Document Type:	Study Protocol
Official Title:	Phase 2, Randomized, Pilot Study to Investigate the Safety, Efficacy, Pharmacokinetics and Bioavailability of HTX-011, HTX-002, or HTX-009 Administered Via Injection and/or Topical Application Following Unilateral Open Inguinal Herniorrhaphy
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CLINICAL STUDY PROTOCOL

PROTOCOL NUMBER HTX-011-C2015-202

A Phase 2, Randomized, Pilot Study to Investigate the Safety, Efficacy, Pharmacokinetics and Bioavailability of HTX-011, HTX-002, or HTX-009 Administered Via Injection and/or Topical Application Following Unilateral Open Inguinal Herniorrhaphy

Compound Name:	HTX-011 (extended-release 2.5% bupivacaine and 0.075% meloxicam) HTX-002 (extended-release 2.5% bupivacaine) HTX-009 (extended-release 0.075% meloxicam)
IND #	125927
Protocol Version:	12
Date of Protocol:	31 January 2017
Previous Versions:	Version 1: 13 May 2015 Version 2: 23 June 2015 Version 3: 13 August 2015 Version 4: 03 September 2015 Version 5: 23 November 2015 Version 6: 22 December 2015 Version 7: 28 February 2016 Version 8: 08 June 2016 Version 9: 08 July 2016 Version 10: 07 October 2016 Version 11: 28 December 2016

SPONSOR DETAILS

Name of Company:	Heron Therapeutics, Inc.
Address:	4242 Campus Point Court, Suite 200 San Diego, CA 92121 USA
Telephone Number:	1-858-251-4400

Medical Monitor

Name:	[redacted]
Telephone Number:	
E-Mail Address:	

INVESTIGATOR AGREEMENT

CLINICAL PROTOCOL HTX-011-C2015-202

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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 therein.

I will provide copies of the protocol and all information on the drug relating to the nonclinical and prior clinical experience which 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 drug and the conduct of the study.

I agree to keep records on all subject information (i.e., 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) regulations.

Principal Investigator: _____

Address: _____

Signature: _____

Date: _____

SYNOPSIS

Name of Sponsor/Company: Heron Therapeutics, Inc.	**Protocol Number:** HTX-011-C2015-202
Name of Investigational Product: HTX-011 (extended-release 2.5% bupivacaine and 0.075% meloxicam) • HTX-011-19 • HTX-011-49 • HTX-011-56 HTX-002 (extended-release 2.5% bupivacaine) HTX-009 (extended-release 0.075% meloxicam)	**Protocol Title:** A Phase 2, Randomized, Pilot Study to Investigate the Safety, Efficacy, Pharmacokinetics and Bioavailability of HTX-011, HTX-002, or HTX-009 Administered Via Injection and/or Topical Application Following Unilateral Open Inguinal Herniorrhaphy
Name of Active Ingredients: • Bupivacaine and Meloxicam (HTX-011) • Bupivacaine (HTX-002) • Meloxicam (HTX-009)	**Phase of Development:** 2

Objectives:

Part A:

The primary objective for Part A is to evaluate the efficacy and duration of analgesia following administration of one of two doses of HTX-011-19 by different techniques.

Parts B through G:

The primary objective of Parts B through G will be to evaluate the efficacy and duration of analgesia following administration of HTX-011-49, HTX-011-56, HTX-002, HTX-009, bupivacaine (Marcaine), or normal saline.

The secondary objectives that will be evaluated in Parts A through G are as follows:

- To determine in Part A the optimal administration technique of study drug
- To determine the safety and tolerability of HTX-011, HTX-002, and HTX-009 as evaluated through physical examination, vital signs, clinical laboratory tests, electrocardiograms (ECGs), and incidence of adverse events (AEs) and serious AEs (SAEs)
- To evaluate the pharmacokinetic (PK) profiles of bupivacaine and/or meloxicam in HTX-011, HTX-002, and HTX-009 over 120 hours
- To evaluate the analgesic effects of HTX-011, HTX-002, and HTX-009 over various intervals using a series of secondary efficacy endpoints for pain intensity (such as the patient's global assessment of pain control, time to administration of first dose of rescue analgesia, and total and average daily rescue consumption)
- To assess the effects of HTX-011, HTX-002, and HTX-009 on wound healing at 72 hours and on Days 10 and 28 post-treatment
- To evaluate nausea at 6, 24, 48, and 72 hours post-treatment
- To evaluate the percentage of subjects pain free over time

Methodology: This is a Phase 2, multi-center, single-dose, randomized study in adult subjects undergoing unilateral open inguinal herniorrhaphy. The total duration of this study for each subject will be up to 88 days (from screening through the Day 60 follow-up phone call).

Pretreatment Phase:

Screening Period (Day -28 to Day -1): Subjects will be consented and screened.

Treatment and Confinement Phase:

Subjects will be confined from Day 0 to 72 hours after receiving study medication in this 7-part study comprising the following groups:

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Part A

108 subjects will be assigned randomly to any 1 of 6 treatment cohorts:

A) 200 mg (3.42 mL) HTX-011-19 by injection into the surgical wound (n=18 subjects)
B) 400 mg (6.84 mL) HTX-011-19 by injection into the surgical wound (n=18 subjects)
C) 200 mg (3.42 mL) HTX-011-19 by topical administration into the surgical wound (n=18 subjects)
D) 400 mg (6.84 mL) HTX-011-19 by topical administration into the surgical wound (n=18 subjects)
E) A combination technique of 200 mg (3.42 mL) HTX-011-19 by injection into the surgical wound and 200 mg (3.42 mL) HTX-011-19 by topical administration into the surgical wound (n=18 subjects)
F) 6.84 mL of saline solution by injection into the surgical wound (n=18 subjects)

Part B

Upon determining the optimal route of administration in Part A, 90 subjects in Part B will be assigned randomly to any 1 of 6 treatment cohorts:

A) 200 mg (6.84 mL) HTX-011-49 via technique determined in Part A (n=15 subjects)
B) 400 mg (13.68 mL) HTX-011-49 via technique determined in Part A (n=15 subjects)
C) 200 mg (6.84 mL) HTX-011-56 via technique determined in Part A (n=15 subjects)
D) 400 mg (13.68 mL) HTX-011-56 via technique determined in Part A (n=15 subjects)
E) 6.84 mL of saline solution via technique determined in Part A (n=15 subjects)
F) 13.68 mL of saline solution via technique determined in Part A (n=15 subjects)

Part C

Approximately 135 subjects in Part C will be assigned randomly to any 1 of 9 treatment cohorts:

A) 200 mg (6.84 mL) HTX-002 by injection into the surgical wound (n=15 subjects)
B) 400 mg (13.68 mL) HTX-002 by injection into the surgical wound (n=15 subjects)
C) 6.84 mL of saline solution by injection into the surgical wound (n=15 subjects)
D) 13.68 mL of saline solution by injection into the surgical wound (n=15 subjects)
E) 200 mg (6.84 mL) HTX-011-56 via instillation (n=15 subjects)
F) 400 mg (13.68 mL) HTX-011-56 via instillation (n=15 subjects)
G) 200 mg (6.84 mL) HTX-002 via instillation (n=15 subjects)
H) 400 mg (13.68 mL) HTX-002 via instillation (n=15 subjects)
I) 30 mL of 0.25% Marcaine without epinephrine via local infiltration (n=15 subjects)

Part D

Approximately 45 subjects will be assigned randomly to 1 of the following 3 treatment cohorts:

A) 400 mg (13.68 mL) HTX-011-56 via a combination of injection and instillation and fentanyl 50 µg IV before wound closure (n=15 subjects)
B) 400 mg (13.68 mL) HTX-011-56 via a combination of injection and instillation and fentanyl 100 µg IV before

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wound closure (n=15 subjects)

C) 400 mg (13.68 mL) HTX-011-56 via a combination of injection and instillation and no fentanyl before wound closure (n=15 subjects)

Part E

Approximately 20 subjects will be assigned randomly to 1 of the following 2 treatment cohorts:

A) 13.68 mL of HTX-009 via a combination of injection and instillation (n=15 subjects)

B) 13.68 mL of normal saline via a combination of injection and instillation (n=5 subjects)

Subject safety will be monitored by regular assessments of vital signs, electrocardiographs (ECGs), physical examination, clinical laboratory tests, wound healing and photographs of the surgical site, and by collection of AEs and concomitant medications.

Part F

Approximately 20 subjects will be assigned randomly to 1 of the following 2 treatment cohorts:

A) 13.68 mL of normal saline via instillation and fentanyl 50 µg IV before wound closure (n=15 subjects)

B) 400 mg (13.68 mL) HTX-011-56 via instillation and fentanyl 50 µg IV before wound closure (n=5 subjects)

Part G

Approximately 35 subjects will be assigned randomly to 1 of the following 3 treatment cohorts:

A) 300 mg (10.26 mL) of HTX-011-56 via instillation and 50 µg fentanyl IV before wound closure (n=15 subjects)

B) 75 mg (30 mL) of 0.25% Marcaine without epinephrine via injection and 50 µg fentanyl IV before wound closure (n=15 subjects)

C) 10.26 mL of normal saline via injection and 50 µg fentanyl IV before wound closure (n=5 subjects)

Symptoms of CNS including those known to be associated with bupivacaine toxicity will be prospectively assessed at regular time points throughout the 72 hour clinic stay for perioral tingling, strange taste, muscle twitching, ringing in ears, seizure, bradycardia, and cardiac arrest, and by neurologic examination which will include a mental status exam and evaluation of cranial nerve, motor, sensory, and cerebellar function.

Blood sample for pharmacokinetic analyses (PK) will be drawn prior to administration of the investigational product (IP), and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 30, 36, 48, 60, 72, 96, and 120 hours following administration of the IP.

Efficacy evaluations will include collection of Pain Intensity scores, Patient Global Assessment of Pain Control, assessments of nausea, and use of analgesia rescue medicine.

Post-Treatment Phase:

Subjects will return to the clinic site at 96 and 120 hours post-administration of study drug and at Day 10 and Day 28 for safety and efficacy evaluations, as follows:

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Post-Confinement Phase:

96 Hours: safety assessments of vital signs, ECG, collection of AEs and concomitant medications, and photographs of the surgical site. A blood sample will be collected for PK. Efficacy assessments will include collection of Pain Intensity scores and PGA evaluations.

120 Hours: obtain blood sample for pharmacokinetic analysis only.

Day 10: a physical examination, vital signs, ECGs collection of AEs and concomitant medications, assessment of wound healing, and photographs of the surgical site.

Day 28: collection of AEs and concomitant medications, assessment of wound healing, and photographs of the surgical site.

Day 60: subjects will receive a phone call from the study site to collect follow-up information on postoperative pain and pain medications.

Number of Subjects: This study will enroll up to approximately 453 subjects (108 in Part A, 90 in Part B, 135 in Part C, 45 in Part D, 20 in Part E, 20 in Part F, and 35 in Part G).

Number of study sites: up to 6

Study country location: United States

Criteria for inclusion: Subjects must meet all of the following criteria to be considered eligible to participate in the study:

1. Be male or female 18 years of age or older
2. Female subjects are eligible only if all of the following apply:
   - Not pregnant (female subject of child bearing potential must have a negative serum pregnancy test at screening and negative urine pregnancy test before surgery)
   - Not lactating
   - Not planning to become pregnant during the study
   - Be surgically sterile; or at least two 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 FDA for greater than 2 months prior to screening visits and commits to the use of an acceptable form of birth control for the duration of the study and for 30 days from completion of the study

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Male:

- Must be surgically sterile (biologically or surgically) or commit to the use of a reliable method of birth control for the duration of the study until at least 1 week after the administration of study medication

3. Plan to undergo a unilateral inguinal herniorrhaphy
4. Have the ability and be willing to comply with the study procedures
5. Must be able to understand study procedures and give informed consent for the conduct for all study procedures, using an IRB approved consent form

Criteria for Exclusion: Subjects will not be eligible to participate in the trial if any of the following criteria are met:

1. Unwilling to sign informed consent or not willing or able to complete all study procedures
2. Have a contraindication or be allergic to any medication to be used during the trial period
3. Have clinically significant cardiac abnormalities, that in the opinion of the investigator would pose a health risk to the subject should they participate in the trial
4. Have American Society of Anesthesiologists (ASA) Physical Status classification system category 4 or greater (Appendix E)
5. Have clinically significant renal or hepatic abnormalities (defined as an AST or ALT > 3x ULN, creatinine > 2x ULN)
6. Have another pre-existing painful condition that may confound pain assessments
7. Have another surgery planned within 30 days of procedure, or presents with bilateral or recurrent inguinal hernia, other hernia presentations, or hernias with large scrotal component that would be difficult to reduce surgically. Note: Subject may present with bilateral hernia; however subject may be scheduled to only have unilateral repair while participating in this study
8. Have a known or suspected history of alcohol or drug abuse, or a positive drug screen
9. Currently taking analgesics for a chronically painful condition, or has taken long acting opioids within 3 days of surgery, or taken any opioids within 24 hours of scheduled surgery for this study
10. Subjects with documented sleep apnea or are on home continuous positive airway pressure (CPAP)
11. Female subjects who are pregnant (positive pregnancy test at screening or on the day of surgery)
12. Subjects who are receiving oxygen therapy at the time of screening
13. Have participated in a clinical trial within 30 days of planned surgery
14. Have a body mass index (BMI) > 39 kg/m^2

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Investigational product:

HTX-011 is a sterile, viscous, extended-release, fixed-ratio combination of bupivacaine and meloxicam to be administered topically or via injection into the surgical site for the prevention of postoperative pain. The term "HTX-011" is used to represent study medication. There are several formulations of HTX-011; HTX-011-19, HTX-011-49, and HTX-011-56 will be the formulations used for this study.

HTX-002 is a sterile, viscous, extended-release formulation of bupivacaine to be locally administered into the surgical site for the prevention of postoperative pain.

HTX-009 is a sterile, viscous, extended-release formulation of meloxicam to be locally administered into the surgical site for the prevention of postoperative pain.

The vehicle formulation for HTX-011-19 is tri[ethylene glycol] based poly[orthoester] polymer with N-methyl-2-pyrrolidone (NMP) and maleic acid excipients.

The vehicle formulation for HTX-011-49, HTX-011-56, HTX-002, and HTX-009 is tri[ethylene glycol] based poly[orthoester] polymer with dimethyl sulfoxide, glycerol triacetate, and maleic acid excipients.

This study is being conducted to evaluate the safety and analgesic efficacy of HTX-011, HTX-002, and HTX-009 in subjects following unilateral herniorrhaphy. All formulations will be supplied by the sponsor for administration to subjects according to their randomization. The calculated doses based on the mass of HTX-011 are as follows:

HTX-011-19

200 mg HTX-011-19:
58.5 mg bupivacaine and 1.8 mg of meloxicam = 1 mL HTX-011-19
200.1 mg bupivacaine and 6.0 mg of meloxicam = 3.42 mL HTX-011-19

400 mg HTX-011-19:
58.5 mg bupivacaine and 1.8 mg of meloxicam = 1 mL HTX-011-19
400.1 mg bupivacaine and 12.0 mg of meloxicam = 6.84 mL HTX-011-19

HTX-011-49

200 mg HTX-011-49:
29.25 mg bupivacaine and 0.88 mg of meloxicam = 1 mL HTX-011-49
200.1 mg bupivacaine and 6.0 mg of meloxicam = 6.84 mL HTX-011-49

400 mg HTX-011-49:
29.25 mg bupivacaine and 0.88 mg of meloxicam = 1 mL HTX-011-49
400.1 mg bupivacaine and 12.0 mg of meloxicam = 13.68 mL HTX-011-49

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HTX-011-56

200 mg HTX-011-56:
29.25 mg bupivacaine and 0.88 mg of meloxicam = 1 mL HTX-011-56
200.1 mg bupivacaine and 6.0 mg of meloxicam = 6.84 mL HTX-011-56

300 mg HTX-011-56:
29.25 mg bupivacaine and 0.88 mg of meloxicam = 1 mL HTX-011-56
299.8 mg bupivacaine and 9.0 mg of meloxicam = 10.26 mL HTX-011-56

400 mg HTX-011-56:
29.25 mg bupivacaine and 0.88 mg of meloxicam = 1 mL HTX-011-56
400.1 mg bupivacaine and 12.0 mg of meloxicam = 13.68 mL HTX-011-56

HTX-002 and HTX-009 are similar formulations to HTX-011-56 except that they contain only bupivacaine or meloxicam, respectively, at the same concentration as the active pharmaceutical product.

Reference therapy: Normal saline solution (saline placebo) and 0.25% Marcaine without epinephrine

Duration of treatment: Each subject will receive a single dose of study medication intra-operatively.

Overview: Subjects will participate in the screening visit within 28 days of the scheduled surgery. At that time, medical history, vital signs, physical examination, clinical laboratory tests, drug and alcohol screening, 12-lead ECG testing and collection of prior and concomitant medications, and a pregnancy test will be performed. ASA classification and assessment of PONV risk factors will be assessed. Review of inclusion/exclusion criteria eligibility, along with training the subject on pain assessment and placebo response will be performed.

On day of surgery, Day 0, subjects will be reassessed for eligibility and undergo the index procedure under general anesthesia. No epidural or spinal anesthesia will be allowed, nor will any local anesthetic infiltration other than the administration of the IP or control be permitted. No prophylactic antiemetic, local anesthetics, or analgesic medications are allowed other than those used with general anesthesia.

Subjects will be dosed in each cohort as described above. Start and stop time of dosing will be recorded. Dosing stop time will be considered T0.

Subjects will be transferred to the post-anesthesia care unit and observed according to institutional standards. While in the unit, subjects may receive morphine IV for pain control as needed as per local practice.

A photograph of the surgical wound will be taken immediately after surgery, at 48, 72, and 96 hours, and at Days 10 and 28.

When subjects have met post-anesthesia care unit discharge criteria, they may be discharged to the clinic floor

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where they will be housed until 72 hours post Time 0 and discharge procedures are performed.

Pain scores **<u>at rest</u>** will be assessed utilizing an 11 point (0–10) numerical pain rating scale (NPRS) 1, 2, 78, 84, and 96 hours after administration of study medication (Time 0). In this NPRS scale, 0-no pain experienced and 10-worst pain imaginable.

Pain scores will be measured **<u>on movement</u>** (sitting up from a supine position) starting at Hour 4 and measured at 6, 8, 10, 12, 14, 18, 24, 30, 36, 42, 48, 54, 60, and 72 hours. Once subjects can tolerate oral medication, subjects may receive oral oxycodone or other comparable analgesic, as required for breakthrough pain every four to six hours as needed. All medications taken by the subject and administered during surgery will be recorded and all adverse events noted throughout the study period. Patients may receive acetaminophen 1000 mg for pain that is grade 4 or lower. A daily dose of acetaminophen must not exceed 4 grams (4000 mg) per day.

Vital signs will be measured at Screening, Baseline and at 1, 2, 4, 6, 12, 18, 24, 36, 48, 60, 72, and 96 hours after administration of study medication (Time 0) and at Day 10 visit.

Subjects will have a 12-lead ECG performed at screening, at baseline (i.e., at check-in on Day 0) and at 24, 48, 72, and 96 hours post-treatment. Study personnel will assess subjects for adverse events which will include a neurologic evaluation for potential bupivacaine toxicity.

Blood PK samples will be drawn prior to administration of the investigational product (IP), and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 30, 36, 48, 60, 72, 96, and 120 hours post-treatment.

The subject will be assessed on Days 10 at the clinic by physical exam, 12-lead ECG, vital signs, and the wound assessed for healing and at Day 28 assessed for wound healing. Any adverse events and concomitant medications will be collected.

Subjects will receive a phone call from the study site on Day 60 and will be asked if they have any current pain related to the operation and to rate their pain intensity over the previous 24 hours using the NRS. Subjects will also be asked about their use of any pain medication over the previous 24 hours to treat pain related to the operation.

Efficacy:

- The primary efficacy endpoint will be the summed pain intensity score (SPI), SPI_{0-24}.

Secondary efficacy endpoints include:

- SPI at various other time points (SPI_{0-6}, SPI_{0-12}, SPI_{12-24}, SPI_{24-48}, SPI_{0-48}, SPI_{48-72}, SPI_{0-72}, SPI_{72-96} and SPI_{0-96}).
- The Patient Global Assessment (PGA) of pain control at 24, 48, 72, and 96 hours post-treatment.
- Time to administration of first dose of rescue analgesia.
- Total and average daily rescue consumption over 24, 48, 72, and 96 hours post-treatment.
- Mean nausea assessment scores at 6, 24, 48, and 72 hours post-treatment.
- The percentage of subjects who remain pain free (Numerical Pain Rating Scale ≤1) at 72 hours and at 96 hours

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after study drug administration.

Pharmacokinetics:

The plasma PK parameters for bupivacaine and meloxicam will be derived by non-compartmental analysis of the plasma concentration-time profiles. The following pharmacokinetic endpoints have been defined:

- The area under the plasma concentration-time curve from time zero to time t of the last measured concentration above the limit of quantification (AUC_{last})
- The area under the plasma concentration-time curve from zero to infinity (AUC_{inf})
- The maximum plasma concentration (C_{max})
- The time to reach maximum plasma concentration (T_{max})
- The terminal elimination rate constant (λ_Z) with the respective half-life ($t_{½}$)

Safety:

The safety endpoints will include the following:

- wound assessment findings
- vital signs
- clinical laboratory tests, including routine blood chemistry and hematology
- ECG findings
- AEs and SAEs

Statistical methods:

Sample size determination: The sample size for this study was selected empirically without a formal statistical assumption.

Efficacy analysis: A comprehensive statistical analysis plan will be developed for this study. Demographic and baseline characteristics will be summarized descriptively by treatment group. Efficacy endpoints will be analyzed using ANOVA, chi-square tests, and log-rank tests, as appropriate.

The efficacy data for all sums scores will be analyzed via analysis of variance via contrast statements for all pairwise and pooled group comparisons.

Pharmacokinetic analysis:

The PK parameters for bupivacaine and meloxicam will be calculated using non-compartmental analysis and summarized for formulations of HTX-011, HTX-002, HTX-009, and Marcaine.

Safety analysis: The Medical Dictionary for Regulatory Activities (Version 16 or higher) will be used to classify all AEs/SAEs with respect to system organ class and preferred term. AEs/SAEs will be summarized by treatment.

Name of Sponsor/Company: Heron Therapeutics, Inc.	**Protocol Number:** HTX-011-C2015-202
Name of Investigational Product: HTX-011 (extended-release 2.5% bupivacaine and 0.075% meloxicam) • HTX-011-19 • HTX-011-49 • HTX-011-56 HTX-002 (extended-release 2.5% bupivacaine) HTX-009 (extended-release 0.075% meloxicam)	**Protocol Title:** A Phase 2, Randomized, Pilot Study to Investigate the Safety, Efficacy, Pharmacokinetics and Bioavailability of HTX-011, HTX-002, or HTX-009 Administered Via Injection and/or Topical Application Following Unilateral Open Inguinal Herniorrhaphy
Name of Active Ingredients: • Bupivacaine and Meloxicam (HTX-011) • Bupivacaine (HTX-002) • Meloxicam (HTX-009)	**Phase of Development:** 2
Changes in vital signs at each post dosing time point will be summarized by treatment using descriptive statistics without formal statistical tests. The number and proportion of subjects with abnormal ECG findings at each assessment will be tabulated by treatment group.	

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LIST OF APPENDICES

ABBREVIATIONS AND DEFINITIONS

AE	adverse event
ANOVA	analysis of variance
APAP	acetyl-para-aminophenol (Acetaminophen)
API	active pharmaceutical ingredient
ASA	American Society of Anesthesiology
AUC	area under the plasma concentration-time curve
BA	bioavailability
BE	bioequivalence
BMI	body mass index
bpm	beats per minute
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
DMSO	dimethyl sulfoxide
ECG	electrocardiogram
eCRF	electronic Case Report Form
ET	early termination
GCP	Good Clinical Practice
HEENT	head, eyes, ears, nose and throat
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
ITT	intent-to-treat
iv	intravenous
kg	kilogram
L	liters
LC-MS/MS	liquid chromatography – tandem mass spectrometry
LMA	laryngeal mask airway
LOCF	last observation carried forward
MAOIs	monoamine oxidase inhibitors
mg	milligram
min	minute

mITT	modified intend-to-treat
NNRS	Nausea Numeric Rating Scale
NPRS	Numerical Pain Rating Scale
NRS	Numeric Rating Scale
NSAIDs	non-steroidal anti-inflammatory drugs
PCP	phencyclidine
PGA	Patient Global Assessment
PI	pain intensity
PK	pharmacokinetic
po	by mouth, orally
PONV	postoperative nausea and vomiting
PRN	when necessary
SAE	serious adverse event
SNRIs	serotonin-norepinephrine reuptake inhibitors
SPI	summed pain intensity
SpO_2	peripheral oxygen saturation
SSRI	selective serotonin reuptake inhibitor
$t_{½}$	half-life
TCAs	tricyclic antidepressants
TEG-POE	tri(ethylene glycol) poly(orthoester)
T_{max}	time to reach maximum plasma concentration
T0	Time 0
VS	vital signs
WBC	white blood cell
WHO	World Health Organization
WLOCF	windowed last observation carried forward
λZ	terminal elimination rate constant

1. INTRODUCTION

The use of local anesthetics within a surgical wound, i.e., "wound infiltration," has found extensive use in a vast number of patients (Renck 1994). Medical opinion suggests that such infiltration with local anesthetics may be a relatively simple and safe means to reduce post-operative pain (Moiniche, Mikkelsen et al. 1998). The major limitation of the current local anesthetics used for infiltration is the limited duration of effect (6–12 hours) that is observed following surgery (Kehlet and Andersen 2011). In recent years there has been a dramatic increase in day-case surgery. In this patient population it is estimated that 30 to 40% of the patients suffer from moderate to severe pain during the first 24 to 48 hours. The development of a long-acting local anesthetic formulation for this patient population would be of clinical significance (Rawal 2001).

While non-steroidal anti-inflammatory drugs (NSAIDs) have long been used in the treatment of post-operative pain (Moote 1992), there is early evidence that there may be a synergistic interaction between local anesthetics and non-steroidal anti-inflammatory compounds when locally administered (Ortiz, Castañeda-Hernández et al. 2011). The Sponsor has identified a combination of bupivacaine and low dose meloxicam in a sustained release formulation (HTX-011), intended for the management of post-operative pain via wound infiltration that has demonstrated positive results in a non-clinical model of post-surgical pain and in an initial study in healthy volunteers with its first formulation HTX-011-19. HTX-011 with the appropriate amount and combination of excipients has been selected for further clinical development. Three distinctly different formulations of HTX-011 have been composed for clinical evaluation:

- HTX-011-19: the vehicle formulation is tri[ethylene glycol] based poly[orthoester] polymer with N-methyl-2-pyrrolidone (NMP) and maleic acid.
- HTX-011-49 the vehicle formulation is tri[ethylene glycol] based poly[orthoester] polymer with dimethyl sulfoxide (DMSO), glycerol triacetate, and maleic acid.
- HTX-011-56: the vehicle formulation is tri[ethylene glycol] based poly[orthoester] polymer with DMSO, glycerol triacetate, and maleic acid.

The three formulations differ from each other solely on the basis of either the percentage content of the active ingredients (bupivacaine and meloxicam) and or the percentage content of excipients comprising the vehicle formulation. The two newer formulations, HTX-011-49 and HTX-011-56, were developed and incorporate two new excipients: these formulations improve the ease of delivery while maintaining the pharmacokinetic and pharmacodynamic properties of HTX-011-19.

The Sponsor has also developed 2 formulations, HTX-002 and HTX-009, which are similar in pharmaceutical composition to HTX-011-56 except that they contain only bupivacaine or meloxicam, respectively, as the active pharmaceutical ingredient (API). Exploratory studies evaluating the antinociceptive effect in a post-operative pain model in domestic piglets and cross-over PK studies in the beagle dogs demonstrate that the primary pharmacodynamics and PK characteristics for HTX-002 are similar to that of HTX-011-56. Both the active ingredients (bupivacaine and meloxicam) and the identical biochronomer polymer vehicle have been studied in humans.

In a placebo-controlled Phase 1 clinical trial, single doses of 1.72 mL, 3.44 mL, and 6.88 mL of HTX-011-19 and single doses of 3.44 mL and 6.88 mL of HTX-011-49 were administered to healthy volunteers. HTX-011 achieved the desired pharmacokinetic profile for both bupivacaine and meloxicam. Therapeutically relevant plasma bupivacaine levels were sustained for 2 to 3 days in the absence of the large initial peak that can be observed with commercially available formulations of the drug. The anesthetic effects of HTX-011 persisted through 96 hours, which closely correlated with plasma bupivacaine concentrations. All five doses were well-tolerated with no serious adverse events, clinically relevant ECG or laboratory changes, or premature discontinuations. Mild redness and bruising were seen at some injection sites due to the subcutaneous administration of the product in this healthy volunteer study.

A placebo-controlled Phase 2 clinical trial in the US, evaluated the efficacy and safety of HTX-011 containing 200 mg and 400 mg of bupivacaine combined with meloxicam, compared with placebo, in 71 subjects undergoing bunionectomy. The primary endpoint was the difference, as compared to placebo, in pain intensity, as measured by the Summed Pain Intensity score (SPI), in the first 24 hours post-surgery. Key secondary endpoints included: the difference in SPI in the first 48 hours post-surgery; the difference in SPI in the first 72 hours post-surgery; time to the first use of opiate rescue medication; and the percentage of subjects who received no opiate rescue medication in the first 72 hours post-surgery. No subject discontinued early from this study. [redacted]

The present Phase 2 study is designed to evaluate the efficacy and duration of analgesia following administration of HTX-011 into the surgical site following unilateral open inguinal herniorrhaphy. The study will include 2 controls (normal saline and Marcaine), a bupivacaine-only formulation (HTX-002), and a meloxicam-only formulation (HTX-009). The study will also evaluate different local administration techniques (injection, instillation, and a combination of the 2 techniques) as well as the effects of a fentanyl administration at the end of surgery and before study drug administration on the analgesic efficacy of HTX-011-56.

Efficacy assessments are intended to characterize the analgesic time action curve and the magnitude of analgesic effect of both administration techniques and both doses of HTX-011 in comparison with HTX-002, HTX-009, Marcaine™, and saline. In addition, the study will further characterize the safety and pharmacokinetic profiles of all formulations of HTX-011, HTX-002, and HTX-009.

See the current edition of the HTX-011 Investigator's Brochure for more information about the formulations (HTX-011, HTX-002, and HTX-009).

2. STUDY OBJECTIVES

The primary objective for Part A is to evaluate the efficacy and duration of analgesia following administration of one of two doses of HTX-011-19 by different techniques.

The primary objective of Parts B through G will be to evaluate the efficacy and duration of analgesia following administration of HTX-011-49, HTX-011-56, HTX-002, HTX-009, bupivacaine (Marcaine), or normal saline.

The secondary objectives to be evaluated in Parts A through G are as follows:

- To determine in Part A the optimal administration technique of study drug
- To determine the safety and tolerability of HTX-011, HTX-002, and HTX-009 as evaluated through physical examination, vital signs, clinical laboratory tests, ECGs, and incidence of adverse events (AEs) and serious AEs (SAEs)
- To evaluate the pharmacokinetic (PK) profiles of bupivacaine and/or meloxicam in HTX-011, HTX-002, and HTX-009 over 120 hours
- To evaluate the analgesic effects of HTX-011, HTX-002, and HTX-009 over various intervals using a series of secondary efficacy endpoints for pain intensity (such as the patient's global assessment of pain control, time to administration of first dose of rescue analgesia, and total and average daily rescue consumption)
- To assess the effects of HTX-011, HTX-002, and HTX-009 on wound healing at 72 hours and on Days 10 and 28 post-treatment
- To evaluate nausea at 6, 24, 48, and 72 hours post-treatment
- To evaluate the percentage of subjects pain free over time

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a Phase 2, multi-center, single-dose, randomized, study in adult subjects undergoing unilateral open inguinal herniorrhaphy. The study will enroll up to approximately 453 subjects.

Subjects at least 18 years of age requiring unilateral open inguinal herniorrhaphy will be screened for participation at the study sites in the United States within 28 days of the planned surgery. After signing the informed consent, subjects will be assessed for medical history, PONV risk factors, physical examination, baseline clinical laboratory tests, drug and alcohol screen, 12 lead electrocardiogram (ECG), pregnancy testing, vital sign measurements, and they will undergo pain and placebo assessment training during the screening visit.

On the day of surgery (Day 0), after having been reassessed for eligibility, subjects will undergo a unilateral open inguinal herniorrhaphy under general anesthesia. No epidural or spinal anesthesia will be allowed, nor will any local anesthetic infiltration, other than the administration of the investigational product (IP), be permitted. No prophylactic antiemetic, local anesthetics, or analgesic medications are allowed at any time. A single dose of study drug (either HTX-011, HTX-002, HTX-009, Marcaine, or saline, according to a randomization schedule) will be administered. Start and stop time of dosing will be recorded. Dosing stop time will be considered Time 0.

Following the completion of surgery and immediate postoperative recovery stay, subjects will be transferred to the unit. Staff members at the unit will be blinded to study treatment. Subjects will stay at the unit for approximately 72 hours after the administration of study medication and will return to the unit 96 and 120 hours after the administration of study medication to complete additional assessments. Subjects will be scheduled to return on Day 10 for additional efficacy and safety assessments and Day 28 for an assessment of wound healing and collection of AEs and concomitant medications. Part A of the study will determine the optimal technique of administration of study drug. Efficacy assessments will include pain intensity scoring, use of rescue medication, Patient Global Assessment (PGA) of pain control, and assessments of nausea, and use of analgesia rescue medicine. Safety assessments will include monitoring of AEs, physical examinations, vital sign measurements, clinical laboratory tests, ECGs, and wound healing assessments and photographs of the surgical site. Blood samples will be obtained to assess meloxicam and bupivacaine pharmacokinetics. Subjects will also receive a phone call from the study site on Day 60 to collect follow-up information on postoperative pain and pain medications.

3.2. Rationale for Study Design and Control Groups

This study will evaluate the efficacy and safety of three formulations of the combination of a known local anesthetic, bupivacaine, and a known anti-inflammatory drug, meloxicam (HTX-011), via different administration techniques (injection into the surgical wound and/or topical administration into the surgical wound).

Bupivacaine (Marcaine) and normal saline will be used as an active control and a placebo control, respectively, for efficacy and safety evaluations. A bupivacaine-only formulation, HTX-002, and a meloxicam-only formulation, HTX-009, will also be evaluated.

This study will explore the analgesic effects of dosing with HTX-011 in subjects following unilateral open inguinal herniorrhaphy. Unilateral open inguinal herniorrhaphy produces generally reliable and persistent pain symptoms for a period typically lasting over 72 hours from the surgical insult, which will allow for analysis of acute analgesia over an extended period of time. Efficacy measures will be collected in order to gain a better knowledge of the analgesic time action curve, following a surgical procedure, of HTX-011 compared with Marcaine and saline in one formulation initially (HTX-011-19), via two administration techniques in Part A. Following the determination of the optimal technique of administration, efficacy measures of two additional formulations of HTX-011 (HTX-011-49 and HTX-011-56), a bupivacaine-only formulation (HTX-002) and a meloxicam-only formulation (HTX-009) will be evaluated. The study will also further characterize the safety and PK profiles of all three formulations of HTX-011 and of HTX-002 and HTX-009, and will examine the effects of fentanyl administration at the end of surgery on the analgesic efficacy of HTX-011-56. [redacted]

4. STUDY POPULATION

4.1. Inclusion Criteria

Subjects must meet all of the following criteria to be considered eligible to participate in the study:

1. Be male or female 18 years of age or older

2. Female subjects are eligible only if all of the following apply:

   - Not pregnant (female subject of child bearing potential must have a negative serum pregnancy tests at screening and negative urine pregnancy test before surgery)
   - Not lactating
   - Not planning to become pregnant during the study
   - Be surgically sterile; or at least two year 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 FDA for greater than 2 months prior to screening visits and commits to the use of an acceptable form of birth control for the duration of the study and for 30 days from completion of the study

   Male:

   - Must be surgically sterile (biologically or surgically) or commit to the use of a reliable method of birth control for the duration of the study until at least 1 week after the administration of study medication

3. Plan to undergo a unilateral inguinal herniorrhaphy

4. Have the ability and be willing to comply with the study procedures

5. Must be able to understand study procedures and give informed consent for the conduct for all study procedures, using an IRB approved consent form

4.2. Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participating in the study:

1. Unwilling to sign informed consent or not willing or able to complete all study procedures

2. Have a contraindication or be allergic to any medication to be used during the trial period

3. Clinically significant cardiac abnormalities that in the opinion of the investigator would pose a health risk to the subject should they participate in the trial

4. Have American Society of Anesthesiologist (ASA) Physical Status classification system category 4 or greater (Appendix E)

5. Have clinically significant renal or hepatic abnormalities (defined as an AST or ALT > 3x ULN, creatinine > 2x ULN)

6. Have another pre-existing painful condition that may confound pain assessments

7. Have another surgery planned within 30 days of procedure, or presents with bilateral or recurrent inguinal hernias, other hernia presentations, or hernias with large scrotal component that would be difficult to reduce surgically. Note: Subject may present with bilateral hernia: however, subject may be scheduled to only have unilateral repair while participating it this study

8. Have a known or suspected history of alcohol or drug abuse or a positive drug screen

9. Currently taking analgesics for a chronically painful condition, or has taken long acting opioids within 3 days of surgery, or taken any opioids within 24 hours of surgery for this study

10. Subjects with documented sleep apnea or are on home continuous positive airway pressure (CPAP)

11. Female subjects who are pregnant (positive pregnancy test at screening or on the day of surgery)

12. Subjects who are receiving oxygen therapy at the time of screening

13. Have participated in a clinical trial within 30 days of planned surgery

14. Have a body mass index (BMI) > 39 kg/m^2

4.3. Discontinuation of Subjects

4.3.1. Procedures for Withdrawal

A subject may be discontinued 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. Subjects who withdraw consent or who are discontinued from the study before completing the protocol specified duration of treatment should be encouraged to complete the early termination assessments. Subjects will be encouraged to agree to be followed for up to 28 days after receiving study medication. The date the subject is withdrawn and the primary reason for discontinuation will be recorded in the subject's electronic case report form (eCRF).

4.3.2. Replacement of Subjects

Subjects who discontinue from this study between 24 and 72 hours post-treatment may be replaced in this study after discussion with the investigator and at the discretion of the Sponsor.

Any subject who is randomly assigned to study drug but who discontinues the study prior to the study drug administration will be replaced by the next study subject who meets the study entry criteria. The replacement subject will be assigned to the same study drug that was intended for the subject being replaced.

4.4. Lifestyle Guidelines

4.4.1. Confinement

Prior to the surgical procedure (Day 0), subjects will arrive at the study clinic in sufficient time to prepare for the procedure and confirm eligibility to participate in the study. In Part A of the study, appropriately qualified subjects will be assigned randomly to one of 5 treatment cohorts of HTX-011-19 or to saline during the unilateral open inguinal herniorrhaphy procedure. In Part B, subjects will be assigned randomly to one of 4 treatment groups of either HTX-011-49 or HTX-011-56 or to saline, via the technique that was determined to be optimal in Part A. In Part C, subjects will be assigned randomly to one of the 9 treatment groups of HTX-002 or HTX-011, Marcaine, or to saline. In Part D, subjects will be assigned randomly to one of the 3 treatment groups of HTX-011-56 with or without fentanyl administration at the conclusion of the case and before study drug administration. In Part E, subjects will be assigned randomly to one of the 2 treatment groups of HTX-009 or normal saline. In Part F, subjects will be assigned randomly to one of the 2 treatment groups of HTX-011-56 or normal saline with fentanyl administration at the conclusion of the case and before study drug administration. In Part G, subjects will be assigned randomly to one of the 3 treatment groups of HTX-011-56, Marcaine, or normal saline with fentanyl administration at the conclusion of the case and before study drug administration. (See Section 4.6 for more information on treatment cohorts for each part of the study.) Subjects will be discharged from the study clinic on Day 3, about 72 hours after receiving study medication. They will be scheduled to return to the study clinic 24 hours later, i.e., approximately 96 hours, and at 120 hours after receiving study medication.

Bathroom privileges will be restricted during the postoperative confinement period. Following completion of the surgery, subjects will be restricted to use of a bedpan, bedside commode, or bathroom privileges via wheelchair through completion of 12-hour assessments; bathroom privileges may be loosened at any time at the discretion of the investigator. While confined at the study clinic following surgery, subjects will be required to remain resting in bed at least 5 minutes prior to any pain intensity assessment. Subjects will be allowed to ambulate according to standard postoperative care instructions.

4.5. Surgical Procedure

On the day of surgery (Day 0), subjects will undergo unilateral open inguinal hernia with tension free technique using implanted mesh. Surgeries should be scheduled so as to allow for all surgical procedures to be completed by approximately 5:00 pm on the day of surgery.

4.5.1. Anesthesia Protocol and Administration of Study Medication

4.5.1.1. Anesthesia

The anesthetic protocol below is a guide that should be followed to minimize inter-subject variability to the greatest extent possible. However, it is understood that hemodynamic fluctuations and other intraoperative events may necessitate some deviation from the standard regimen.

The surgery will be performed under general anesthesia according to local practices; for example, inducing sedation with up to 2 mg midazolam is permitted, or induction with propofol (and lidocaine to decrease injection pain from propofol is permitted), and fentanyl should be limited to no more than 100 micrograms. Should intubation be required, non-depolarizing muscle relaxants may be used and reversed, if needed, per local practice. Laryngeal mask airway (LMA) placement is preferred over intubation. Succinylcholine is not permitted. Volatile anesthetics are to be used for maintenance of anesthesia, and nitrous oxide is not permitted. No epidural or spinal anesthesia will be allowed, nor will any local anesthetic infiltration, other than the administration of the IP, be permitted. No prophylactic antiemetics, local anesthetics, or analgesic medications are allowed at any time.

4.5.1.2. Study Drug Administration (Parts A, B, C, F, and G)

Once the hernia repair is completed, study medication will be administered by local administration into the surgical site utilizing either the technique of wound infiltration ("injection"), instillation ("topical"), or both, depending on the study group assignment.

Wound Infiltration

For subjects receiving wound infiltration of study drug only:

- Approximately 1/3 of the study drug is placed into the upper third of subcutaneous tissue just above the level of the fascia,
- Approximately 1/3 is placed immediately underneath the aponeurosis of the external oblique above the inguinal canal (taking care to avoid the nerves), and
- Approximately 1/3 is placed into the canal itself

For the first two steps, it is expected that a number of intrusions of the needle will be necessary to cover the area.

Instillation

For subjects receiving the topical administration dosing cohort, the study drug is prepared in the syringe and then evenly applied throughout the surgical wound prior to closure at both the level below and the level above the fascia.

Both

For subjects receiving both wound infiltration and instillation, both of the above steps are to be followed.

In all cases, start and stop time of dosing will be recorded; dosing stop time will then be considered Time 0 (T0). Details of an 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.

4.5.1.3. Study Drug Administration (Parts D and E)

Once the hernia repair is completed, study drug will be administered by local administration into the surgical site using a "combination" technique comprising both wound infiltration ("injection") and instillation ("topical").

Use approximately ½ the study drug for wound infiltration. This portion of study drug should be administered as follows:

- Approximately 1/3 of the study drug is placed into the subcutaneous tissue just above the level of the fascia.
- Approximately 1/3 is placed immediately underneath the aponeurosis of the external oblique above the inguinal canal (taking care to avoid the nerves).
- Approximately 1/3 is placed into the canal.

For the first two steps, it is expected that a number of intrusions of the needle will be necessary to cover the area.

Use the remaining amount of study drug for instillation:

The study drug is prepared in the syringe and then evenly applied throughout the surgical wound prior to closure at both the level below and the level above the fascia.

In all cases, start and stop time of dosing will be recorded; dosing stop time will then be considered Time 0 (T0). Details of an 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.

4.5.2. Identity of Study Medication

Study drug is defined as HTX-011 (HTX-011-19, HTX-011-49, HTX-011-56), HTX-002, HTX-009, Marcaine, or normal saline.

HTX-011

HTX-011 is a sterile, viscous, extended-release, fixed-ratio combination of bupivacaine and meloxicam to be administered via injection into the surgical site for the prevention of postoperative pain. There will be three HTX-011 formulations used in this study, HTX-011-19, HTX-011-49, and HTX-011-56.

The specific gravity of all formulations is approximately 1.17 g/mL. A mass of 1000 mg of HTX-011, therefore, is equivalent to a volume of 0.855 mL.

The vehicle formulation for HTX-011-19 is tri[ethylene glycol] based poly[orthoester] polymer with N-methyl-2-pyrrolidone (NMP) and maleic acid. Each mL of HTX-011-19 contains 58.5 mg bupivacaine base and 1.8 mg of meloxicam. The proposed drug product contains 5.00% w/w bupivacaine base, 0.15% meloxicam, in 79.25% w/w AP135 and 0.60% w/w maleic acid and 15% w/w NMP.

The vehicle formulation for HTX-011-49 is tri[ethylene glycol] based poly[orthoester] polymer with dimethyl sulfoxide (DMSO), glycerol triacetate, and maleic acid. One mL of HTX-011-49 contains 29.25 mg bupivacaine base and 0.88 mg of meloxicam. The proposed drug product contains 2.50% w/w bupivacaine base, 0.075% w/w meloxicam, in 54.275% w/w AP135 and 0.15% w/w maleic acid, 8.00% w/w DMSO, and 35% w/w glycerol triacetate (or triacetin).

The vehicle formulation for HTX-011-56 is tri[ethylene glycol] based poly[orthoester] polymer with dimethyl sulfoxide, glycerol triacetate, and maleic acid. One mL of HTX-011-56 contains 29.25 mg bupivacaine base and 0.88 mg of meloxicam. The proposed drug product contains 2.5% w/w bupivacaine base and 0.075% w/w meloxicam in 62.375% w/w tri(ethylene glycol) poly(orthoester) (TEG-POE), 10.00% (w/w) DMSO, 25.00% w/w glycerol triacetate, and 0.05% w/w maleic acid.

HTX-002

HTX-002 has a similar composition as HTX-011-56 except that it contains only bupivacaine as the API. The vehicle formulation for HTX-002 is tri[ethylene glycol] based poly[orthoester] polymer with DMSO, glycerol triacetate, and maleic acid. One mL of HTX-002 contains 29.25 mg bupivacaine base. The proposed drug product contains 2.5% (w/w) bupivacaine base in 62.45% (w/w) tri(ethylene glycol) poly(orthoester) (TEG-POE), 10.00% (w/w) DMSO, 25.00% glycerol triacetate, and 0.05% (w/w) maleic acid.

HTX-009

HTX-009 has a similar composition as HTX-011-56 except that it contains only meloxicam as the API. The vehicle formulation for HTX-009 is tri[ethylene glycol] based poly[orthoester] polymer with DMSO, glycerol triacetate, and maleic acid. One mL of HTX-009 contains 0.88 mg of meloxicam. The proposed drug product contains 0.075% w/w meloxicam in 64.92% w/w tri(ethylene glycol) poly(orthoester) (TEG-POE), 10.00% (w/w) DMSO, 25.00% w/w glycerol triacetate.

HTX-011, HTX-002, and HTX-009 formulations will be provided by the Sponsor.

Normal saline and 0.25% Marcaine without epinephrine for injection should be provided by the site.

4.5.2.1. HTX-011, HTX-002, and HTX-009 Dose Calculations

The calculated doses based on the mass of HTX-011, HTX-002, and HTX-009 are as follows:

HTX-011-19

200 mg HTX-011-19:

58.5 mg bupivacaine and 1.8 mg of meloxicam = 1 mL HTX-011-19

200.1 mg bupivacaine and 6.0 mg of meloxicam = 3.42 mL HTX-011-19

400 mg HTX-011-19:

58.5 mg bupivacaine and 1.8 mg of meloxicam = 1 mL HTX-011-19

400.1 mg bupivacaine and 12.0 mg of meloxicam = 6.84 mL HTX-011-19

HTX-011-49

200 mg HTX-011-49:

29.25 mg bupivacaine and 0.88 mg of meloxicam = 1 mL HTX-011-49

200.1 mg bupivacaine and 6.0 mg of meloxicam = 6.84 mL HTX-011-49

400 mg HTX-011-49:

29.25 mg bupivacaine and 0.88 mg of meloxicam = 1 mL HTX-011-49

400.1 mg bupivacaine and 12.0 mg of meloxicam = 13.68 mL HTX-011-49

HTX-011-56

200 mg HTX-011-56:

29.25 mg bupivacaine and 0.88 mg of meloxicam = 1 mL HTX-011-56

200.1 mg bupivacaine and 6.0 mg of meloxicam = 6.84 mL HTX-011-56

300 mg HTX-011-56:

29.25 mg bupivacaine and 0.88 mg of meloxicam = 1 mL HTX-011-56

299.8 mg bupivacaine and 9.0 mg of meloxicam = 10.26 mL HTX-011-56

400 mg HTX-011-56:

29.25 mg bupivacaine and 0.88 mg of meloxicam = 1 mL HTX-011-56

400.1 mg bupivacaine and 12.0 mg of meloxicam = 13.68 mL HTX-011-56

HTX-002

200 mg HTX-002:

29.25 mg bupivacaine = 1 mL HTX-002

200.1 mg bupivacaine = 6.84 mL HTX-002

400 mg HTX-002:

29.25 mg bupivacaine = 1 mL HTX-002

400.1 mg bupivacaine = 13.68 mL HTX-002

HTX-009

0.88 mg of meloxicam = 1 mL HTX-009

12.0 mg of meloxicam = 13.68 mL HTX-009

Refer to the Pharmacy Manual for details on the preparation of study medication for administration to subjects enrolled in the study.

4.6. Method of Assigning Subjects to Treatment Groups

In Part A, 108 subjects will be assigned randomly to treatment with HTX-011-19 or with saline according to the randomization scheme, to 1 of 6 treatment cohorts:

A. 200 mg (3.42 mL) HTX-011-19 by injection into the surgical wound (n=18 subjects)

B. 400 mg (6.84 mL) HTX-011-19 by injection into the surgical wound (n=18 subjects)

C. 200 mg (3.42 mL) HTX-011-19 by topical administration into the surgical wound (n=18 subjects)

D. 400 mg (6.84 mL) HTX-011-19 by topical administration into the surgical wound (n=18 subjects)

E. A combination of 200 mg (3.42 mL) HTX-011-19 by injection into the surgical wound and 200 mg (3.42 mL) HTX-011-19 by topical administration into the surgical wound (n=18 subjects)

F. 6.84 mL of saline solution by injection into the surgical wound (n=18 subjects)

Upon determination of the optimal route of administration in Part A, 90 subjects in Part B will be assigned randomly to any 1 of 6 treatment cohorts:

A. 200 mg (6.84 mL) HTX-011-49 via technique determined in Part A (n=15 subjects)

B. 400 mg (13.68 mL) HTX-011-49 via technique determined in Part A (n=15 subjects)

C. 200 mg (6.84 mL) HTX-011-56 via technique in Part A (n=15 subjects)

D. 400 mg (13.68 mL) HTX-011-56 via technique determined in Part A (n=15 subjects)

E. 6.84 mL of saline solution via technique determined in Part A (n=15 subjects)

F. 13.68 mL of saline solution via technique determined in Part A (n=15 subjects)

Approximately 135 subjects in Part C will be assigned randomly to any 1 of 9 treatment cohorts:

A. 200 mg (6.84 mL) HTX-002 by injection into the surgical wound (n=15 subjects)

B. 400 mg (13.68 mL) HTX-002 by injection into surgical wound (n=15 subjects)

C. 6.84 mL of saline solution by injection into the surgical wound (n=15 subjects)

D. 13.68 mL of saline solution by injection into the surgical wound (n=15 subjects)

E. 200 mg (6.84 mL) HTX-011-59 via instillation (n=15 subjects)

F. 400 mg (13.68 mL) HTX-011-59 via instillation (n=15 subjects)

G. 200 mg (6.84 mL) HTX-002 via instillation (n=15 subjects)

H. 400 mg (13.68 mL) HTX-002 via instillation (n=15 subjects)

I. 30 mL of 0.25% Marcaine without epinephrine via infiltration (n=15 subjects)

Approximately 45 subjects in Part D will be assigned randomly to 1 of the following 3 treatment cohorts:

A. 400 mg (13.68 mL) HTX-011-56 via a combination of injection and instillation and fentanyl 50 µg IV before wound closure (n=15 subjects)

B. 400 mg (13.68 mL) HTX-011-56 via a combination of injection and instillation and fentanyl 100 µg IV before wound closure (n=15 subjects)

C. 400 mg (13.68 mL) HTX-011-56 via a combination of injection and instillation and no fentanyl before wound closure (n=15 subjects)

Approximately 20 subjects in Part E will be assigned randomly to 1 of the following 2 treatment cohorts:

A. 13.68 mL of HTX-009 via a combination of injection and instillation (n=15 subjects)

B. 13.68 mL of normal saline via a combination of injection and instillation (n=5 subjects)

Approximately 20 subjects in Part F will be assigned randomly to 1 of the following 2 treatment cohorts:

A. 13.68 mL of normal saline via instillation and fentanyl 50 µg IV before wound closure (n=15 subjects)

B. 400 mg (13.68 mL) HTX-011-56 via instillation and fentanyl 50 µg IV before wound closure (n=5 subjects)

Approximately 35 subjects in Part G will be assigned randomly to 1 of the following 3 treatment cohorts:

A. 300 mg (10.26 mL) of HTX-011-56 via instillation and fentanyl 50 µg IV before wound closure (n=15 subjects)

B. 75 mg (30 mL) of 0.25% Marcaine without epinephrine via injection and fentanyl 50 µg IV before wound closure (n=15 subjects)

C. 10.26 mL of normal saline via injection and fentanyl 50 µg IV before wound closure (n=5 subjects)

All study doses administered will be according to the original treatment assignment. Only the site staff directly involved in the surgery and the unblinded pharmacy staff will have access to the randomization scheme.

Subject and site staff involved in the post-surgical assessments of safety and efficacy will not have access to the randomization scheme and will be blinded to study treatment.

4.7. Selection of Doses

To ensure analgesic efficacy is demonstrated and to better understand the dose response effect of the HTX-011 formulations, 3 dose levels (200, 300, and 400 mg) will be evaluated in this study. HTX-011 doses up to 600 mg have been evaluated in previous and ongoing clinical studies and have been generally well tolerated.

In a placebo-controlled Phase 1 clinical trial, single doses of 100 mg, 200 mg, and 400 mg of HTX-011-19, and single doses of 100 mg and 200 mg mL of HTX-011-49 were administered to healthy adult volunteers. HTX-011 elicited the desired pharmacokinetic profile for both bupivacaine and meloxicam. Therapeutically relevant plasma bupivacaine levels were sustained for 2 to 3 days in the absence of large initial peak plasma concentrations that can be observed with commercially available formulations of the drug. The anesthetic effects of HTX-011 persisted through 96 hours, which closely correlated with plasma bupivacaine concentrations. All five doses were well-tolerated with no serious adverse events, clinically relevant ECG or laboratory changes, or premature discontinuations. Mild redness and bruising were seen at some injection sites due to the subcutaneous administration of the product in this healthy volunteer study.

4.8. Blinding and Unblinding of Study Medications

Since HTX-011, HTX-002, and HTX-009 formulations are colored and viscous solutions whereas saline and Marcaine are not, and the volume administered varies with dose, this renders obsolete any double-blinded study drug administration. Therefore, the site's surgical and pharmacy staff will not be blinded to the study medication administered. However, the conduct of the study will be observer blind. Once surgery is completed and subjects have been transferred to the clinical unit, all site staff in the clinical unit involved in the assessment of safety and efficacy will be blinded to the treatment assignment, and (s)he will remain masked to treatment assignments throughout the conduct of this study. The study blind may be broken only if the safety of a subject is at risk and the treatment plan for that subject depends on which study medication he or she received. If knowledge of the treatment assignment is absolutely necessary for the management of a subject's safety, the investigator must contact the medical monitor for unblinding information. If a subject's data are unblinded without the prior knowledge of the sponsor, the investigator must notify the sponsor as soon as possible and no later than the next business morning. All circumstances surrounding a premature unblinding must be clearly documented.

4.9. Treatment Compliance

Since study medication is being administered as a component of the surgical procedure, a lack of treatment compliance is not expected. The exact date, time, and dose of study medication

administration will be recorded in the subject's eCRF. It is important that all study medication is administered and that the syringes are emptied.

4.10. Drug Accountability

The investigator (or designee) will sign for the study medications when they are received. The study medication must be handled and stored as described in the pharmacy manual and dispensed only to those subjects formally entered into the study.

At the completion of the study and after reconciliation of all delivery and usage records, any unused study medication supplied by the sponsor will be returned to the sponsor (or designee) or destroyed per written instructions from the sponsor.

4.11. Packaging, Labeling, and Storage

All study medication (HTX-011, HTX-002, and HTX-009) will be prepared by the sponsor or the sponsor's designee. All study medication will be dispensed by the investigator or a person under his/her supervision and will be administered by the individual performing the surgery.

4.11.1. Study Drug Packaging

HTX-011, HTX-002, HTX-009 will be packed and dispatched in refrigerated shipping containers with a temperature monitor enclosed. The lot number and a manufacturing date will be provided.

4.11.2. Study Drug Labeling

HTX-011, HTX-002, HTX-009 labeling will comply with federal applicable laws and regulations. At the minimum, the following information will be provided:

- Study number (HTX-011-C2015-202)
- Drug identification
- Name, address, and telephone number of sponsor or manufacturer
- Lot number
- Contents of Package
- Storage conditions
- CAUTION: New Drug – Limited by United States Law to Investigational Use Only

All HTX-011, HTX-002, and HTX-009 formulations at the study site(s) should be stored in a refrigerator at 2–8^{o}C. The refrigerator should be in a locked area with restricted access. A temperature log or chart should be maintained to monitor the environment at the study site.

4.12. Prior and Concomitant Medications

All medications and other treatments taken by subjects within 30 days before dosing and during the study will be recorded in the eCRF.

All chronic medications that have not been at a stable dose for at least 30 days prior to the scheduled surgery procedure will be prohibited.

4.13. Prohibited Medications

The following medications are prohibited throughout the study: anticonvulsants, monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), neuroleptics, or serotonin-norepinephrine reuptake inhibitors (SNRIs), gabapentin, and pregabalin, and administration of any of these agents, while participating in the study will disqualify the subject from the efficacy evaluation.

Selective serotonin reuptake inhibitor (SSRI) treatments are allowed if taken for at least 30 days before the screening period of the study at an unchanged stable dose.

Analgesic medications other than those pre-specified for post-randomization rescue use (Section 4.15) are prohibited during the period from T0 to T72 and the prohibited medications include, but are not limited to: hydromorphone, hydrocodone, codeine, fentanyl, meperidine, tramadol, opioid combinations, and NSAIDs. Aspirin (acetylsalicylic acid) is also prohibited excluding low dose ASA for cardiac prophylaxis.

Sedatives (including benzodiazepines) used as minor tranquilizers or hypnotics are not allowed unless approved by the investigator and the Sponsor's medical monitor.

Agents for post-surgical nausea prophylaxis, including 5-HT_3 receptor blockers (e.g., ondansetron), scopolamine, dexamethasone, or haloperidol, are prohibited during or upon completion of the surgical procedure. Anti-nausea medication will only be administered during the post-operative period for any of the following: (1) subject records a score of ≥ 5 on the nausea numeric rating scale; (2) subject is actively vomiting; (3) subject requests anti-nausea medication.

Note: Midazolam 1–2 mg IV may be administered preoperatively for anxiolysis.

4.14. Concomitant Interventions and Procedures

All interventions or procedures, whether diagnostic or therapeutic, and concomitant medications used for these interventions will be recorded in the eCRF, along with time, date, and reason for the intervention or procedure. If an intervention or procedure is implemented to treat an AE, the event must be recorded as an AE, along with all relevant information.

4.15. Rescue Medication

Study investigators will review the HTX-011/HTX-002 Investigator's Brochure so as to be aware of the safety related events which may be anticipated with its use. Investigators will be versed in the latest standard of care guidelines. A fully stocked emergency crash cart, oxygen, and personnel trained in emergency resuscitation will be available at the study center at all times during the confinement period. Pain intensity assessments (NPRS) must be completed prior to each dose of rescue medication.

Rescue analgesia (from T0 to T72) will be available to subjects with inadequately controlled pain symptoms. The approved rescue regimen will be morphine 2 mg IV bolus doses by titration as needed in the post-anesthesia care area. Once effective analgesia has been reached using the morphine administered, subjects will be transitioned to oral oxycodone 10 mg every 4–6 hours, as needed for analgesia. Additional morphine 2 mg IV every 2 hours may be administered for inadequate analgesia with oxycodone. A subject who indicates a PI score that is ≤ 4 may be given acetaminophen 1000 mg for analgesia; however, a daily dose of acetaminophen must not exceed 4 grams (4000 mg).

Efforts should be made to encourage subjects to wait at least 60 minutes after the end of study drug administration prior to receiving rescue medication. Subjects do not need to have a qualifying pain score to receive rescue analgesia; however, whenever possible staff should try to ensure that rescue analgesia is administered only when the numerical pain intensity rating score prior to rescue is NPRS ≥ 4.

Between T72 (i.e., after discharge from the research unit) and T96, pain medication (if needed) will be prescribed according to the investigator's discretion and institutional standard of care.

After T96, PI scores will not be recorded: subjects may resume standard of care pain medication as advised by their surgeon. This may include, but is not limited to, ibuprofen, acetaminophen, opioids, or opiate/APAP combo medication, if still needed. The name, dose, reason, route, and time of administration of analgesics consumed after T96 will be recorded at the time of Day 10 visit to the study center.

Subjects who do not achieve adequate analgesia from the rescue regimen or experience intolerable opioid-related side effects will be discontinued from study drug efficacy *evaluations,* and they can be administered the standard of care regimen of analgesics. However, the subject must remain in the study for all planned visits (i.e., safety evaluations and for obtaining PK blood samples) until completion of participation in the study or early termination from the study for any other reason.

5. STUDY PROCEDURES

A schedule of study procedures for overall study assessments and day-of-dosing assessments is provided in Appendix A.

5.1. Order of Study Procedures

The order of the procedures to be performed at any scheduled time will be as follows (where appropriate):

1. Pain Intensity
2. PGA
3. Nausea assessment
4. Vital signs
5. 12-Lead ECG
6. Physical Examination (± 30 minutes at 72 hours)
7. Blood draw for PK and blood chemistry
8. Wound assessment (Appendix F)
9. Bupivacaine Toxicity Evaluation (Appendix G)
10. Photographs of wound site (Appendix H)

Study procedures have a ± 15 minutes window unless otherwise stated.

5.2. Demographic and Efficacy Assessments

5.2.1. Demographics

Demographic information will be collected during screening visit including age, sex, ethnicity, race, weight, height, and BMI.

5.2.2. Medical History

The investigator or designee will document each subject's medical history (including PONV risk factors; Appendix C.3) during the screening visit. Medical history will be obtained through subject interview. A review of the subject's medical records from their primary care physician will not be conducted. Medical history will be updated on Day 0 when the subject reports for surgery, and the subject will be interviewed to confirm that they continue to meet the required study inclusion and exclusion criteria.

5.2.3. Physical Examination

The investigator or designee will perform a physical examination (HEENT, cardiovascular, respiratory, gastrointestinal, neurological, dermatologic, and musculoskeletal systems) during the screening visit, at admission (Day 0) to the study site on the day of surgery, at 72 hours post dosing, and at the Day 10 visit. Body weight and height will be measured, and BMI (Appendix D) will be calculated during the screening visit; all other physical examinations will include weight only. Weight does not need to be measured at 72 hours after administration of study medication.

The neurologic examination includes a mental status exam and evaluation of cranial nerve, motor, sensory, and cerebellar function. In addition, the findings will be summarized in a neurologic assessment. The examiner will be asked to record whether the subject's overall neurologic status is better, worse, or the same.

The study investigator should perform a physical examination (the extent of which is determined by the study investigator) at any time during the study if indicated by change in a subject's condition.

5.2.4. Pain Intensity (PI)

PI will be assessed by the subject for their current pain according to an 11-point NPRS (0-10) where 0 equates to no pain and 10 equates to the worst pain imaginable. PI scores will be measured two ways: on movement and at rest.

PI scores will be assessed utilizing an 11 point (0–10) numerical pain rating scale (NPRS) at the following time points: 1, 2, 4, 6, 8, 10, 12, 14, 18, 24, 30, 36, 42, 48, 54, 60, 72, 78, 84, and 96 hours post study drug administration. Assessments performed at 78 and 84 hours will be performed by subjects on an out subject basis. PI assessments scheduled between 24:00 and 06:00 must be collected, even if subjects are asleep at the time of the assessment.

Pain scores will be measured **on movement** (sitting up from a supine position) starting at Hour 4 and measured at 6, 8, 10, 12, 14, 18, 24, 30, 36, 42, 48, 54, 60, and 72 hours.

Pain Scores will be measured **at rest** at 1, 2, 78, 84, and 96 hours after administration of study medication. The pain score will be measured after the patient has been supine for a minimum of 5 minutes and a resting pain score has been obtained.

There will be a ± 15 minute window allowed for the collection of each PI assessment unless otherwise stated.

PI will also be assessed within 5 minutes prior to administration of each dose of rescue analgesia and at time of early discontinuation (should it occur and only if the subject was discontinued prior to 96 hour).

5.2.5. Patient Global Assessment of Pain Control (PGA)

Subjects will be asked to evaluate the performance of their study medication as a pain treatment in response to the following inquiry: "Overall, please rate how well your pain has been controlled during the last 24, 48, 72, and 96 hours since you received study medication?: 0-poor, 1-fair, 2-good, 3-very good, or 4-excellent."

The PGA of pain control will be completed at 24, 48, 72, and 96 hours after study medication administration and at time of early discontinuation (should it occur and only if the subject was discontinued prior to 96 hours post-treatment).

5.2.6. Nausea Assessment

Nausea will be assessed during the study using an 11-point NRS where 0 equates to no nausea and 10 equates to the worst nausea imaginable. Assessment of nausea will be completed by subjects at the following time points: 6, 24, 48, and 72 hours within a ± 15 minute window unless otherwise stated.

5.3. Safety Assessments Description

5.3.1. Clinical Laboratory Tests

During the screening visit, on Day 0 during check-in, at 72 (± 1) hours following study drug administration, and in the event of subject early discontinuation, subjects will have blood samples collected for routine clinical laboratory testing as follows:

- hematology: complete blood count consisting of white blood cell (WBC) and red blood cell count, platelet count, hemoglobin, hematocrit, and differential counts (total neutrophils, eosinophils, basophils, lymphocytes, and monocytes)
- clinical chemistry tests: urea, glucose, creatinine, sodium, potassium, chloride, bicarbonate, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, direct bilirubin, gamma-glutamyltransferase, lactate dehydrogenase, calcium, total protein, magnesium, phosphate, albumin, and uric acid

Additional urine or blood samples will be collected and tested as follows:

- urine drug screen and alcohol breath test at the screening visit, and during admission to the study unit on Day 0. Urine drug screen will include screening of (at minimum): cocaine, marijuana, opiates/opioids, amphetamines, methamphetamines, phencyclidine (PCP), benzodiazepines, barbiturates, methadone, and oxycodone.
- serum pregnancy test at the screening visit, and a urine pregnancy test at check-in on Day 0 (female subjects of child bearing potential only).

Screening laboratory results will be used for assessing eligibility for randomization. Clinical laboratory test done on Day 0 prior to surgery will be used as baseline reference and not for assessing study randomization eligibility.

5.3.2. Vital Sign Measurements

Resting vital signs will include resting blood pressure, resting pulse, respiratory rate, oral temperature, and peripheral oxygen saturation (SpO_2). Resting tests must be obtained after resting (seated/supine) for ≥ 5 minutes.

After the administration of study medication, subjects will have vital signs (resting only) measured and recorded at the following times: 1, 2, 4, 6, 12, 18, 24, 36, 48, 60, 72, and 96 hours and at the Day 10 visit. Vital signs will have a collection window of ± 15 minutes unless otherwise stated.

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.

5.3.3. 12-Lead Electrocardiogram (ECG)

A 12-lead ECG will be performed after the subject has been supine for at least 5 minutes and will be completed for all subjects at screening, at check-in on Day (0) and at 24, 48, 72, 96 hours, and at the Day 10 visit and at time of early discontinuation. 12-lead ECG will be used to exclude subjects with a clinically significant abnormal ECG.

The findings (i.e., classification as "normal," "abnormal not clinically significant," or "abnormal clinically significant [including heart block]") will be recorded in the subject's eCRF. The ECG tracings will not be collected for Data Management.

5.3.4. Surgical Wound Healing Evaluation

The wound evaluator will be a blinded investigator or will be other medically qualified clinical site personnel (S)he and will assess the surgical site to determine if healing is normal or abnormal at 72 hours, Day 10, and Day 28 or Early Termination, and record observations (Appendix F) on the appropriate eCRF and source document. Normal is defined as expected post-surgical findings as assessed by a blinded investigator or other medically qualified clinical site personnel, including but not limited to wound dry, no dehiscence, no erythema, no drainage, mild bruising, oozing, and swelling. A normal finding will not be recorded as an AE.

Photographs of the subject's surgical site will be taken immediately after surgery, 48 and 72 hours, Day 10, and Day 28 (Appendix H). If a wound is assessed as having an abnormal and unexpected post-surgical finding, the finding will be recorded as an AE.

5.3.5. Blood Sampling for Bupivacaine/Meloxicam Pharmacokinetics Analysis

Blood samples for the pharmacokinetic analysis of bupivacaine and meloxicam will be collected at the following times: prior to surgery, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 30, 36, 48, 60, 72, 96, and 120 hours after study medication administration (± 15 minutes unless otherwise stated).

5.3.6. Assessment of Adverse Events

Physical examinations including neurologic and cardiovascular evaluations will be performed to determine if there are any changes in the patient's condition from baseline as noted in the schedule of events. Close attention should be given to conditions that may represent reported toxicities associated with bupivacaine including, but not limited to, perioral tingling, strange taste, visual and auditory disturbances, muscle twitching, seizure, acidosis, shortness of breath, bradycardia (heart rate < 50 bpm with symptoms), hypotension (BP < 90 mmHg or symptomatic decrease from baseline), low oxygen saturation (≤ 90% for ≥ 1 minute), and cardiac arrest. Adverse events and any interventions will be documented in the eCRF.

5.3.6.1. Procedures for Blood Sampling and Further Handling for PK Analysis

Blood samples for the assay of bupivacaine and meloxicam will be taken in Li-Heparin collection tubes (BD Vacutainer cat no 367886; 13 x 100 mm x 6.0 mL BD Vacutainer plus plastic plasma tube, additive lithium heparin). Tube volume should allow collection of 6 mL blood. Blood samples will be stored at approximately 4°C on ice until further processing which should start within 30 minutes after blood collection. Processing of blood to plasma concerns centrifugation at 1500 g at a temperature between 0°C and 4°C and subsequent pipetting of the plasma layer into cryovial sample tubes for a maximum of 15 minutes. Plasma will be equally divided over 2 of these tubes. Samples/tubes will be deep frozen (at approximately -20°C) prior to shipment to the central laboratory.

Blood samples and derived plasma samples must be properly labeled at every stage of the process. Refer to the Laboratory Manual for more details.

5.3.6.2. Bioanalysis of Bupivacaine and Meloxicam

The concentrations of bupivacaine and meloxicam in plasma will be determined using validated LC-MS/MS assays. Concentrations will be calculated by interpolation from a calibration curve. Quality control samples will be analyzed throughout the study. Their measured concentrations will be used to determine between-run, overall precision, and accuracy of the analyses.

5.3.6.3. Pharmacokinetic Analysis

The plasma PK parameters for bupivacaine and meloxicam will be derived by noncompartmental analysis of the plasma concentration-time profiles. The following pharmacokinetic endpoints will be defined:

- The area under the plasma concentration-time curve from time zero to time t of the last measured concentration above the limit of quantification (AUC_{last})
- The area under the plasma concentration-time curve from zero to infinity (AUC_{inf})
- The maximum plasma concentration (C_{max})
- The time to reach maximum plasma concentration (T_{max})
- The terminal elimination rate constant (λ_Z) with the respective half-life ($t_{½}$)

5.4. Assessments by Visit

5.4.1. Screening Visit

Subjects meeting the eligibility criteria listed in Sections 4.1 and 4.2 may be enrolled in the study after the nature and purpose of the protocol have been explained to them and they have voluntarily granted written informed consent to participate. All subjects will have a screening evaluation within 28 days before surgery (Day 0). After informed consent is obtained, the following procedures will be performed at the screening visit for all subjects:

- Demographics and medical history
- Measurement of resting vital signs
- 12-lead ECG
- Physical examination including height, weight, and BMI
- Clinical laboratory tests and serology
- Drug and alcohol screen
- Serum pregnancy test for women of childbearing potential
- Review of inclusion/exclusion criteria eligibility
- ASA Classification Assessment
- Assessment of PONV risk factors
- Training on pain assessment and placebo response
- Prior and concomitant medications (within 30 days of D0)

5.4.2. Day 0 Check-in and Surgery

The following assessments will be conducted on the day of admission (Day 0, prior to surgery) for all subjects:

- Review of inclusion/exclusion criteria eligibility
- Medical history update
- Measurement of resting vital signs
- 12-lead ECG
- Physical examination, including weight only
- Clinical laboratory tests
- Drug and alcohol screen
- Urine pregnancy test
- Training reminders on pain assessments and placebo response
- Blood draw for PK analysis of bupivacaine and meloxicam
- Prior and concomitant medications (within 30 days of D0)
- Neurologic Exam
- Monitoring of Serious Adverse Events
- Use of Rescue Medication

Subjects who continue to meet eligibility criteria will undergo primary unilateral open inguinal herniorrhaphy. Subjects who don't experience a clinically significant event during surgery (e.g., excessive bleeding, hemodynamic instability) that would render the subject medically unstable or

complicate their postsurgical course will be administered study medication according to the randomization scheme.

In Part D, F, and G, subjects will be administered fentanyl IV at the end of surgery and before study drug administration according to the randomization scheme (see Section 4.6). Fentanyl will be administered per the product label instructions.

5.4.3. Day 0 (Treatment) – Day 5

The following assessments will be conducted during the treatment phase on Days 0 – 5 subsequent to the administration of study medication:

- PI assessments
- PGA evaluations
- Assessment of NRS for nausea
- Measurement of resting vital signs
- 12-lead ECG
- Blood samples for PK
- Physical examination (weight not required at the 72 hour exam)
- Clinical laboratory tests (72 hour only)
- Monitoring of AEs and concomitant medications
- Use of Rescue Medication
- Assessment of wound healing (72 hour only)
- Bupivacaine Toxicity and Neurological Assessment (8, 16, 24, 48, and 72 hours only)
- Photographs of the surgical site will be taken at 48, 72, and 96 hours

One hour after administration of study medication (T0) assessments will be completed if the subject is awake and alert.

Rescue analgesia will be available to subjects with inadequately controlled pain symptoms during the treatment phase on Days 0 until T72. After T72, subjects may resume standard of care pain medication as advised by their surgeon.

5.4.4. Day 10 ± 2, and Day 28 ± 2 (Follow-Up Procedures)

The following procedures will be conducted for all subjects during the Day 10 and 28 visits.

- Physical examination, including weight only (Day 10 only)
- 12-lead ECG (Day 10 only)
- Measurement of resting vital signs (Day 10 only)
- Monitoring of AEs and concomitant medications
- Assessment of wound healing for healing, and discoloration
- Photograph of the surgical site

Clinically significant adverse events, examination, or test results will be followed until appropriate resolution can be documented.

5.4.5. Day 60 Follow-Up Phone Call (±8 days)

Subjects will receive a phone call from the study site. Subjects will be asked if they have any current pain related to the operation. Subjects will also be asked to think about the previous 24 hours and to rate their pain intensity related to the operation using the NRS, and to report any medication(s) to treat the pain (name, dose, and route). See Appendix I for details on the information to be collected. The results will be recorded in source documents.

5.4.6. Early Termination (ET) Procedures

Subjects who discontinue participation or who are discontinued prior to the Day 28 visit will be asked to complete ET procedures, including:

- PI assessment (only if the subject was discontinued prior to 96 hour)
- PGA assessment (only if the subject was discontinued prior to 96 hour)
- Assessment of nausea NRS
- Measurement of resting vital signs
- 12-lead ECG
- Physical examination, including weight only
- Clinical laboratory tests
- Assessment of AEs and review of concomitant medications
- Assessment of wound healing
- Bupivacaine Toxicity and Neurological Assessment (only if the subject was discontinued prior to 72 hour)

5.4.7. Unscheduled Visits

Unscheduled visits should be performed on an 'as-needed' basis if a subject's medical situation warrants it. For each unscheduled visit, the following will be recorded:

- Assessment of any new AEs.
- Assessment of concomitant medications.
- A blood sample draw (to be used for determination of bupivacaine levels) when the unscheduled visit(s) is precipitated by AE(s) associated with neurologic or cardiac symptoms.

5.5. Appropriateness of Assessments

The efficacy measures utilized in this study are commonly used in clinical studies performed in acute postoperative pain populations. The timing of assessments is intended to evaluate the time to onset of analgesia, duration of effect, and magnitude of benefit.

Safety measures used in this study are standard for clinical trials of investigational medications.

6. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND SERIOUS SUSPECTED ADVERSE REACTIONS

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE, SAE, or serious suspected adverse reaction as provided in this protocol. During the study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

6.1. 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 medication, whether or not considered causally associated with the use of the study medication. Any abnormal laboratory value deemed clinically significant by the investigator, regardless of causal relationship, must be reported as an AE.

Examples of an AE 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 (e.g., 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 medication or a concurrent medication (overdose per se should not be reported as an AE or SAE, unless nonserious or serious sequelae occur)

The following examples are not considered AEs:

- medical or surgical procedure (e.g., 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 are considered to be clinically normal (would be expected to occur as a long-acting local anesthetic wears off)

All AEs, whether volunteered, elicited, or noted on physical examination and regardless of causality or seriousness, will be assessed and recorded in the eCRF beginning after administration of study medication through the Day 10 study visit.

6.2. Definition of a Serious Adverse Event

An SAE is defined as any event that meets the following criteria:

- It results in death or is life-threatening (i.e., presents 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.)
- It results in persistent or substantial disability or incapacitation. (This criterion is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, diarrhea, or sprained ankle.)
- It results in hospitalization.
- It results in prolongation of an existing hospitalization.
- It is a congenital anomaly or birth defect.
- It requires medical or surgical intervention to prevent any of the above outcomes.

Medical and scientific judgment should be exercised in determining whether an AE is serious when considering important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent any of the other outcomes listed. Examples of such medical events that may also be considered serious include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline does not meet the definition of an SAE.

Social or convenience admission to a hospital or prolongation of a hospitalization for social or convenience reasons not associated with the occurrence of an AE does not meet the definition of an SAE.

6.2.1. Serious Adverse Events That Occur Before Administration of Study Medication

Before administration of study medication, only SAEs assessed by the investigator as related to study participation (e.g., related to study procedures or a change in existing therapy) will be transcribed onto the SAE reporting form and reported to the sponsor.

6.2.2. Serious Adverse Events That Occur After Study Completion

If an investigator becomes aware of an SAE or death that occurs in a subject more than 28 days of the subject's last study visit and that investigator considers the event to be related to the study medication, the investigator is obligated to report the SAE to the sponsor as outlined in Section 6.7.

6.3. Definition of a Suspected Adverse Reaction

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the adverse event was caused by the study drug. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship

between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

6.4. Definition of a Serious Suspected Adverse Reaction

A serious suspected adverse reaction is any suspected adverse reaction that is determined to be serious, based on the outcomes of a SAE described in Section 6.2; i.e. death, life-threatening, causes or prolongs inpatient hospitalization, causes a persistent of significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital abnormality/birth defect.

6.5. Recording and Evaluating Adverse Events and Serious Adverse Events

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, or other clinical information. In such cases, the diagnosis, not the individual signs or symptoms, should be documented as the AE or SAE.

6.5.1. Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study, using his or her clinical judgment. The intensity of each AE and SAE recorded in the eCRF should be assigned to one of the following categories:

- mild: an event that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities
- moderate: an event that is sufficiently discomforting to interfere with normal everyday activities
- severe: an event that prevents normal everyday activities

An AE that is assessed as severe should not be confused with an SAE. Severity is a term used to describe the intensity of a specific event, and both AEs and SAEs can be assessed as severe. The event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as serious, which is based on the subject's or event's outcome or on action criteria usually associated with events that pose a threat to a subject's life or functioning (see Section 6.2).

6.5.2. Assessment of Causality

The investigator is obligated to use his or her clinical judgment to assess the relationship between the study medication and the occurrence of each AE or SAE. For this study, adverse events that are considered by the Investigator to have a Possible, Probable, or Definite relationship to the investigational product are considered to be "related" to the investigational product; unlikely and unrelated are considered to be "not related" to the investigational product. Sponsor assessment of causality may differ from Investigator assessment in accordance with FDA guidance, Safety Reporting Requirements for INDs and BA/BE studies.

The investigator will assess the relationship to the study medication by using the following criteria:

- Definitely Related: An AE has a strong temporal relationship to the study drug. The AE is most likely explained by study drug. Dechallenge and rechallenge (if possible) are positive. The AE is consistent with a known response to the study drug. Another etiology is unlikely or significantly less likely.
- Probably Related: An AE has a strong temporal relationship to the study drug. The AE is more likely explained by study drug than by another cause. Dechallenge (if performed) is positive.
- Possibly Related: An AE has a reasonable temporal relationship to study drug. The AE could have been due to another equally likely cause. Dechallenge is positive.
- Not Related: The subject did not receive the study drug OR the AE has no temporal relationship to study drug OR the AE has a much more likely alternate etiology OR the AE is due to an underlying or concurrent illness or effect of another drug.

Even in situations in which minimal information is available for the initial SAE report, it is important that the investigator always make an assessment of causality for every event before transmitting the SAE reporting form and completing the AE eCRF page(s). 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 reporting form and AE eCRF page(s) accordingly.

6.5.3. Assessment of Outcome

All SAEs must be followed until they are resolved, the condition stabilizes, the events are otherwise explained, or the subject is lost to follow-up. The investigator will assess the outcome of the event by using the following terms:

- 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

6.5.4. Assessment of Expectedness

For the purposes of IND safety reporting, adverse events and suspected adverse events should be assessed as being expected or unexpected. An AE or suspected adverse reaction is considered

unexpected if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

6.6. Follow-up of Adverse Events and Serious Adverse Events

Nonserious AEs will be followed after the last scheduled study visit until an appropriate resolution can be documented.

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.

SAEs will be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost to follow-up. 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 on the originally completed SAE reporting form and entered into the eCRF pages, with all changes signed and dated by the investigator. The updated SAE reporting form should be resubmitted to the sponsor within the time frames outlined in Section 6.7.

6.7. Prompt Reporting of Serious Adverse Events to the Sponsor

Once the investigator determines that an event meets the protocol definition of an SAE, he or she must notify the sponsor within 24 hours.

ANY SAE OR ANY OUTCOME OF DEATH DUE TO ANY CAUSE WHICH OCCURS DURING THE COURSE OF THIS STUDY, REGARDLESS OF RELATIONSHIP TO STUDY MEDICATION, MUST BE REPORTED TO THE SPONSOR IMMEDIATELY (within 24 hours).

COMPLETE THE SAE DETAILS REPORTING FORM AND FORWARD BY E-MAIL TO THE FOLLOWING SPONSOR CONTACT:

Medical Monitor

Name:	Gilad Gordon, MD
Address:	4242 Campus Point Court, Suite 200 San Diego, CA 92121 USA
Telephone Number:	1-303-517-6212
Fax Number:	1-858-251-4401
E-Mail Address:	htx011safety@herontx.com

In the initial e-mail, 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.

E-mail transmission is the preferred method to transmit SAE information. In rare circumstances and in the absence of e-mail 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 reporting form and eCRF pages within the time frames outlined.

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

6.8. Regulatory Reporting Requirements

The investigator must promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 6.7, "Prompt Reporting of Serious Adverse Events to the Sponsor." 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 reaction 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 medication, 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 IRB or IEC.

6.9. Precautions

Any subject who becomes pregnant during the study must be discontinued immediately but should be followed through delivery or termination of the pregnancy. A subject should also notify the investigator if she becomes pregnant within 28 days after receiving study medication.

The sponsor must be notified of all pregnancies reported to the investigator (see Section 6.7 for contact information).

7. STATISTICAL METHODOLOGY

7.1. Determination of Sample Size

The sample size of up to approximately 453 subjects (108 subjects for Part A, 90 subjects for Part B, 135 subjects for Part C, 45 for Part D, 20 for Part E, 20 for Part F, and 35 for Part G) for this study was selected empirically without a formal statistical assumption.

7.2. Study Endpoints

7.2.1. Efficacy Endpoints

The primary efficacy endpoint will be the SPI_{0-24}.

Secondary efficacy variables will include the following:

- SPI at various other time points (SPI_{0-6}, SPI_{0-12}, SPI_{12-24}, SPI_{24-48}, SPI_{0-48}, SPI_{48-72}, SPI_{0-72}, SPI_{72-96}, and SPI_{0-96}).
- The Patient global assessment (PGA) of pain control at 24, 48, 72, and 96 hours post-treatment.
- Time to administration of first dose of rescue analgesia.
- Total and average daily rescue consumption over 24, 48, 72, and 96 hours post-treatment.
- Mean nausea assessment scores at 6, 24, 48, and 72 hours post-treatment.
- The percentage of subjects who remain pain free (Numerical Pain Rating Scale ≤ 1) at 72 hours and at 96 hours after study drug administration.

7.2.2. Pharmacokinetic Endpoints

The plasma PK parameters for bupivacaine and meloxicam will be derived by non-compartmental analysis of the plasma concentration-time profiles. The following pharmacokinetic endpoints have been defined:

- The area under the plasma concentration-time curve from time zero to time t of the last measured concentration above the limit of quantification (AUC_{last})
- The area under the plasma concentration-time curve from zero to infinity (AUC_{inf})
- The maximum plasma concentration (C_{max})
- The time to reach maximum plasma concentration (T_{max})
- The terminal elimination rate constant (λ_Z) with the respective half-life ($t_{½}$)

7.2.3. Safety Endpoints

The safety endpoints will include the following:

- wound assessment findings
- vital signs
- clinical laboratory tests, including routine blood chemistry and hematology

- ECG findings
- AEs and SAEs

7.3. General Considerations for Statistical Analysis

7.3.1. Analysis Datasets

Intent-to-Treat (ITT) Analysis Set: The ITT set will include all subjects who are randomized to receive study medication.

Efficacy Set: The efficacy analysis set will include all subjects who are randomized to receive study medication and have recorded at least one post dosing PI scores. This analysis set is noted as the modified Intend-to-Treat (mITT) set.

Safety Set: The safety set will include all treated subjects and will be used for safety and tolerability assessments.

7.3.2. Test Hypothesis and *P* Value Justification

The null hypothesis is that there is no difference between each comparison (pairwise or pooled group comparison). The alternative hypothesis is there is a difference for the comparison.

Each pairwise or pooled group comparison will be evaluated via 2-sided 2-sample t-test at the 0.05 level of significance. Nominal *p* value will be reported without adjustment for multiplicity.

7.3.3. Procedures for Handling Missing Data

Unless indicated otherwise (see Section 7.3.3.1 and 7.3.3.2), no imputation will be done for missing data.

7.3.3.1. PI Score Before and After Analgesic Rescue Medication

All subjects are expected to assess their postoperative pain intensity according to the pain intensity schedule; those PI assessments are referenced as the scheduled PIs. Subjects who require rescue analgesia are expected to report their pain intensity immediately before taking the rescue medication; this PI is referenced as the pre-rescue PI. The duration of analgesic effect will be determined for the rescue medication (e.g., the analgesic window for one oxycodone 10 mg tablet is 6 hours); this analgesic duration is referenced as the analgesic window of this rescue medication. When the assessment of a scheduled PI is done after the rescue medication and the time is within the analgesic window (inclusive) of the rescue medication, the scheduled PI score will be replaced by the pre-rescue PI score for the purpose of efficacy analysis. This method is referenced as the Windowed Last Observation Carried Forward (WLOCF). The original scheduled PI scores will be displayed on data listing along with the "imputed" PI score.

7.3.3.2. Other Missing PI Score(s)

After the scheduled PI scores are appropriately replaced by the pre-rescue PI score for all subjects who had rescue medication based on the WLOCF method, if there are additional time

points where the PI scores are missing, the standard LOCF method will be used to impute the missing PI score. All imputed PI scores will be clearly marked on data listings.

Additional missing data imputation methods may be used to assess the robustness of the efficacy data. The details will be discussed in the statistical analysis plan for the study.

7.3.4. Derived Variables

Prior to data base lock, a complete statistical analysis plan will be developed which will describe in detail the calculation of all efficacy variables.

7.3.4.1. Study Population Summaries

Population summaries will be provided for the safety analysis set included in this study.

7.3.5. Disposition

The summary tables will provide frequency counts for subject disposition (all treated subjects, subjects who completed the study, subjects who discontinued from the study, and reason for discontinuation) by treatment group and study overall.

Disposition in terms of number of subjects excluded from each analysis sets (mITT, safety) will also be provided by treatment groups and study overall.

7.3.6. Demographics

The demographic summary will include descriptive statistics for age, sex, race, weight, height, and BMI for the overall and by treatment group.

7.3.7. Protocol Violations

All protocol violations and deviations will be identified. Tabulation may be provided if data is warranted.

7.3.8. Treatment Compliance

Since study medication is administered intra-operatively, no formal summary of treatment compliance will be produced.

7.3.9. Prior and Concomitant Medications

All prior and concomitant medications will be tabulated for the overall study population. Prior and concomitant medications will be coded to the therapeutic drug classes and generic drug names using the World Health Organization (WHO) drug classifications version 1Q2013 or higher.

7.4. Efficacy Analysis

7.4.1. SPI and PI Analyses

The analyses of the primary and all secondary endpoints will be described in the statistical analysis plan.

7.4.2. Time to First Dose of Rescue Medication

A description of the analysis of time to first dose of rescue medication will be presented in the Statistical Analysis Plan.

7.4.3. Patient Global Assessment (PGA) of Pain Control

Number and percent of subjects in each global pain control category (0-poor, 1-fair, 2-good, 3-very good, or 4-excellent) will be tabulated by treatment group. The difference between the groups in global pain control will be evaluated based on proportion of subjects rated their pain control as good, very good, or excellent using Fisher's exact test.

7.4.4. Proportion of Subjects Requiring Rescue Medication

The analysis will evaluate the relative risk (each HTX-011 formulation vs. saline, each HTX-011 formulation vs. Marcaine, HTX-011-56 vs. HTX-002, and HTX-009 vs. saline) to require rescue medications during the treatment phase of the study. Proportion of subjects that used rescue medications at least once will be tabulated by treatment group; treatment group differences will be assessed as described in the Statistical Analysis Plan.

7.4.5. Nausea Assessments

The mean nausea assessment scores at 6, 24, 48, and 72 hours will be calculated, and the analysis of the data will be described in the Statistical Analysis Plan.

7.4.6. Opioid Consumption and Symptoms Associated with Opioid Use

Average daily opioid use will be calculated for each 24 hour period post study medication administration. Subjects who did not use any opioid during a period will be assigned to "0." Average daily opioid data will be tabulated by treatment group with descriptive statistics.

7.4.7. Subgroup Analyses for Efficacy

No subgroup analysis for efficacy endpoints is planned.

7.5. Safety and Tolerability Evaluations

7.5.1. Adverse Events

The Medical Dictionary for Regulatory Activities (Version 16 or higher) will be used to classify all AEs with respect to system organ class and preferred term.

Three types of summaries will be produced for the AE summary:

1. an overall summary of AEs: number of subjects with at least one event and number of events for all AEs and SAEs

2. a summary table of AEs and SAEs by system organ class and preferred term and severity

3. a summary table of AEs and SAEs by preferred terms in descending order of total incidence

AEs will be tabulated by treatment group. AEs that lead to premature discontinuation from the study or to death will be listed separately via data listings.

7.5.2. Clinical Laboratory Tests

Laboratory values will be collected at screening, Day 0 during check-in, 72 hours, and ET. Observed values at each time point and change from baseline (Day 0) at the end of study will be summarized for the by treatment group without formal statistical testing.

7.5.3. Vital Sign Measurements

Resting vital sign values at each time point collected will be summarized by treatment without formal statistical testing.

7.5.4. Electrocardiograms

The number and proportion of subjects with abnormal ECG findings at each time point collected will be tabulated by treatment group. A data listing will be provided for subjects with changes from normal at baseline to abnormal and clinically significant after baseline by treatment.

7.5.5. Subgroup Analyses for Safety Endpoints

No subgroup analysis is planned for safety endpoints.

7.6. Pharmacokinetic Analysis

The PK parameters for bupivacaine and/or meloxicam will be calculated using non-compartmental analysis and summarized for formulations of HTX-011, HTX-002, HTX-009, and for Marcaine.

7.7. Interim Evaluation

An evaluation of the data in Part A will be used to determine the optimal technique of administration of study drug for Part B and Part C. An evaluation of the data in Part B is also planned to determine which formulation/dose to be used for Part C.

8. STUDY ADMINISTRATION

8.1. Regulatory and Ethical Considerations

8.1.1. 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.

8.1.2. Ethical Conduct of the Study and Ethics Approval

This study will be conducted according to GCP; US 21 Code of Federal Regulations (CFR) Part 50 (Protection of Human Subjects); US 21 CFR Part 56 (IRBs); US 21 CFR Part 54 (Financial Disclosure); International Conference on Harmonisation (ICH) Guidance for Industry, E6 GCP: Consolidated Guidance; the Nuremberg Code; and, where applicable the principles of the Declaration of Helsinki (Recommendations guiding Medical Doctors in Biomedical Research Involving Human Subjects), and with the NH&MRC National Statement on Ethical Conduct in Human Research (2007).

8.1.2.1. Ethics Committees

The investigator (or sponsor, where applicable) is responsible for ensuring that this protocol, the site's informed consent form, and any other information that will be presented to potential subjects (e.g., advertisements or information that supports or supplements the informed consent form) are reviewed and approved by the appropriate IRB or IEC. The investigator agrees to allow the IRB or IEC direct access to all relevant documents. The IRB or IEC must be constituted in accordance with all applicable regulatory requirements. The sponsor will provide the investigator with relevant documents or data needed for IRB or IEC review and approval of the study. Before investigational products can be shipped to the site, the sponsor must receive copies of the IRB or IEC approval, the approved informed consent form, and any other information that the IRB or IEC has approved for presentation to potential subjects.

If the protocol, the informed consent form, or any other information that the IRB or IEC has approved for presentation to potential subjects is amended during the study, the investigator is responsible for ensuring that the IRB or IEC reviews and approves, where applicable, these amended documents. The investigator must follow all applicable regulatory requirements pertaining to the use of an amended informed consent form, including obtaining IRB or IEC approval of the amended form, before new subjects consent to take part in the study using the new version of the form. The investigator must promptly forward to the sponsor copies of the IRB or IEC approval of the amended informed consent form or other information and the approved amended informed consent form or other information. IRB or IEC approval of the consent forms must be obtained in addition to the approval given for the clinical study. Regulatory review and approval may be required in some countries before IRB or IEC approval can be sought.

8.1.2.2. General Considerations

The ethical standards defined within GCP are intended to ensure the following:

- Human subjects are provided with an adequate understanding of the possible risks of their participation in the study, and they have a free choice to participate or not.
- The study is conducted with diligence and in conformance with the protocol in such a way as to ensure the integrity of the findings.
- The potential benefits of the research justify the risks.

Heron Therapeutics, Inc. is the sponsor of study HTX-011-C2015-202. The sponsor (or its designee) is responsible for all of the following:

- selecting qualified investigators
- providing investigators with the information they need to conduct the investigation properly
- ensuring proper monitoring of the investigation
- ensuring that appropriate regulatory agencies and all participating investigators are properly informed of significant new information regarding AEs or risks associated with HTX-011, HTX-002, or HTX-009.

8.1.3. Informed Consent

The sponsor (or its designee) will provide investigators with a multicenter informed consent form 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 informed consent form must be accepted by the sponsor and approved by the IRB or IEC. Investigators must provide the sponsor with an unsigned copy of the final informed consent form before and after it is approved by the IRB or IEC. If any new information becomes available that might affect subjects' willingness to participate in the study, or if any amendments to the protocol require changes to the informed consent form, the sponsor will provide investigators with a revised informed consent form. The IRB or IEC must provide written approval of any revisions to the informed consent form in advance of its use.

Investigators must provide subjects with all the information necessary to make an informed decision about their participation in the study, including the nature and intended purpose of the study, possible benefits, and possible risks.

All information in the informed consent form should be provided in a language (whether written or spoken) that is as nontechnical as practical and that is understandable to the subjects.

Before written 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 (or his or her legally authorized representative).

Before a subject undergoes procedures specific to the protocol, the informed consent form must be signed and dated by the subject (or his or her legally authorized representative) and any other signatories as required by the IRB or IEC.

If a subject (or legally authorized representative) cannot read, a short form approved by the IRB or IEC may be used. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign the copy of the summary in accordance with 21 CFR 50.27 (b2).

After all required signatures have been obtained, a copy of the informed consent form should be provided to the subject, and the original must be kept on file at the site and made available for review by the sponsor. Documentation of the informed consent discussion must be noted in the subject's case history.

8.1.4. Investigator Reporting Requirements

The investigator is responsible for completing and maintaining adequate and accurate eCRFs and source documentation. Source documentation constitutes original records (first point of entry, either hard copy or electronic), which may include progress notes, medication administration records, operation reports, laboratory reports, discharge summaries, and so on.

8.2. Study Monitoring

The sponsor (or its designee) is responsible for ensuring the proper conduct of the study with regard to subject protection, ethics, protocol adherence, site procedures, and integrity of the data. At regular intervals during the study, the sponsor's study monitors will contact the study site via visits to the site, telephone calls, and letters in order to review study progress and eCRF completion and to address any concerns or questions regarding the study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: subjects' informed consent documents, subject recruitment procedures, subjects' compliance with the study procedures, source-data verification, drug accountability, use of concomitant therapy by subjects, AE and SAE documentation and reporting, and quality of data.

8.3. Quality Assurance

The sponsor, a regulatory authority, or an IRB representative may visit the study site at any time during the study or after completion of the study to perform audits or inspections. The purpose of a sponsor audit or regulatory inspection is to examine systematically and independently all study related activities and documents to determine whether these activities were conducted according to the protocol, GCP, ICH guidelines, and any other applicable regulatory requirements. Investigators should contact the sponsor immediately if contacted by a regulatory agency about an inspection at their site.

8.4. Study and Site Closure

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 the study site should be

closed, this action may be taken after appropriate consultation between the sponsor and investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study
- submission of knowingly false information from the research facility to the sponsor, study monitor, or regulatory agencies
- failure of the investigator to comply with GCP (e.g., ICH guidelines, regulatory agency guidelines)
- insufficient adherence to protocol requirements or an unacceptably high rate of missing, erroneous, or improperly collected data
- evidence from the blinded data of sufficient technical problems with the study that one could believe with a high degree of certainty that subjects are being exposed to the investigational drug without a realistic expectation of evaluable data
- a decision on the part of the sponsor to suspend or discontinue testing evaluation or development of the product
- failure of the investigator to enroll subjects into the study at an acceptable rate

8.5. Records Retention

8.5.1. Health Insurance Portability and Accountability Act of 1996

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subjects' health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR Parts 160 and 164 (the Health Insurance Portability and Accountability Act of 1996 privacy regulation). 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 and in a form satisfactory to the sponsor.

8.5.2. Financial Disclosure

Financial disclosure is required for this study.

8.5.3. Access to Original Records

Regulatory authorities expect that monitors, auditors, and representatives of national and international government regulatory agency bodies have access to original source documentation (see examples in Section 8.1.4) to ensure data integrity. "Original" in this context is defined as the first documentation of an observation and does not differentiate between hard copy and electronic records.

8.5.4. Archiving of Study-Related Documents

Records related to this clinical study must be retained either 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. The sponsor will notify the investigator as to when these documents no longer need to be retained for this use.

8.6. Provision of Study Results and Information to Investigators

When a clinical study report is completed, the sponsor will provide the major findings of the study to the investigators.

In addition, details of the study treatment assignment will be provided to the investigators to enable them to review the data to determine the outcome of the study for their subjects.

The sponsor may list and summarize the results from coded samples by subject number in the clinical study report. In this event, the investigator and study staff would have access to the research results and would be able to link the results to a particular subject. The investigator and study staff would be directed to hold this information confidentially.

8.7. Information Disclosure and Inventions

8.7.1. Ownership

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.

All rights, title, and interests in any inventions, know how, or other intellectual or industrial property rights that are conceived or reduced to practice by site staff during the course of or as a result of the study are the sole property of Heron Therapeutics, Inc. and are hereby assigned to Heron Therapeutics, Inc.

If a written contract is executed between Heron Therapeutics, Inc. and the study site for the conduct of the study and that contract includes ownership provisions inconsistent with this statement, that contract's ownership provisions shall apply rather than this statement.

8.7.2. 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 other 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. 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 IEC or IRB 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 8.7.3. 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.

8.7.3. Publication

For multicenter studies, the first publication or disclosure of study results shall be a complete, joint, multicenter publication or disclosure coordinated by Heron Therapeutics, Inc. Thereafter, any secondary publications will reference the original publication(s). If no multicenter publication is submitted for publication within 18 months of study database hard lock, then the site shall be free to disclose its own results, subject to sponsor rights under Section 8.7.1.

Before submitting material for publication, presentation, or use for instructional purposes, or before otherwise disclosing the study results generated by the site (collectively, a "publication"), the investigator shall provide Heron Therapeutics, Inc. with a copy of the proposed publication and allow Heron Therapeutics, Inc. a period of at least 90 days to review the proposed publication. Proposed publications shall not include either Heron Therapeutics, Inc. confidential information (other than the study results) or the personal data (such as name or initials) of any subject.

At Heron Therapeutics, Inc.'s request, the submission or other disclosure of a proposed publication will be delayed a further 90 days to allow Heron Therapeutics, Inc. to seek patent or similar protection of any inventions, know-how, or other intellectual or industrial property rights disclosed in the proposed publication.

If a written contract is executed for the conduct of the study and that contract includes publication provisions inconsistent with this statement, that contract's publication provisions shall apply rather than this statement.

8.7.4. Data Management

The investigator (or designee) will enter subject data by using the eCRF defined by Heron Therapeutics, Inc. or its designee. Clinical data management will be performed in accordance with applicable Heron Therapeutics, Inc. standards and data cleaning procedures. Database freeze will occur when data management quality-control procedures are completed.

In addition, validated laboratory data will be transmitted electronically from the clinical laboratory to Heron Therapeutics, Inc. or its designee.

The investigator or designee must record all required data using the previously specified data collection method defined by Heron Therapeutics, Inc. or its designee. An explanation must be documented for any critical data points. The investigator must sign and date a declaration in the eCRF attesting that he or she is responsible for the quality of all data recorded and that the data represent a complete and accurate record of each subject's participation in the study.

8.7.5. Data Security

Access to the data will be strictly controlled.

8.8. Subject Tracking

Drug accountability logs, a subject identification log (to be retained by the investigator only), and a subject enrollment log will be used to track subject participation in the study.

9. REFERENCES

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Moote, C. (1992). "Efficacy of nonsteroidal anti-inflammatory drugs in the management of postoperative pain." Drugs 44 Suppl 5: 14-29; discussion 29-30.

Ortiz, Mario I., Gilberto Castañeda-Hernández, Jeannett A. Izquierdo-Vega and Héctor A. Ponce-Monter (2011). "Peripheral synergistic interaction between lidocaine and lumiracoxib on the 1% formalin test in rats." The Open Pain Journal 4: 8-14.

Rawal, N. (2001). "Analgesia for day-case surgery." Br J Anaesth 87(1): 73-87.

Renck, H. (1994). "Wound infiltration with local anaesthetics." Acta Anaesthesiol Scand 38(1): 2-6.

10. APPENDICES

Appendix A: OVERVIEW OF STUDY SCHEDULE

Table 1: SCREENING

Procedure	Day -28 to Day -1
	Screening
Informed Consent	X
Eligibility Assessment	X
Demographics and Medical History	X
Assessment of PONV Risk Factors	X
ASA Classification Assessment	X
Physical Examination	X
Pregnancy Test (female subjects of child bearing potential only)	X[serum]
Urine Drug Screen	X
Alcohol Breath Test	X
Clinical Laboratory Tests [a]	X
Vital Signs [b]	X
BMI Determination	X
12-lead ECG	X
Pain Training	X
Prior and Concomitant Medication [c]	X
Serious Adverse Event Monitoring [d]	X

[a] Laboratory tests will include hematology and chemistry screenings in all subjects. Results will determine subject eligibility for the study.
[b] Resting vital signs (VS) will be collected at screening. Resting VS include: resting blood pressure, resting pulse, respiratory rate, oral temperature and SpO2. Resting tests must be obtained after resting (seated/reclined) for ≥ 5 minutes.
[c] ConMeds taken within 30 days before dosing will be recorded.
[d] SAEs will be reported if considered related to study participation.

Appendix A: OVERVIEW OF STUDY SCHEDULE

Table 2: DAY 0 PRIOR TO SURGERY AND SURGERY

	Day 0	
	Prior to Surgery	**Surgery**
Eligibility Assessment	X	
Demographics and Medical History	X	
Physical Examination [c]	X	
Pregnancy Test (female subjects of child bearing potential only)	X[urine]	
Urine Drug Screen	X	
Alcohol Breath Test	X	
Clinical Laboratory Tests [a]	X [d]	
Vital Signs [b]	X	
12-lead ECG	X	
Pain Training	X	
Blood Draw for PK	X [d]	
Neurologic Exam	X	
Surgery Procedure		X
Study Drug Administration		X
Prior and Concomitant Medication [f]	X	
Serious Adverse Event Monitoring[g]	X	X

[a] Laboratory tests will include hematology and chemistry and will be used as baseline reference and not for determining subject eligibility.

[b] Resting vital signs (VS) will be collected at screening and check-in only, all other assessments will include resting VS only. Resting VS include: resting blood pressure, resting pulse, respiratory rate, oral temperature and SpO2. Resting tests must be obtained after resting (seated/reclined) for ≥ 5 minutes. VS will have a ± 15 minute window.

[c] Physical examination will include weight only but not height or BMI.

[d] Baseline laboratory samples can be collected prior to surgery.

[f] ConMeds taken within 30 days before dosing will be recorded

[g] SAEs that occur before study drug administration will be reported only if considered related to study participation. After study drug administration, all SAEs that occur through Day 28 post-treatment must be reported.

Appendix A: OVERVIEW OF STUDY SCHEDULE

Table 3: POST STUDY MEDICATION ADMINISTRATION

	Day 0 to 5																						D10 (±2d)	D28 (±2d)	D60 (±8d)
	Post Study Drug Administration Time Points (hrs)																								
	0.5	1[f]	1.5	2	3	4	6	8, 10, 12	14	18	24	30	36	42	48[g]	54[g]	60[g]	72[g]	78[g]	84[g]	96[g]	120			
Confinement	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Physical Examination																		X[g]					X[c]		
Clinical Laboratory Tests [a]																		X							
Vital Signs [b]		X		X		X	X	X (12hr only)		X	X		X		X		X	X			X		X		
12-lead ECG											X				X			X			X		X		
Pain Intensity (PI)		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
PGA of Pain Control											X				X			X			X				
Use of Rescue Medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[e]	X[e]	
PK Blood Draws (±15 min)	X	X	X	X	X	X	X	X		X	X	X	X		X		X	X			X	X[g]			
Numerical Rating Scale for Nausea							X				X				X			X							
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Assessment of Wound Healing																		X					X	X	
Photos	X														X			X			X		X	X	
Bupivacaine Toxicity and Neurological Assessment											X				X			X							
AE Monitoring [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Phone Call [h]																									X

Abbreviations: AE, adverse event; D, day; ECG, electrocardiogram; hr(s), hour(s); min, minutes; PK, pharmacokinetics.

[a] Laboratory tests will include hematology and chemistry.

[b] Resting VS only. Resting VS include: resting blood pressure, resting pulse, respiratory rate, oral temperature and SpO2. Resting tests must be obtained after resting (seated/supine) for ≥ 5 minutes.
[c] Physical examination will include weight only, but not height or BMI. Weight not required at 72 hour exam.
[d] AEs will be monitored after administration of study medication through the Day 10 study visit. SAEs will be monitored through Day 28.
[e] Subjects may resume standard of care pain medication as advised by their surgeon after the 72 hour study visit.
[f] 1 hour assessments to be completed if subject is awake and alert.
[g] ± 30 minutes for 72hr Physical Exam, ± 60 minutes for the 48, 54, 60 and 72 hr assessments, and ± 4 hours for the 96 and 120 hr assessments
[h] Subjects will receive a phone call from the study site on Day 60 (±8 days). Subjects will be asked if they have any current pain related to the operation. Subjects will also be asked to think about the previous 24 hours and to rate their pain intensity related to the operation using the NRS and to report any medication(s) taken to treat the pain (name, dose, and route).

Appendix B: INVESTIGATOR OBLIGATIONS

As an investigator, you are responsible for ensuring that the study is conducted according to the protocol, the signed Statement of Investigator, and all applicable regulations.

Debarment

Individuals ineligible to conduct or be involved with clinical studies, including those ineligible as a result of debarment under the Generic Drug Enforcement Act of 1992, will not be allowed to conduct or work on studies sponsored by Heron Therapeutics, Inc. You are required to disclose immediately to the sponsor, in writing, if any person involved in the conduct of the study is debarred pursuant to a hearing by FDA under this antifraud law or if any proceeding for debarment is pending or is (to the best of your knowledge) threatened.

Institutional Review Board

You are required to obtain initial and continuing review and approval by an IRB or IEC that complies with the requirements specified in 21 CFR Part 56. Before initiating the trial, you must have written approval from the IRB or IEC for the protocol, informed consent form, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to the subjects. You must submit the Investigator's Brochure and any updates to the IRB or IEC for review. The IRB or IEC must also provide written approval of any amendments to the protocol that affect the conduct of the study and any changes to the informed consent form in advance of use. If the duration of the study is longer than 1 year, reapproval by the IRB or IEC must be obtained on a yearly basis (or at more frequent intervals if required by the IRB or IEC). All IRB or IEC approvals must be forwarded to the sponsor.

You must provide reports of all SAEs from your site to the IRB or IEC. You are also responsible for providing the IRB or IEC with Safety Reports of any SAEs from any other study conducted with the study medication. The latter will be provided to you by the sponsor.

Confidentiality and Safety of Subjects

You are responsible for protecting the rights, safety, and welfare of subjects under your care and for the control of the drug(s) under investigation.

You are responsible for keeping a record of all screened subjects, including full names and last known addresses. All subjects will be identified on the eCRFs by initials and subject numbers. Demographic information including date of birth, sex, and race will also be recorded on the eCRFs. Confidentiality of subject data will be maintained in accordance with local laws.

In addition to your responsibilities for reporting AEs identified during the course of a subject's participation in the study, you must also report any SAEs that occur within 28 days after the last dose of study medication (regardless of relationship to study medication) and

any serious adverse drug reactions (SAEs for which you consider that there is a reasonable possibility that the study medication caused the response) that you become aware of at any time (even if the event occurs more than 28 days after the subject's last exposure to study medication). This obligation is in addition to any protocol-specified requirement for reporting AEs occurring after the last dose of study medication. Please refer to Sections 6.7 and 6.8 of this protocol for contact information and SAE reporting requirements.

Study-Related Records

You are required to maintain complete and accurate study documentation in compliance with current GCP standards and all applicable federal, state, and local laws, rules, and regulations related to the conduct of a clinical study.

You are required to make all study documentation promptly available for inspection, review, or audit at your study site upon request by the sponsor, its representatives, or any appropriate regulatory agencies.

Accountability of the Investigational Product

You or your designee (i.e., the pharmacist) is responsible for accountability of the investigational product at the site. You or your designee must maintain records of the product's delivery to the site, inventory at the site, use by each subject, and the return to the sponsor or alternative disposition of any unused product. These records must include dates; quantities; batch, serial, or lot numbers; and expiration dates (if applicable).

You should ensure that the investigational product is used only in accordance with the protocol.

Appendix C: STUDY-SPECIFIC INFORMATION

Appendix C.1: Pain Intensity Assessments

PAIN INTENSITY- NUMERICAL PAIN RATING SCALE (NPRS)

On a scale of 0–10, please rate your pain by marking an 'X" in the appropriate box that best describes your pain NOW.

☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐9	☐10
No Pain										*Worst Pain Imaginable*

Appendix C.2.: Patient Global Assessment (PGA) of Pain Control

The following question will be answered by the subject 24, 48, 72, and 96 hours after study treatment initiation:

"Overall, please rate how well your pain has been controlled during the last 24 (48, 72, 96) hours since you received study medication?"

Response to each question will be: (Check (√) one box)

☐ Poor (0)

☐ Fair (1)

☐ Good (2)

☐ Very Good (3)

☐ Excellent (4)

Appendix C.3: Risk Factors for Postoperative Nausea and Vomiting

- Past history of postoperative nausea and vomiting and/or motion sickness
- Habitual nonsmoking status
- Female sex
- Expected to receive opioid analgesia postoperatively.

Appendix C.4: Nausea Numerical Rating Scale

At 6, 24, 48, and 72 hours after the administration of study medication, subjects will answer the following question:

On a scale of 0–10, please rate your nausea by marking an 'X" in the appropriate box that best describes your nausea level NOW.

☐0	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐9	☐10
No Nausea										*Worst Nausea Imaginable*

Appendix D: BMI CALCULATION

Body Mass Index Calculations

Body Mass Index = Weight in kilograms / (height in meters)^2

Meters = inches × 0.0254

Kilograms = pounds × 0.45

Example:

For a man who weighs 165 pounds and is 71 inches tall:

165 lbs. × 0.45 = 74.25 kg

71 in. × 0.0254 = 1.8 m

74.25 / (1.8 × 1.8) = 22.92 kg/m^2

Appendix E: AMERICAN SOCIETY OF ANESTHESIOLOGISTS PHYSICAL STATUS CLASSIFICATION SYSTEM

I Normal healthy subject

II Subject with mild systemic disease; no functional limitation – e.g. smoker with well-controlled hypertension

III Subject with severe systemic disease; definite functional impairment – e.g. diabetes and angina with relatively stable disease, but requiring therapy

IV Subject with severe systemic disease that is a constant threat to life – e.g. diabetes and angina and congestive heart failure; subjects with dyspnea on mild exertion and chest pain

V Unstable moribund subject who is not expected to survive 24 hours with or without operation

VI Brain dead subject whose organs are removed for donation to another

E Emergency operation of any type, which is added to any of the above six categories, an in ASA II E

Appendix F: WOUND SITE EVALUATION

WOUND SITE EVALUATION

Timepoint: ☐ 72 Hour ☐ Day 10 ☐ Day 28

NOT DONE ☐

	Normal (Expected Post-Surgical Findings)	Abnormal	Not Done	Please Describe Abnormalities
Wound Site	☐	☐	☐	
Other, *specify*: _____	☐	☐	☐	

- Normal expected post-surgical findings is defined as but is not limited to: wound dry, no dehiscence, no erythema, no drainage, and swelling consistent with expected post-surgery findings.
- Abnormal findings should be recorded as adverse events.

Investigator's Signature Date

Appendix G: BUPIVACAINE TOXICITY EVALUATION

Time point: ☐ 24 Hour ☐ 48 Hour ☐ 72 Hour

NOT DONE ☐

	Absent	Present	Describe Abnormalities and note if clinically significant
Perioral tingling	☐	☐	
Strange taste	☐	☐	
Muscle twitching	☐	☐	
Ringing in ears	☐	☐	
Seizure	☐	☐	
Bradycardia	☐	☐	
Cardiac Arrest	☐	☐	

Abnormal findings should be recorded as adverse events if determined to be clinically significant.

Investigator's Signature Date

Appendix H: INSTRUCTIONS FOR TAKING PHOTOGRAPHS OF SURGICAL WOUND AFTER HERNIORRHAPHY

Materials

- Camera (specify type and model). Identify camera settings.
- ID tag: Complete for **Protocol#, Subject #, Study Hour or Day, Date, Time, and area photographed**
- Adhesive Backed Decal (on a roll) ruler

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1. Ensure the batteries in the camera are charged. If low, replace the batteries prior to using the camera.
2. Expose the area to be photographed.
3. Remove any dressing and place the completed ID tag and adhesive backed ruler decal adjacent to the area to be photographed, taking care not to obscure any area of the wound.
4. Ensure that **Protocol #**, **Subject #, Study Hour or Day, Date, Time, and area being photographed** are documented for reference purposes in the photograph.
5. At each photographic time point (immediately after surgery, 48, 72, and 96 hours, and Days 10 and 28) take 3 photos from different angles clearly showing the surgical incision in the hope that there will be at least one taken from each view that best represents the wound area.

Appendix I: DAY 60 FOLLOW-UP PHONE CALL

Subjects will receive a follow-up phone call from the site on Day 60 (± 8 days). Sites will attempt to contact subjects at least twice to complete this assessment; attempts must be recorded, including the phone number called, in source documents.

During the Day 60 call, subjects will be asked the following questions. The results will be recorded in source documents.

1. Are you having any pain related to the operation?

   Yes/No

2. Thinking about the past 24 hours, on a scale of 0 – 10 with 0 being no pain and 10 being the worst possible pain, what is your pain related to the operation?

   0 – 10

3. Thinking about the past 24 hours, have you taken any medication(s) to treat pain related to the operation?

   Yes/No

4. If you answered Yes to Question 3, what medications (name, dose, and route) have you taken?

   _____

   _____

   _____

   Enter "N/A" if not applicable

Signature Manifest

Document Number: PRT-0032 **Revision:** 06

Title: A Phase 2, Randomized, Pilot Study to Investigate the Safety, Efficacy, Pharmacokinetics and Bioavailability of HTX-011 Administered Via Injection or Topical Application Following Unilateral Open Inguinal Herniorrhaphy - PROTOCOL NUMBER HTX-011-C2015-202

All dates and times are in Pacific Standard Time .

PRT-0032 V12

Document Approval

Name/Signature	Title	Date	Meaning/Reason
[redacted]	VP. Clinical Operations	01 Feb 2017, 01:18:39 PM	Approved

Final Approval

Name/Signature	Title	Date	Meaning/Reason
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