intended to interfere with the hospital's policy for determining when the subject should be discharged. Only subjects who achieve a score of 9 or higher will be considered ready for discharge.

Parameter	Score
Vital Signs	
≤20% of preoperative value	2
20% to 40% of preoperative value	1
>40% of preoperative value	0
Ambulation	
Steady gait/no dizziness	2
With assistance	1
None/dizziness	0
Nausea/Vomiting	
Minimal	2
Moderate	1
Severe	0
Pain	
Minimal	2
Moderate	1
Severe	0
Surgical Bleeding	
Minimal	2
Moderate	1
Severe	0

Reference: Chung, F. (1995). "Discharge criteria--a new trend." Can J Anaesth 42(11): 1056-1058.

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 (≤2 cm)
	b	Along wound (>2 cm)
	c	Large volume
	d	Prolonged (>3 days)
	Major complication	
IV	**Pus:**	
	a	At 1 point only (<2 cm)
	b	Along wound
V	**Deep or severe wound infection with or without tissue breakdown; haematoma requiring aspiration**	

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

Appendix D. Patient Global Assessment (PGA) of Pain Control

Sites will ask each subject the following question:

"Overall, please rate how well your pain has been controlled during the last 24 hours?"

The response must be one of the following:

- Poor (0)
- Fair (1)
- Good (2)
- Excellent (3)

Reference: Rothman, M., S. Vallow, C. V. Damaraju and D. J. Hewitt (2009). "Using the patient global assessment of the method of pain control to assess new analgesic modalities in clinical trials." Current Medical Research and Opinion 25(6): 1433-1443.

Appendix E. Overall Benefit of Analgesia Assessment

Sites will ask each subject the statements listed below, and the rating scale below will be used to calculate the overall OBAS score.

		Rating
1	Please rate your current pain at rest on a scale between 0=minimal pain and 4=maximum imaginable pain	|__|
2	Please grade any distress and bother from vomiting in the past 24 hr (0=not at all to 4=very much)	|__|
3	Please grade any distress and bother from itching in the past 24 hr (0=not at all to 4=very much)	|__|
4	Please grade any distress and bother from sweating in the past 24 hr (0=not at all to 4=very much)	|__|
5	Please grade any distress and bother from freezing in the past 24 hr (0=not at all to 4=very much)	|__|
6	Please grade any distress and bother from dizziness in the past 24 hr (0=not at all to 4=very much)	|__|
7	How satisfied are you with your pain treatment during the past 24 hr (0=not at all to 4= very much)?	4 - |__| = |__|
	Overall Benefit of Analgesia Score:	|__|__|

To calculate the OBAS score, compute the sum of the scores in items 1 through 6 and add '4-score in item 7'

Example OBAS calculation: A subject patient with minimal pain (NRS=0), severe vomiting (NRS=4), and no itching, sweating, and freezing who is slightly dizzy (NRS=1), and is not very satisfied with his postoperative pain treatment (NRS=1) has an OBAS of 8.

Note that a low score indicates high benefit.

Reference: Lehmann, N., G. P. Joshi, D. Dirkmann, M. Weiss, P. Gulur, J. Peters and M. Eikermann (2010). "Development and longitudinal validation of the overall benefit of analgesia score: a simple multi-dimensional quality assessment instrument." Br J Anaesth **105**(4): 511-518.

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