Document Type:	Study Protocol
Official Title:	A Phase 2, Randomized, Controlled, Multicenter, Evaluation of the Efficacy and Safety of Locally Administered HTX-011, HTX-002, or HTX-009 for Postoperative Analgesia Following Bunionectomy
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CLINICAL STUDY PROTOCOL: HTX-011-C2016-208

A Phase 2, Randomized, Controlled, Multicenter, Evaluation of the Efficacy and Safety of Locally Administered HTX-011, HTX-002, or HTX-009 for Postoperative Analgesia Following Bunionectomy

Compound Name:	Injectable Bupivacaine/Meloxicam (HTX-011) Injectable Bupivacaine (HTX-002) Injectable Meloxicam (HTX-009)	
IND #	125927	
Protocol Version:	7	
Date of Protocol:	23 January 2017	
Previous Versions:	Version 1.1:	24 March 2016
	Version 2:	09 May 2016
	Version 3:	08 June 2016
	Version 4:	24 June 2016
	Version 5:	28 September 2016
	Version 6:	20 December 2016

SPONSOR DETAILS

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Medical Monitor

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INVESTIGATOR AGREEMENT

CLINICAL PROTOCOL HTX-011-C2016-208

A Phase 2, Randomized, Controlled, Multicenter, Evaluation of the Efficacy and Safety of Locally Administered HTX-011, HTX-002, or HTX-009 for Postoperative Analgesia Following Bunionectomy

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 (ie, medical records, case report forms, and informed consent statements), study drug shipment and return forms, and all other information collected during the study in accordance with local and national Good Clinical Practice (GCP) regulations.

Principal Investigator: _____

Address: _____

Signature: _____

Date: _____

SYNOPSIS

Name of Sponsor/Company: Heron Therapeutics, Inc.	**Protocol Number:** HTX-011-C2016-208
Name of Study Drug: • HTX-011-49 Injectable Bupivacaine/Meloxicam • HTX-011-56 Injectable Bupivacaine/Meloxicam • HTX-002 Injectable Bupivacaine • HTX-009 Injectable Meloxicam • Bupivacaine Hydrochloride Injection (Marcaine™) • Normal Saline	**Protocol Title:** A Phase 2, Randomized, Controlled, Multicenter, Evaluation of the Efficacy and Safety of Locally Administered HTX-011, HTX-002, or HTX-009 for Postoperative Analgesia Following Bunionectomy
Name of Active Ingredients: Bupivacaine/Meloxicam Bupivacaine Meloxicam	**Phase of Development:** 2

Study Objectives:

Primary Objective:

- To evaluate the efficacy and duration of analgesia following administration of HTX-011, HTX-002, and HTX-009 formulations by three different techniques.

Secondary Objectives:

- To determine the optimum study drug administration technique
- To determine the safety and tolerability of HTX-011, HTX-002, and HTX-009 formulations
- To evaluate the pharmacokinetic (PK) profiles of bupivacaine and meloxicam in HTX-011,the PK profile of bupivacaine in HTX-002, and the PK profile of meloxicam in HTX-009 over 120 hours after study drug administration
- To evaluate the analgesic effects of HTX-011, HTX-002, and HTX-009 formulations over various intervals using a series of secondary efficacy endpoints for pain intensity
- To assess the effects of HTX-011, HTX-002, and HTX-009 formulations on wound healing at 48 hours, 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 who remain pain free over time

Methodology: This is a Phase 2, randomized, 9-part, multicenter, controlled, evaluation of the efficacy and safety of the intraoperative administration of study drug, in adult subjects undergoing simple unilateral bunionectomy. In Study Parts 1 and 2, 6.84 mL (200 mg bupivacaine) of HTX-011 or HTX-002, in Study Part 3, 4.1 mL of HTX-011-056 (120 mg bupivacaine),and Part 4, 2.05 mL HTX-011-56 (60 mg bupivacaine) and Part 5, 4.1 mL of HTX-002 (120 mg) or normal saline will be administered. Part 6, 1.0 mL of HTX-011-56 or normal saline will be administered and Part 7, 4.1 mL of HTX-009 or normal saline will be administered. In Part 8, 2.05 mL of HTX-002 (60 mg bupivacaine), 10 mL of bupivacaine hydrochloride, or 2.05 mL of normal saline will be administered. Part 9, 4.1 mL of HTX-011-056 (120 mg bupivacaine), 2.05 mL of HTX-011-056 (60 mg bupivacaine), or 4.1 mL of normal saline will be administered. The total duration of this study for each subject will be a maximum of 56 days that comprise 28-day screening period, 72 hours in-house treatment period, and 25 days post-treatment follow-up period. In addition, an X-ray will be obtained between Day 28 and Day 42 as part of the subject's routine surgical follow-up visit.

Part 1

In Part 1, 90 subjects will be enrolled and studied in six randomly assigned cohorts (1:1:1:1:1:1) as follows:

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Cohort A (15 subjects) will be enrolled to evaluate the analgesic efficacy of 6.84 mL (200 mg) of HTX-011-49 via closed wound infiltration (post-closure dosing technique)

Cohort B (15 subjects) will be enrolled to evaluate the analgesic efficacy of 6.84 mL (200 mg) of HTX-011-49 via open wound infiltration (pre-closure dosing technique)

Cohort C (15 subjects) will be enrolled to evaluate the analgesic efficacy of 6.84 mL (200 mg) of HTX-011-56 via closed wound infiltration (post-closure dosing technique)

Cohort D (15 subjects) will be enrolled to evaluate the analgesic efficacy of 6.84 mL (200 mg) of HTX 011-56 via open wound infiltration (pre-closure dosing technique)

Cohort E (15 subjects) will be enrolled to evaluate the analgesic efficacy of 10 mL (50 mg) 0.5% bupivacaine hydrochloride injection (Marcaine) via a closed wound infiltration (post- closure dosing technique)

Cohort F (15 subjects) will be enrolled to evaluate 6.84 mL of normal saline via a closed wound infiltration (post- closure dosing technique)

Part 2

An additional 60 subjects will be enrolled in Part 2 and randomized (1:1:1:1) as follows:

Cohort G (15 subjects) will be enrolled to evaluate the analgesic efficacy of 6.84 mL (200 mg) of HTX-002-013 via closed wound infiltration (post-closure dosing technique)

Cohort H (15 subjects) will be enrolled to evaluate the analgesic efficacy of 6.84 mL (200 mg) of HTX-002-013 via open wound infiltration (pre-closure dosing technique)

Cohort I (15 subjects) will be enrolled to evaluate 6.84 mL of normal saline via a closed wound infiltration (post-closure dosing technique)

Cohort J (15 subjects) will be enrolled to evaluate 6.84 mL of normal saline via open wound infiltration (pre-closure dosing technique)

Part 3

An additional 60 subjects will be enrolled and randomized (1:1:1:1) as follows:

Cohort K (15 subjects) will be enrolled to evaluate the analgesic efficacy of 4.1 mL (120 mg) of HTX-011-56 via closed wound infiltration (post-closure dosing technique).

Cohort L (15 subjects) will be enrolled to evaluate the analgesic efficacy of 4.1 mL (120 mg) of HTX-011-56 via open wound infiltration (pre-closure dosing technique).

Cohort M (15 subjects) will be enrolled to evaluate the analgesic efficacy of 4.1 mL (120 mg) of HTX-011-56 local administration via instillation.

Cohort N (15 subjects) will be enrolled to evaluate the analgesic efficacy of 4.1 mL of normal saline via open wound infiltration (pre-closure dosing technique).

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Part 4

An additional 45 subjects will be enrolled and randomized (1:1:1) as follows:

Cohort O (15 subjects) will be enrolled to evaluate the analgesic efficacy of 2.05 mL (60 mg) of HTX-011-56 via closed wound infiltration (post-closure dosing technique).

Cohort P (15 subjects) will be enrolled to evaluate the analgesic efficacy of 2.05 mL (60 mg) of HTX-011-56 via open wound infiltration (pre-closure dosing technique).

Cohort R (15 subjects) will be enrolled to evaluate the analgesic efficacy of 2.05 mL of normal saline via open wound infiltration (pre-closure dosing technique).

Part 5

An additional 45 subjects will be enrolled and randomized (1:1:1) as follows:

Cohort S (15 subjects) will be enrolled to evaluate the analgesic efficacy of 4.1 mL (120 mg) of HTX-002 via closed wound infiltration (post-closure dosing technique)

Cohort T (15 subjects) will be enrolled to evaluate the analgesic efficacy of a dose up to 4.1 mL (120 mg) of HTX-002 via open wound infiltration (pre-closure dosing technique)

Cohort U (15 subjects) will be enrolled to evaluate a dose up to 4.1 mL of normal saline via open wound infiltration (pre-closure dosing technique)

Part 6

An additional 20 subjects will be enrolled and randomized (3:1) as follows:

Cohort X (15 subjects) will be enrolled to evaluate the analgesic efficacy of 1.0 mL (30 mg) of HTX-011-56 via closed wound infiltration (post-closure dosing technique)

Cohort Y (5 subjects) will be enrolled to evaluate a dose up to 1.0 mL of normal saline via closed wound infiltration (post-closure dosing technique)

Part 7

An additional 40 subjects will be enrolled and randomized (3:3:1:1) as follows:

Cohort Z1 (15 subjects) will be enrolled to evaluate the analgesic efficacy of 4.1 mL (3.61 mg) of HTX-009 via closed wound infiltration (post-closure dosing technique)

Cohort Z2 (15 subjects) will be enrolled to evaluate the analgesic efficacy of 4.1 mL (3.61 mg) of HTX-009 via open wound infiltration (pre-closure dosing technique)

Cohort Z3 (5 subjects) will be enrolled to evaluate a dose up to 4.1 mL normal saline via closed wound infiltration (post-closure dosing technique)

Cohort Z4 (5 subjects) will be enrolled to evaluate a dose up to 4.1 mL normal saline via open wound infiltration (pre-closure dosing technique)

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Name of Active Ingredients: Bupivacaine/Meloxicam Bupivacaine Meloxicam	**Phase of Development:** 2

Part 8

An additional 35 subjects will be enrolled and randomized (2:2:1:1:1) as follows:

Cohort Z5 (10 subjects) will be enrolled to evaluate the analgesic efficacy of 2.05 mL (60 mg) of HTX-002 via closed wound infiltration (post-closure dosing technique)

Cohort Z6 (10 subjects) will be enrolled to evaluate the analgesic efficacy of a dose of 2.05 mL (60 mg) of HTX-002 via open wound infiltration (pre-closure dosing technique)

Cohort Z7 (5 subjects) will be enrolled to evaluate the analgesic efficacy of 10 mL (50 mg) 0.5% bupivacaine hydrochloride (Marcaine) via a closed wound infiltration (post- closure dosing technique)

Cohort Z8 (5 subjects) will be enrolled to evaluate the analgesic efficacy of 10 mL (50 mg) 0.5% bupivacaine hydrochloride (Marcaine) via open wound infiltration (pre- closure dosing technique)

Cohort Z9 (5 subjects) will be enrolled to evaluate a dose of 2.05 mL of normal saline via open wound infiltration (pre-closure dosing technique)

Part 9

An additional 35 subjects will be enrolled and randomized (3:3:1) as follows:

Cohort A1 (15 subjects) will be enrolled to evaluate the analgesic efficacy of 4.1 mL (120 mg) of HTX-011-056 local administration via instillation

Cohort A2 (15 subjects) will be enrolled to evaluate the analgesic efficacy of a dose of 2.05 mL (60 mg) of HTX-011-056 local administration via instillation

Cohort A3 (5 subjects) will be enrolled to evaluate a dose of 4.1 mL of normal saline via open wound infiltration

Pretreatment Phase (Day -28 to Day -1):

Subjects will be consented and screened.

Treatment and Confinement Phase (Day 0 to Day 5):

Subjects will be re-assessed on Day 0 for eligibility to continue in this study, and will be confined from Day 0 to 72 hours after receiving study medication.

Efficacy evaluations will include collection of Pain Intensity scores and Patient Global Assessment of pain control at pre-defined time intervals throughout the study.

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

Name of Sponsor/Company: Heron Therapeutics, Inc.	**Protocol Number:** HTX-011-C2016-208
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Name of Active Ingredients: Bupivacaine/Meloxicam Bupivacaine Meloxicam	**Phase of Development:** 2

Blood samples will be obtained to evaluate pharmacokinetic (PK) profiles of bupivacaine and meloxicam.

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

- 96 (±2) Hours: assessments of vital signs, ECG, collection of AEs and concomitant medications, photograph of the surgical intervention area, and a blood sample for PK. Efficacy assessments will include collection of Pain Intensity scores and Patient Global Assessment (PGA) of pain control evaluations.
- 120 (±2) Hours: obtain blood sample for pharmacokinetic analysis.

Follow-Up Phase (Day 10 and Day 28):

Subjects will return to the clinic site at Days 10 and 28:

Day 10: physical examination, vital signs, ECG, photograph of the surgical intervention area, and assessments of wound healing, AEs and concomitant medications.

Day 28: assessment of AEs, concomitant medications, wound healing, and, photograph of the surgical intervention area.

Routine Surgical Follow Up (Day 28 to Day 42)

X-ray of surgical intervention area as part of routine surgical follow up visit (evaluate bone healing).

Number of subjects to be enrolled: The study will enroll approximately 430 subjects, 90 in Part 1 and 60 each in Part 2 and Part 3, Part 4 will enroll 45 subjects, Part 5 may enroll up to 45 subjects and Part 6 may enroll up to an additional 20 subjects, Part 7 may enroll an additional 40 subjects, Part 8, up to 35 subjects may enroll and Part 9, up to 35 subjects may enroll.

Number of study sites: Up to 6 total

Study country location: United States

Criteria for inclusion:

Subject 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:
    a. Not pregnant (female subject of child bearing potential must have a negative serum pregnancy test at screening and negative urine pregnancy test before surgery)
    b. Not lactating
    c. Not planning to become pregnant while participating in the study
    d. Be surgically sterile; or be at least two years post-menopausal; or have a monogamous partner who is surgically sterile; or be practicing double-barrier contraception; or practicing abstinence (must

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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 1 month 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

3. Male subjects 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
4. Be scheduled to undergo a primary unilateral first metatarsal bunionectomy repair, without collateral procedures, under regional anesthesia (Section 5.5.1).
5. Subject has not had a contralateral bunionectomy in the non-study foot in the past 3 months
6. Have the ability and be willing to comply with the study procedures.
7. 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:

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
4. Have American Society of Anesthesiologists (ASA) Physical Status classification system category ≥ 4 (Appendix D)
5. Has AST or ALT > 3 x ULN, and/or creatinine > 2 x ULN
6. Have another pre-existing painful condition that may confound pain assessments, in the opinion of the Investigator
7. Have another surgery planned within 30 days of procedure
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. Subjects who are receiving oxygen therapy at the time of screening
12. Have participated in a clinical trial within 30 days of planned surgery

Investigational product: HTX-011 is a sterile, viscous, extended release formulation of the active entities bupivacaine and meloxicam to be administered via injection or instillation into the surgical site for the prevention of postoperative pain. The term “HTX-011” is used to represent the extended release formulations comprising the active ingredients.

HTX-002 is a sterile, viscous, extended release formulation of bupivacaine only to be locally administered into

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the surgical site for the prevention of postoperative pain.

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

The vehicle formulation for HTX-011-49, HTX-011-56, HTX-002, and HTX-009 comprises 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 doses of HTX-011 of 200 mg or lower, HTX-002 of 200 mg or lower, and doses of HTX-009 of 4.1 mL or lower in subjects following unilateral bunionectomy. HTX-011, HTX-002 and HTX-009 formulations will be supplied by the sponsor for administration to subjects according to their randomization.

For both HTX-011-49 and HTX-011-56, the content of active ingredients per volume is identical: 4.1 mL = 119.9 mg bupivacaine and 3.59 mg of meloxicam; 6.84 mL = 200.1 mg bupivacaine and 6.0 mg of meloxicam. A lower volume with a corresponding lower dose of bupivacaine may be also administered. The two formulations of HTX-011 differ from each other in their respective quantities of the vehicle excipients.

HTX-002 is an identical formulation as that of HTX-011-56 except that it contains only bupivacaine (at the same concentration) as the active pharmaceutical ingredient.

The content of active ingredients per volume in HTX-009 is 4.1 mL of meloxicam.

Reference therapy: Normal saline and bupivacaine hydrochloride (Marcaine). Both will be procured by sites.

Duration of treatment: Each subject is planned to receive a single dose of study medication in divided aliquots.

Overview: This study is designed to evaluate the safety and analgesic efficacy of multiple formulations of HTX-011, HTX-002, and HTX-009 at doses not to exceed 6.84 mL (200 mg) in subjects following unilateral bunionectomy. Efficacy assessments are intended to characterize the analgesic effect time curve and the magnitude of analgesic effect of HTX-011, HTX-002, and HTX-009 in comparison with bupivacaine (Marcaine) and normal saline. In addition, the study will further characterize the safety and PK profiles of bupivacaine and meloxicam in the HTX-011, HTX-002, HTX-009 and bupivacaine.

Subjects will participate in the screening visit within 28 days of the scheduled surgery. ASA classification and inclusion/exclusion criteria for eligibility to participate in the study will be assessed. Medical history, vital signs, physical examination, clinical laboratory tests, drug and alcohol screening, 12-lead ECG, collection of prior/concomitant medications, and a serum pregnancy test will be performed. PONV risk factors will be assessed, and subject will be trained on providing pain intensity assessments.

On the day of surgery, Day 0, subjects will be reassessed for eligibility. 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 for

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inducing regional anesthesia as detailed in the protocol.

Subjects will be assigned randomly to a cohort and dosed as described above. Start and stop time of dosing will be recorded. Dosing stop time will be considered Time 0 (T0).

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

Each subject will be sequestered in the post-anesthesia care area at each study center for 72 hours post-Time 0 (T72), after which discharge procedures will be performed.

Efficacy analyses:

Pain intensity (PI) scores will be assessed utilizing an 11 point (0–10) numerical pain rating scale (NPRS), at 1, 2, 78, 84, and 96 hours after completion of administration of study medication (T0). In this NPRS scale, 0 equates to no pain experienced and 10 equates to worst pain imaginable.

PI scores will be measured two ways: in a dependent position, and, in an elevated position at rest. PI scores will be measured in the ***dependent position*** (ie, subject sitting on the bed with the surgically attended foot resting at least partially on the floor) at the following time-points: 4, 6, 8, 10, 12, 14, 18, 24, 30, 36, 42, 48, 54, 60, and 72 hours post-T0. PI scores in an ***elevated position at rest*** will be measured at 1, 2, 78, 84, and 96 hours post-T0.

Rescue analgesia (from T0 to T72) will be available to subjects with inadequately controlled pain symptoms. Pain intensity assessment must be completed prior to administration of any rescue dose administered. 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). Between T72 and T96, pain medication 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 for inadequately controlled pain, as advised by their surgeon.

Each subject's PGA of pain control will be obtained at 24, 48, 72, and 96 hours post-T0.

Safety analyses:

A neurologic exam and assessment will be completed at the following time points: at Day 0 any time prior to anesthesia induction, and at 12, 24, 36, 48, 60, 72, and 96 hours post-T0. The exam will include awareness and assessment for signs and symptoms of potential bupivacaine toxicity.

Vital signs will be measured at Screening, at Baseline (ie, Day 0, prior to anesthetic pre-operative procedures), and at 1, 2, 4, 6, 12, 18, 24, 36, 48, 60, 72, and 96 hours, and at Day 10 after T0.

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Name of Study Drug: • HTX-011-49 Injectable Bupivacaine/Meloxicam • HTX-011-56 Injectable Bupivacaine/Meloxicam • HTX-002 Injectable Bupivacaine • HTX-009 Injectable Meloxicam • Bupivacaine Hydrochloride Injection (Marcaine™) • Normal Saline	**Protocol Title:** A Phase 2, Randomized, Controlled, Multicenter, Evaluation of the Efficacy and Safety of Locally Administered HTX-011, HTX-002, or HTX-009 for Postoperative Analgesia Following Bunionectomy
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Each subject will have a 12-lead ECG performed at screening, at baseline (ie, Day 0, prior to anesthetic pre-operative procedures), and at 24, 48, 72, and 96 hours, and, at Day 10 post-T0.

Blood samples for clinical laboratory tests will be obtained at screening visit, at baseline, and at 72 hours post-T0.

Each subject will be assessed for nausea 6, 24, 48, and 72 hours post T0 using a nausea numerical rating scale.

Each subject will be assessed for wound healing at 48 and 72 hours, and at Days 10 and 28 post-T0.

A photograph of the surgical intervention area will be taken immediately after surgery, and at 48, 72, and 96 hours, and at Days 10 and 28 post-T0. In parts 4, 5, 6 and 7 one of the 3 photos taken at each specific timepoint should be a photo of both feet together.

An x-ray will be taken between Day 28 and Day 42 as part of routine surgical follow-up to evaluate the status of the bone healing process.

Subjects will be assessed for adverse events and concomitant medications throughout the study.

Pharmacokinetics analyses:

Blood samples for PK analyses will be drawn prior to administration of the investigational product (IP), and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 36, 48, 60, 72, 96, and 120 hours post-T0.

Study Endpoints

Efficacy Endpoints:

Primary:

Summed pain intensity score (SPI) over 24 hours (SPI_{0-24})

Secondary:

- SPI at 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 PGA of pain control at 24, 48, 72, and 96 hours post-T0
- Time to administration of first dose of rescue analgesia
- Total and average daily rescue consumption over 24, 48, 72, and 96 hours post-T0
- Mean nausea assessment scores at 6, 24, 48, and 72 hours post-T0.
- The percentage of subjects who remain pain free (Numerical Pain Rating Scale ≤ 1) at 72 hours and at 96 hours after study drug administration

Safety Endpoints:

Safety will be evaluated by assessment of AEs, including SAEs, as described in Section 6.4.8.

Name of Sponsor/Company: Heron Therapeutics, Inc.	**Protocol Number:** HTX-011-C2016-208
Name of Study Drug: • HTX-011-49 Injectable Bupivacaine/Meloxicam • HTX-011-56 Injectable Bupivacaine/Meloxicam • HTX-002 Injectable Bupivacaine • HTX-009 Injectable Meloxicam • Bupivacaine Hydrochloride Injection (Marcaine™) • Normal Saline	**Protocol Title:** A Phase 2, Randomized, Controlled, Multicenter, Evaluation of the Efficacy and Safety of Locally Administered HTX-011, HTX-002, or HTX-009 for Postoperative Analgesia Following Bunionectomy
Name of Active Ingredients: Bupivacaine/Meloxicam Bupivacaine Meloxicam	**Phase of Development:** 2

Additional safety endpoints include the following parameters:

- Nausea assessments
- Wound assessments of the surgical intervention area
- Vital signs
- Neurological examinations
- Clinical laboratory tests (serum chemistry, hematology)
- Electrocardiograms (ECGs)
- Use of concomitant medications

Pharmacokinetic Endpoints:

- The area under the plasma concentration-time curve from time zero to time t of the last measured concentration above the limit of quantification ($AUC_{0\text{-last}}$)
- The area under the plasma concentration-time curve from zero to infinity ($AUC_{0\text{-inf}}$)
- The maximum plasma concentration (C_{max})
- Apparent total body clearance over bioavailability (Cl/F)
- Apparent total volume of distribution over bioavailability (V_z/F)
- The time to reach maximum plasma concentration (T_{max})
- The terminal elimination rate constant (λ_Z) with the respective half-life ($t_{½}$)

Statistical methods:

Sample size determination:

The sample size up to 430 subjects in this study was selected empirically without a formal statistical assumption. The primary efficacy endpoint for this study is the summed pain intensity scores over the first 24 hours ($SPI_{0\text{-}24}$). The primary analysis will be via an analysis of variance with contrasts to test for differences between the cohorts or pooled cohorts and for differences between linear combinations of the cohorts or pooled cohorts.

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.

Pharmacokinetic analysis:

The PK parameters for bupivacaine and meloxicam will be calculated using non-compartmental analysis and

Name of Sponsor/Company: Heron Therapeutics, Inc.	**Protocol Number:** HTX-011-C2016-208
Name of Study Drug: • HTX-011-49 Injectable Bupivacaine/Meloxicam • HTX-011-56 Injectable Bupivacaine/Meloxicam • HTX-002 Injectable Bupivacaine • HTX-009 Injectable Meloxicam • Bupivacaine Hydrochloride Injection (Marcaine™) • Normal Saline	**Protocol Title:** A Phase 2, Randomized, Controlled, Multicenter, Evaluation of the Efficacy and Safety of Locally Administered HTX-011, HTX-002, or HTX-009 for Postoperative Analgesia Following Bunionectomy
Name of Active Ingredients: Bupivacaine/Meloxicam Bupivacaine Meloxicam	**Phase of Development:** 2

summarized for HTX 011, HTX-002 and HTX-009 formulations, in accordance with the defined PK endpoints.

Safety analysis:

Safety analyses will be conducted on the safety population. Treatment duration and amount of study drug received will be summarized by treatment group.

All treatment-emergent adverse events and serious adverse events will be summarized for each treatment group using the MedDRA coding system, by system organ class, preferred term, relationship to study drug, and severity.

Narratives of deaths, serious adverse events, including early withdrawals from study drug and from study due to adverse events, will also be provided.

Laboratory tests including chemistry panel, complete blood count with differential, etc., will be summarized by study visit for each treatment group. These safety variables will also be presented over time after study drug administration, as appropriate. Vital signs data will be presented similarly.

Physical and neurological examination findings and results from ECG will be listed for review. As appropriate, results will also be summarized descriptively for each treatment group. Concomitant medication usage for each subject will be listed for review.

TABLE OF CONTENTS

LIST OF APPENDICES

LIST OF TABLES

ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
ALT	Alanine aminotransferase
ANOVA	analysis of variance
APAP	acetyl-para-aminophenol (Acetaminophen)
API	active pharmaceutical ingredient
ASA	American Society of Anesthesiology
AST	Aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BMI	body mass index
bpm	beats per minute
CFR	Code of Federal Regulations
C_{max}	Maximum Plasma Concentration
CPAP	Continuous positive airway pressure
ECG	Electrocardiogram
eCRF	electronic Case Report Form
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HEENT	head, eyes, ears, nose and throat
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
iv	Intravenous
kg	Kilogram
L	Liters
LC-MS/MS	liquid chromatography – tandem mass spectrometry
LOCF	last observation carried forward
MAC	minimum alveolar concentration
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	as needed
SAE	Serious Adverse Event
SAR	Suspected Adverse Reaction
SD	standard deviation
SNRIs	serotonin-norepinephrine reuptake inhibitors
SPI	summed pain intensity
SpO_2	peripheral oxygen saturation
SSAR	Serious Suspected Adverse Reaction
SSRI	Selective serotonin reuptake inhibitor
$t_{½}$	half-life
TCAs	tricyclic antidepressants
T_{max}	time to reach maximum plasma concentration
VAS	Visual Analog Scale
VS	vital signs
WBC	white blood cell
WHO	World Health Organization
WLOCF	Windowed Last Observation Carried Forward
λ_Z	terminal elimination rate constant

1. INTRODUCTION

The use of local anesthetics has found extensive use in a vast number of patients (Renck 1994). Medical opinion would suggest that using 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 is the limited duration of effect (6 to 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 two sustained release formulations (HTX-011-49 and HTX-011-56), intended for the management of post-operative pain via wound infiltration, that have demonstrated positive results in a non-clinical model of post-surgical pain. These formulations have been selected for further clinical investigation. Both HTX-011-49 and HTX-011-56 contain bupivacaine and meloxicam as active ingredients and both have vehicle formulations comprising tri[ethylene glycol] based poly[orthoester] polymer with dimethyl sulfoxide (DMSO), glycerol triacetate, and maleic acid. The two formulations differ from each other in their respective quantities of the vehicle excipients.

The Sponsor has also developed a formulation, HTX-002, which is identical in pharmaceutical composition to HTX-011-56 *except* that it contains only bupivacaine as the active pharmaceutical ingredient (API). Therefore, the HTX-002 formulation is a bupivacaine-only comparator to the HTX-011-56 formulation. 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 pharmacokinetic (PK) characteristics of HTX-002 are similar to that of HTX-011-56. Both the active ingredient (bupivacaine) and the identical biochronomer polymer vehicle have been studied in humans, whereas HTX-002 has not yet been studied.

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 of HTX-011-49 were administered to healthy volunteers. HTX-011 achieved the desired PK 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 because of 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. Other 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 opioid rescue medication; and the percentage of subjects who received no opioid rescue medication in the first 72 hours post-surgery. No subject discontinued early from this study. Of the five total SAEs reported, four were cellulitis consisting of pain, redness, and swelling reported. These four subjects experienced skin infections that required hospitalization with IV antibiotics, and, subsequently, two of the four subjects underwent a second surgery. The fifth SAE case presented with erythematous vesicular reaction with noted presence of eschar on study Day 30 and was treated with oral antibiotics and topical cream. The sponsor conducted thorough investigations of these cases and concluded that, while causality by drug cannot be definitively ruled out, these events were likely not the result of exposure to HTX-011.

This present study is designed to evaluate the safety and analgesic efficacy of HTX-011, HTX-002 and HTX-009 formulations in subjects following unilateral bunionectomy. Efficacy assessments are intended to characterize the analgesic effect-time curve and the magnitude of analgesic effect of HTX-011 and HTX-002 in comparison with Marcaine and with saline. In addition, the study will further characterize the safety and PK profiles of bupivacaine and meloxicam present in HTX-011 and HTX-009, and the PK profile of bupivacaine present in HTX-002.

The current edition of the HTX-011/HTX-002/HTX-009 Investigator's Brochure should be consulted for more detailed information on the formulations under investigation (HTX-011, HTX-009, and HTX-002).

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to evaluate the efficacy and duration of analgesia following administration of HTX-011, HTX-002, and HTX-009 formulations by three different techniques and multiple doses.

2.2. Secondary Objective

The secondary objectives will be:

- To determine the optimum study drug administration technique
- To determine the safety and tolerability of HTX-011, HTX-002, and HTX-009 formulations
- To evaluate the pharmacokinetic (PK) profiles of bupivacaine and meloxicam in HTX-011 and the PK profile of bupivacaine in HTX-002, and the PK profile of meloxicam in HTX-009 over 120 hours after study drug administration
- To evaluate the analgesic effects of HTX-011, HTX-002, and HTX-009 formulations over various intervals using a series of secondary efficacy endpoints for pain intensity
- To assess the effects of HTX-011, HTX-002, and HTX-009 formulations on wound healing at 48 hours, 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 who remain pain free over time

3. STUDY ENDPOINTS

3.1. Efficacy Endpoints

3.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint for this study will be the summed pain intensity score (SPI) over 24 hours (SPI_{0-24}).

3.1.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints for this study will include:

- SPI at 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 PGA of pain control at 24, 48, 72, and 96 hours post-T0.
- Time to administration of first dose of rescue analgesia.
- Total and average daily rescue consumption over 24, 48, 72, and 96 hours post-T0.
- Mean nausea assessment scores at 6, 24, 48, and 72 hours post-T0.
- The percentage of subjects who remain pain free (Numerical Pain Rating Scale ≤ 1) at 72 hours and at 96 hours after study drug administration.

3.2. Safety Endpoints

Safety will be evaluated by assessment of AEs including SAEs as described in Section 6.4.8.

Additional safety endpoints include the following parameters:

- Nausea assessments
- Wound assessments of the surgical intervention area
- Vital signs
- Neurological examinations
- Clinical laboratory tests (serum chemistry, hematology)
- Electrocardiograms (ECGs)
- Use of concomitant medications

3.3. Pharmacokinetic Endpoints:

- 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_{0-last})
- The area under the plasma concentration-time curve from zero to infinity (AUC_{0-inf})
- The maximum plasma concentration (C_{max})
- Apparent total body clearance over bioavailability (Cl/F)
- Apparent total volume of distribution over bioavailability (V_z/F)
- The time to reach maximum plasma concentration (T_{max})
- The terminal elimination rate constant (λ_Z) with the respective half-life ($t_{½}$)

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is a Phase 2, randomized, 9-part, multicenter, controlled, evaluation of the efficacy and safety of the intraoperative administration of study drug in adult subjects undergoing simple unilateral bunionectomy. In Study Parts 1 and 2, 6.84 mL (200 mg bupivacaine) of HTX-011 or HTX-002, in Study Part 3, 4.1 mL HTX-011-56 (120 mg bupivacaine) and Part 4, 2.05 mL HTX-011-56 (60 mg bupivacaine), Part 5, 4.1 mL of HTX-002 (120 mg bupivacaine), Part 6, 1.0 mL of HTX-011-56 (30 mg bupivacaine) or normal saline will be administered, Part 7, 4.1 mL of HTX-009 or normal saline will be administered, Part 8, 2.05 mL of HTX-002 (60 mg bupivacaine), bupivacaine hydrochloride, or normal saline will be administered and Part 9, 4.1 mL of HTX-011-056 (120 mg bupivacaine), 2.05 mL of HTX-011-056 (60 mg bupivacaine), or 4.1 mL of normal saline will be administered. Up to 34 cohorts of subjects may be enrolled for an approximate total of 430 subjects. In Part 1 (Cohorts A through F), approximately 90 subjects will receive HTX-011-49, HTX-011-56, bupivacaine (Marcaine), or normal saline (Table 1). In Part 2 (Cohorts G through J), approximately 60 subjects will receive HTX-002 or normal saline (Table 2). Part 3 (Cohorts K through N), approximately 60 subjects will receive HTX-011-56 or normal saline (Table 3). In Part 4, up to 45 additional subjects may be enrolled (Table 4), and in Part 5 up to an additional 45 subjects may be enrolled (Table 5). Part 6 (Cohorts X and Y) up to an additional 20 subjects may be enrolled to HTX-011-56 or normal saline (Table 6). Part 7 (Cohorts Z1, Z2, Z3, and Z4) up to an additional 40 subjects may be enrolled to HTX-009 or normal saline (Table 7). In Part 8, Cohorts Z5, Z6, Z7, Z8, and Z9 35 subjects may be enrolled to HTX-002, bupivacaine hydrochloride, or normal saline (Table 8). Part 9, (Cohorts A1, A2 and A3) up to 35 subjects may be enrolled to HTX-011-056 (120 or 60 mg bupivacaine) or 4.1 mL of normal saline (Table 9).

Table 1: Treatment Cohorts in Part 1

Cohort	Study Drug	Administration Technique	Number of Subjects
Cohort A	HTX-011-49 (200 mg)	Closed wound infiltration	15
Cohort B	HTX-011-49 (200 mg)	Open wound infiltration	15
Cohort C	HTX-011-56 (200 mg)	Closed wound infiltration	15
Cohort D	HTX-011-56 (200 mg)	Open wound infiltration	15
Cohort E	Bupivacaine (Marcaine)	Closed wound infiltration	15
Cohort F	Normal saline	Closed wound infiltration	15

Table 2: Treatment Cohorts in Part 2

Cohort	Study Drug	Administration Technique	Number of Subjects
Cohort G	HTX-002 (200 mg)	Closed wound infiltration	15
Cohort H	HTX-002 (200 mg)	Open wound infiltration	15
Cohort I	Normal saline	Closed wound infiltration	15

Cohort J	Normal saline	Open wound infiltration	15

Table 3: Treatment Cohorts in Part 3

Cohort	Study Drug	Administration Technique	Number of Subjects
Cohort K	HTX-011-056 (120 mg)	Closed wound infiltration	15
Cohort L	HTX-011-056 (120 mg)	Open wound infiltration	15
Cohort M	HTX-011-056 (120 mg)	Local administration via instillation	15
Cohort N	Normal saline	Open wound infiltration	15

Table 4: Treatment Cohorts in Part 4

Cohort	Study Drug	Administration Technique	Number of Subjects
Cohort O	HTX-011-056 (60 mg)	Closed wound infiltration	15
Cohort P	HTX-011-056 (60 mg)	Open wound infiltration	15
Cohort R	Normal saline	Open wound infiltration	15

Table 5: Treatment Cohorts in Part 5

Cohort	Study Drug	Administration Technique	Number of Subjects
Cohort S	HTX-002 (120 mg)	Closed wound infiltration	15
Cohort T	HTX-002 (120 mg)	Open wound infiltration	15
Cohort U	Normal saline	Open wound infiltration	15

Table 6: Treatment Cohorts in Part 6

Cohort	Study Drug	Administration Technique	Number of Subjects
Cohort X	HTX-011-56 (30 mg)	Closed wound infiltration	15
Cohort Y	Normal saline	Closed wound infiltration	5

Table 7: Treatment Cohorts in Part 7

Cohort	Study Drug	Administration Technique	Number of Subjects
Cohort Z1	HTX-009 (3.61 mg)	Closed wound infiltration	15
Cohort Z2	HTX-009 (3.61 mg)	Open wound infiltration	15
Cohort Z3	Normal saline	Closed wound infiltration	5
Cohort Z4	Normal saline	Open wound infiltration	5

Table 8: Treatment Cohorts in Part 8

Cohort	Study Drug	Administration Technique	Number of Subjects
Cohort Z5	HTX-002 (60 mg)	Closed wound infiltration	10
Cohort Z6	HTX-002 (60 mg)	Open wound infiltration	10
Cohort Z7	Bupivacaine (Marcaine)	Closed wound infiltration	5
Cohort Z8	Bupivacaine (Marcaine)	Open wound infiltration	5
Cohort Z9	Normal Saline	Open wound infiltration	5

Table 9: Treatment Cohorts in Part 9

Cohort	Study Drug	Administration Technique	Number of Subjects
Cohort A1	HTX-011-056 (120 mg)	Local administration via instillation	15
Cohort A2	HTX-011-056 (60 mg)	Local administration via instillation	15
Cohort A3	Normal saline	Open wound infiltration	5

Adult subjects ≥ 18 years old undergoing elective bunionectomy will be screened for participation within 28 days of the scheduled surgery. After signing the informed consent, subjects will be assessed for ASA classification, medical history and prior/concomitant medications, vital sign measurements, physical examination, clinical laboratory tests, drug and alcohol screen tests, 12-lead electrocardiogram (ECG), serum pregnancy test. Post-operative nausea and vomiting (PONV) risk factors will be assessed, and subject will be trained on providing pain assessments.

On the day of surgery (Day 0), each subject will be reassessed first for continued participation in the study. Subjects will undergo a primary, unilateral, first metatarsal bunionectomy procedure under regional anesthesia. Upon completion of the bunionectomy, a single dose of study drug (assigned randomly to any one of HTX-011-49, HTX-011-56, HTX-002, HTX-009, Marcaine or normal saline) will be administered by local infiltration. The operating surgeon and the attendant surgical staff will not be blinded to study medication because HTX-011, HTX-002, and HTX-009 are colored preparations, whereas Marcaine and normal saline control are not.

Following the completion of surgery and immediate postoperative recovery, subjects will be transferred to the post-anesthesia care area. Staff members in the post-anesthesia care area will be blinded to study treatment administered. Subjects will stay in the post-anesthesia care area for 72 hours after completion of the administration of study medication (ie, T0) prior to discharge from study center. Each subject will return to the study center 96 hours elapsed time after T0 to complete additional assessments. After completion of the 96-hour assessments, subjects will be scheduled to return on Days 10 and 28 for specific study assessments; each subject will also be asked to return to the site specifically for a PK blood sample draw at 120 hours.

Efficacy assessments will include pain intensity scoring, use of rescue medication, and Patient Global Assessment (PGA) of pain control.

Blood samples will be obtained to assess meloxicam and bupivacaine pharmacokinetics out to 120 hours post-T0.

Safety assessments will include AEs, bupivacaine toxicity, concomitant medications, physical examinations, neurologic assessments (including those for potential bupivacaine toxicity), vital sign measurements, clinical laboratory tests, ECGs, nausea assessments, and, wound healing assessments and photographs of the surgical intervention area.

The following sections summarize the three phases of activities for this study:
1) Pretreatment Phase, 2) Treatment and Confinement Phase, and 3) Follow-up Phase.

4.1.1. Pretreatment Phase (Day -28 to Day -1)

Subjects will be consented and screened during this phase by assessments as described in Section 6.5. The screening period will be at any time between Day -28 and Day -1.

4.1.2. Treatment and Confinement Phase (Day 0 through Day 5)

a. Pre-surgery (Day 0): Subjects will be admitted to the surgical unit and reassessed for eligibility to continue participation in the study. Standard pre-surgery activities will be conducted once eligibility has been re-confirmed.

b. Surgery (Day 0): Subjects will undergo primary unilateral first metatarsal bunionectomy procedure via propofol sedation and regional local anesthesia via a Mayo block technique utilizing 1% lidocaine without epinephrine. A standard anesthetic regimen will be followed for all subjects as outlined in Section 5.5.1. Upon completion of the bunionectomy, a single dose of study drug (ie, any one of HTX-011-49, HTX-011-56, HTX-002, HTX-009, Marcaine, or normal saline, according to random assignment) will be administered by local infiltration/instillation (Section 5.5.1.2). Start and stop times of dose administration will be recorded. Dosing stop time will be considered as T0.

c. Postoperative Period (Days 0–5): Following surgery, subjects will be transferred to a post-anesthesia care area where, over the next 72 hours, they will undergo efficacy (see Section 6.3) and safety (see Section 6.4) assessments, and collection of blood samples for PK analyses (see Section 6.4.8.1). Treatments allowed during the postoperative period will include rescue medications for inadequately controlled pain symptoms (see Section 5.15). Subjects will be discharged from the clinic site after completion of the 72 hour assessments. Efficacy assessments scheduled at 78 and 84 hours will be completed at home. Subjects will return to the site to complete the T96 efficacy and safety assessments, and they will return at T120 to allow a blood sample for PK analysis to be collected.

4.1.3. Follow-up Phase (Day 10 ± 2 and Day 28 ± 2)

Subjects will return to the clinical site on Days 10 and 28 post-T0 for safety assessments (see Section 6.5.4).

4.1.4. Routine Surgical Follow Up (Day 28 to Day 42)

Between Days 28 and 42, an x-ray will be performed as part of routine surgical follow up to evaluate bone healing.

4.1.5. Follow Up Phone Call (Day 60 ± 7)

A follow up phone call will occur at Day 60 ± 7.

4.2. Rationale for Study Design and Control Groups

This study will evaluate the efficacy and safety of multiple formulations of HTX-011, HTX-002, and HTX-009. Previous research has demonstrated the safety and sustained concentrations over 96 hours of single doses of 100 mg, 200 mg, 400 mg of HTX-011 when administered subcutaneously to healthy subjects.

Bunionectomy produces generally reliable and persistent pain symptoms for a period typically lasting over 72 hours after the surgical insult, which will allow for analysis of the acute analgesic effect of HTX-011, HTX-002 and HTX-009 over an extended period of time. Efficacy measures will be collected so as to gain a better knowledge of the analgesic effect-time curve of HTX-011, HTX-002, and HTX-009 compared with Marcaine and with normal saline following a surgical procedure. In addition, the study will further characterize the safety and pharmacokinetic profiles of bupivacaine and meloxicam. Based on the overall PI, PK and safety data from the study cohorts, the optimum administration technique for HTX-011, HTX-002, and HTX-009 will be decided: the methodology will be detailed in the statistical analysis plan for this study.

Bupivacaine is one of the local anesthetics commonly administered for acute analgesic effect and is therefore employed in this study as a positive control, and normal saline employed as a negative control, for efficacy and safety evaluations.

5. STUDY POPULATION

5.1. 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 test at screening and negative urine pregnancy test before surgery)
    - Not lactating
    - Not planning to become pregnant while participating in the study
    - Be surgically sterile; or be at least two years post-menopausal; or have a monogamous partner who is surgically sterile; or be 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 1 month prior to screening visit 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

3. Male subjects 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

4. Be scheduled to undergo a primary unilateral first metatarsal bunionectomy repair, without collateral procedures, under regional anesthesia

5. Subject has not had a contralateral bunionectomy in the non-study foot in the past 3 months

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

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

5.2. 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. Have clinically significant cardiac abnormalities, that in the opinion of the investigator would pose a health risk to the subject

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

5. Has AST or ALT > 3 x ULN, and/or creatinine > 2 x ULN

6. Have another pre-existing painful condition that may confound pain assessments, in the opinion of the Investigator

7. Have another surgery planned within 30 days of procedure

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

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

5.3. Discontinuation of Subjects

5.3.1. 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. Any subject who withdraws consent to continue treatment, or who is discontinued from the study, before completing the protocol specified duration of treatment should be encouraged to complete the early termination assessments. All subjects will be encouraged to agree to be followed for up to 28 ± 2 days after completion of study drug administration. The date at which any subject is withdrawn, and the primary reason for the discontinuation, will be recorded in the subject's electronic case report form (eCRF).

5.3.2. 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. Subjects who discontinue after the 72-hour post-treatment timeframe will not be replaced in this study.

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.

5.4. Lifestyle Guideline During Confinement

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* 30 minutes prior to any pain intensity assessment. Subjects will be encouraged to maintain the operative foot elevated at all times while in bed. Subjects will be allowed to ambulate according to standard postoperative care instructions.

5.5. Surgical Procedure

On the day of surgery (Day 0), subjects will undergo primary unilateral first metatarsal bunionectomy without collateral procedures. The surgery should be completed using the Austin bunion procedure with internal fixation; use of other procedures including base wedge procedures is not acceptable as part of this study protocol. Surgeries should be scheduled to accommodate induction of anesthesia so that all surgical procedures can be completed by approximately 5:00 pm on the day of surgery.

5.5.1. Anesthesia and Study Drug Administration

5.5.1.1. Anesthesia for Surgery

The anesthetic protocol described below should be followed to minimize inter-subject variability owing to administration of these agents. However, it is understood that hemodynamic fluctuations and other intraoperative events may necessitate some deviation from the standard regimen to ensure that necessary measures are undertaken to preserve subject safety.

The surgery will be performed under regional anesthesia. Epidural or spinal anesthesia is not allowed. The surgical procedure should be limited to a maximum duration of 120 minutes with a target duration ≤ 90 minutes. The start time of surgery is defined by the time of first incision, and the stop time is defined by the time of last suture. A pneumatic ankle tourniquet inflated between 150 and 250 mmHg may be applied to achieve hemostasis.

A single dose of fentanyl 100 µg IV and/or midazolam up to 5 mg IV may be administered, as part of the pre-anesthesia induction procedure, at the investigator/anesthesiologist's discretion. A small dose of lidocaine (up to 5 mL of 1% lidocaine without epinephrine) may also be administered initially to reduce venous irritation at the propofol injection site. MAC sedation with propofol will be initiated utilizing propofol either as an infusion or as a slow injection method. An initial slow IV propofol 0.5 mg/kg bolus dose may be followed by either a) a maintenance IV propofol infusion at 0.025–0.075 mg/kg/min, or b) incremental IV

propofol bolus doses of 10–20 mg, titrated to the desired clinical effect. Administration of propofol infusion (if utilized) may be discontinued prior to completion of the surgery, at the discretion of the investigator/anesthesiologist.

Initiation of propofol sedation will be followed by administration of lidocaine (up to 20 mL of 1% lidocaine without epinephrine) via the Mayo block technique (Worrell and Barbour 1996) to facilitate the necessary regional anesthesia for the bunionectomy procedure. The surgical procedure itself will proceed in accordance with the standard accepted clinical practice and preferences of the surgical team.

Agents for nausea prophylaxis, including 5-HT3 receptor blockers (eg, 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.

5.5.1.2. Study Drug Administration

Before any study drug can be administered, at least 15 minutes must have elapsed after the lidocaine was administered for the Mayo block. The start and stop times of study drug dosing will be recorded in the CRF. Study drug dosing stop time will be considered as 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.

Administration of study drug for the three techniques in this study will be as follows:

Closed wound infiltration (Cohorts A, C, E, F, G, I, K, O, S, X, Y, Z1, Z3, Z5, and Z7):

Following skin closure, and while maintaining a sterile environment, the study drug will be administered in a Mayo Block-type administration in accordance with the guidance provided in the study Pharmacy Manual.

A ring of medication is injected at the proximal aspect of the first interspace, to maximal depth, across the dorsal metatarsal base, and along the medial aspect of the first metatarsal base. An injection is then placed across the plantar metatarsal base, to maximal depth, to complete the ring. A similar ring of study drug is then administered at the level of the first metatarsal phalangeal joint.

Open wound infiltration (Cohorts B, D, H, J, L,N, P, R, T, U, Z2, Z4, Z6, Z8, and Z9):

The study drug will be administered throughout the tissue planes to ensure equal distribution across the surgical field. The medication should form rings of anesthetic around both the proximal and distal aspects of the metatarsal. An appropriate way of doing this is as follows:

- Start proximal to the bony incision and administer half the contents of the 3 mL syringe distally past the bony incision (blue arrows below)

- Repeat the procedure with the rest of the syringe but now start distally and inject proximally (red arrows below)
- Adequate saturation of all exposed tissues in the surgical field will be ensured
- Thereafter, skin closure will commence to complete the surgical procedure.

Local administration via instillation (Cohort M, A1, A2, and A3)

The study drug will be administered throughout the deep tissue planes to ensure equal distribution across the surgical field. The medication should form rings of anesthetic around both the proximal and distal aspects of the metatarsal. Care must be taken to ensure adequate exposure of the proximal and distal ends (ie, beyond the bony incision) of the wound to study drug. To ensure adequate saturation of all exposed tissues in the surgical field, it may be necessary to administer study drug in layers. Thereafter, skin closure will commence to complete the surgical procedure.

5.5.2. Identity of Study Medication

Study drug in this study is defined as the investigational drugs HTX-011 (HTX-011-49 and HTX-011-56), HTX-002, and HTX-009 and the comparator agents bupivacaine hydrochloride 0.5% (Marcaine) and normal saline.

The excipients in the vehicle formulations for HTX-011-49, HTX-011-56, HTX-002, HTX-009 are 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% meloxicam, in 54.275% w/w AP135, 0.15% w/w maleic acid, 8.00% w/w DMSO and 35% w/w glycerol triacetate (or triacetin). HTX-011-49 will be supplied by the Sponsor.

One mL of HTX-011-56 contains 29.25 mg bupivacaine base and 0.88 mg of meloxicam. The proposed drug product contains 2.50% w/w bupivacaine base and 0.075% w/w meloxicam in 62.375% w/w AP135, 0.05% w/w maleic acid, 10.00% w/w DMSO, and 25.00% w/w glycerol triacetate. HTX-011-56 will be supplied by the Sponsor.

One mL of HTX-002 contains 29.25 mg bupivacaine base. The proposed drug product contains 2.50% w/w bupivacaine base in 62.375% w/w AP135, 0.05% w/w maleic acid, 10.00% w/w DMSO, and 25.00% w/w glycerol triacetate. HTX-002-013 will be supplied by the Sponsor.

One mL of HTX-009 contains 0.88 mg of meloxicam. The proposed drug product contains 0.075% w/w meloxicam, in 64.925% (w/w) tri(ethylene glycol) poly(orthoester) (TEG-POE), 10.0% (w/w) dimethyl sulfoxide (DMSO) and 25% glycerol triacetate (w/w).

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

Bupivacaine hydrochloride 0.5% Injection (Marcaine) and normal saline will be procured by the site and sequestered in sufficient quantities to ensure that the batch numbers for both agents will be respectively the same across all subjects studied at the study center.

5.5.2.1. HTX-011 and HTX-002 Dose Calculation

For both HTX-011-49 and HTX-011-56, the content of active ingredients per volume is identical: 4.1 mL = 119.9 mg bupivacaine and 3.59 mg of meloxicam; 6.84 mL HTX-011-49 (or HTX-011-56) = 200.1 mg bupivacaine and 6.0 mg of meloxicam; A lower volume with a corresponding lower dose of bupivacaine may be also administered.

The calculated dose for HTX-002 is such that 6.84 mL HTX-002 = 200.1 mg bupivacaine.

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

5.6. Method of Assigning Subjects to Treatment Groups

A computer generated randomization scheme will be prepared prior to study initiation. Subjects in Cohorts A through F will be randomly assigned to treatment with any one of HTX-011-49, HTX-011-56, bupivacaine (Marcaine), or normal saline in a 1:1:1:1:1:1 assignment. All study doses administered will be according to the original treatment assignment. Subjects in Cohorts G, H, I, and J will be assigned randomly on a 1:1:1:1 basis. Subjects in Cohorts K, L, M, and N will be assigned randomly on a 1:1:1:1 basis. Subjects in Cohorts O, P, and R will be assigned randomly on a 1:1:1 basis. Subjects in Cohorts S, T, and U will be assigned randomly on a 1:1:1 basis and subjects in Cohorts X and Y will be assigned randomly on a 3:1 basis. Subjects in Cohorts Z1, Z2, Z3, and Z4 will be assigned

randomly on a 3:3:1:1 basis. Subjects in Cohorts Z5, Z6, Z7, Z8, and Z9 will be assigned randomly on a 2:2:1:1:1 basis. Subjects in Cohorts A1, A2 and A3 will be assigned randomly on a 3:3:1 basis.

5.7. Selection of Doses

In a placebo-controlled Phase 1 clinical trial, single doses of 100 mg, 200 mg, and 400 mg of HTX-011-19 (another different formulation of the HTX-011 combination of bupivacaine and meloxicam), 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 analgesic 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 because of the subcutaneous administration of the product in this healthy volunteer study.

To further demonstrate analgesic efficacy and to understand better the analgesia effect-time curve of the two HTX-011 formulations, the bupivacaine-only formulation (HTX-002) and the meloxicam-only formulation (HTX-009), this study will evaluate the analgesic effects of multiple formulations of HTX-011, HTX-002, and HTX-009 at doses not to exceed 6.84 mL (200 mg) in subjects following unilateral bunionectomy.

5.8. Blinding and Unblinding of Study Medications

Because HTX-011, HTX-002, and HTX-009 formulations are colored and viscous in contrast to Marcaine and normal saline, 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 the subject has been transferred to the post-anesthesia recovery area, all site staff in the clinical unit involved in the safety and efficacy assessments 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 subject's treatment assignment is 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 leading to the premature unblinding must be clearly documented.

5.9. Treatment Compliance

Because the study medication is being administered as a component of the surgical procedure, a lack of treatment compliance is not expected. The exact date, start and stop

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 completely emptied as part of the study drug infiltration procedure.

5.10. 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 for those subjects formally entered and assigned randomly to a study cohort.

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 as per written instructions from the Sponsor.

5.11. Packaging, Labeling, and Storage

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

5.11.1. Study Drug Packaging

HTX-011, HTX-002, and 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.

5.11.2. Study Drug Labeling and Storage

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-C2016-208)
- 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, HTX-009 formulations at the study site(s) should be stored in a refrigerator at 2–8ºC. The refrigerator should be in a locked area with restricted access. A temperature log or chart should be maintained to monitor the refrigerator at the study site.

5.12. Prior and Concomitant Medications

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

Unless a medication has been prescribed at a stable dose for at least 30 days prior to the scheduled bunionectomy, it will be prohibited for administration before the surgical procedure within five half-lives of that specific medication, or, if half-life is unknown, within 48 hours.

Anti-nausea medication can 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 (NNRS); (2) subject is actively vomiting; (3) subject requests anti-nausea medication.

5.13. Prohibited Medications

The following medications are prohibited throughout the study: corticosteroids (by any means of administration), 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 5.15) are prohibited during the period from T0 to T72, and the prohibited medications include, but are not limited to, 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 medical monitor.

Agents for post-surgical nausea prophylaxis, including 5-HT_3 receptor blockers (eg, ondansetron), scopolamine, dexamethasone, or haloperidol, are prohibited during or upon completion of the surgical procedure.

5.14. 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.

5.15. Analgesia Rescue Medication

Study investigators will review the HTX-011/HTX-002/HTX-009 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. Pain intensity (PI) assessment must be completed prior to administration of any rescue doses administered. 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 (ie, 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 (ie, 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.

6. STUDY PROCEDURES

A schedule of all study procedures is provided in Appendix A.

6.1. Order of Study Procedures

With the exception of demographic data, medical history (including PONV risk), and height and weight measurements at the screening visit, all attempts will be made by assessors to ensure that the order of study procedures performed at any scheduled time will be as follows (where appropriate):

1. Pain Intensity score (Appendix C-1)
2. Patient Global Assessment (PGA) (Appendix C-2)
3. Nausea assessment (Appendix C-4)
4. Vital signs
5. 12-Lead ECG
6. Physical Examination (±30 minutes at 72 hours)
7. Neurologic Exam
8. Blood sample collection for PK and for clinical laboratory assessments
9. Surgical Wound site assessment (Appendix E)
10. Photograph of wound (Appendix F)
11. Adverse events
12. Concomitant medications

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

6.2. Demographic Assessments

6.2.1. Demographics

Demographic information will be collected during screening visit including age, sex, ethnicity, race, weight (also measured at Day 0 and at any early termination from the study), and height.

6.2.2. 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. The review of subject's medical records from their primary care physician will not be required. Medical history will be updated on Day 0 when the subject reports for surgery, and the subject will be interviewed to confirm that (s)he continues to meet the required study inclusion and exclusion criteria.

6.2.3. 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, at Day 10 (including weight), or at early termination from the study.

The study investigator may 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 medical history or condition.

6.3. Efficacy Assessments

At Screening visit each subject will be trained with how to provide pain intensity assessments as determined by the 11 point (0–10) numerical pain rating scale (NPRS). A refresher training will be provided when subject returns to study center on Day 0 prior to surgery.

6.3.1. 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: in a dependent position, and, in an elevated position at rest.

PI scores will be assessed in a dependent position (ie, subject sitting on the bed with the surgically attended foot resting at least partially on the floor) at the following time-points: 4, 6, 8, 10, 12, 14, 18, 24, 30, 36, 42, 48, 54, 60, 72 hours post study drug administration (ie, post-T0).

PI scores will be measured in an *elevated position at rest* at the following time-points: 1, 2, 78, 84, and 96 (±2) hours post-T0. The assessments at 78 and 84 hours will be performed by subjects on an outpatient basis.

All PI assessments scheduled between 24:00 and 06:00 must be collected, even if a subject is asleep at the time of the assessment. A ±15-minute window is allowed for the collection of each PI assessment.

PI will also be assessed within 5 minutes prior to administration of each dose of rescue analgesia, and, at the time of early discontinuation in the event it occurs, and only if the subject is discontinued prior to T96.

6.3.2. Patient Global Assessment (PGA) of Pain Control

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 (±2) hours after study medication administration (ie, T0), and, at the time of early discontinuation if it should occur and only if the subject is discontinued prior to T96.

6.3.3. Analgesia Rescue Medication Usage

All subjects will be monitored for analgesia rescue medication administration/usage beginning at T0 and ending at T96. The medication name, dose, reason, route and time of administration will be recorded in the subject's eCRF. Rescue analgesia (from T0 to T96) will be available to subjects with inadequately controlled pain symptoms. Between T72 and T96, pain medication (if needed) may be prescribed according to the PI's discretion and institutional standard of care. PI assessment must be completed prior to administration of any rescue dose administered from T0 to T72.

Any analgesic medication usage (name, dose, reason, route and time of administration) by the subject will also be recorded at the time of Day 10 visit.

6.4. Safety Assessments

6.4.1. Clinical Laboratory Tests

During the screening visit, on Day 0 during check-in, and at 72 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, tricyclic antidepressant, methylenedioxymethamphetamine, methadone, and oxycodone.

- serum pregnancy testing at the screening visit, and a urine pregnancy test at check-in on Day 0 (female subjects of child bearing potential only).

Screening clinical laboratory results will be used for assessing eligibility for study randomization. Clinical laboratory test data from Day 0 prior to surgery will be used as the "baseline" reference for study analyses and not for assessing study randomization eligibility. Blood samples for baseline clinical laboratory assessments must be collected prior to the first surgical incision.

6.4.2. Nausea Assessment

Nausea will be assessed during the study using an 11-point NNRS (0-10) 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, and, at the time of early discontinuation if it should occur and only if the subject is discontinued prior to T96.

6.4.3. 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 (ie, post-T0), 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, 96 hours, and Day 10, and at the time of early discontinuation from the study. Vital signs will have a collection window of ±15 minutes for 1 through 72 hours and ±2 hours for 96 hours.

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.

6.4.4. 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 (if screening ECG was done > 7 days prior to Day 0), and at the following post-T0 time-points: 24, 48, 72, and 96 (±2) hours, and, at Day 10 and at the time of early discontinuation. Data from the 12-lead ECG will be used to exclude a subject from participation in the study if (s)he has a clinically significant abnormal ECG.

The findings (ie, classification as "normal," "abnormal not clinically significant," or "abnormal clinically significant [including heart block]") will be recorded in the subject's eCRF. A copy of the actual ECG tracings may be collected for Data Management purposes.

6.4.5. Surgical Wound Healing Evaluation and Photographs

The wound evaluator will be a blinded investigator or other medically qualified clinical site person who will assess the surgical site to determine if healing is normal or abnormal at 48 hours, 72 hours, Day 10, and Day 28 or Early Termination, and who will record the observations (Appendix E) on the appropriate eCRF and source document. If the institutional standard post-surgical recovery procedure does not facilitate this assessment to be conducted at 48 and at 72 hours, then is acceptable to forgo this assessment at both these timepoints. Normal expected post-surgical findings include but not limited to wound dry, no dehiscence, no erythema, no drainage, mild bruising, or mild swelling consistent with expected bunionectomy – none of which will be recorded as an AE. However, if a wound is assessed as abnormal with unexpected post-surgical finding(s), then the finding(s) will be recorded as an AE(s).

Photographs of the subject's surgical site will be taken immediately after surgery, 48, 72, and 96 (±2) hours, Day 10, and Day 28 or early termination (Appendix F). In Parts 4, 5, 6, and 7, one of the 3 photos taken at each specific timepoint should be a photo of both feet together.

6.4.6. Neurologic Exam/Assessment

The neurologic examination includes a mental status exam and evaluation of cranial nerve, motor, sensory, and cerebellar function. The potential for bupivacaine toxicity will be assessed during the neurologic exam, and may include (but not necessarily limited to) any of following: perioral tingling, strange taste, muscle twitching, ringing in ears, seizure, bradycardia and cardiac arrest.

Neurologic examinations should be completed by a physician or other health professional qualified to perform such examinations, *and*, if possible, the number of different staff members who perform the neurologic exam for each subject should be limited to as few as possible throughout the study. 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 neurologic exam and assessment will be completed at the following time points: at Day 0 any time prior to anesthesia induction, and at 12, 24, 36, 48, 60, 72, and 96 (± 2) hours post-T0 within a ± 15 minute window. A neurologic exam and assessment will also be completed at early termination from the study if it occurs at ≤ T72.

6.4.7. X-Ray

When subject visits the clinical study center as part of the routine surgical follow-up within 4 to 6 weeks (ie, Day 28 to Day 42 timeframe) of the surgery, an X-ray of the intervention site will be obtained to evaluate the status of the cartilage and bone healing process. A copy of the X-ray and/or the X-ray report will be retained for the Sponsor study files.

A report on the status of the bone healing will be provided by the investigator or in the X-ray report: proper healing or not. If healing is not proper, then provide one of three assessments: mal-union, non-union, improper healing.

6.4.8. Assessment of Adverse Events and Prior/Concomitant Medications

Prior/concomitant medications and AE assessments will be conducted throughout the study conduct after Day 0 until Day 28 post-T0 or at early termination from the study. Serious AEs will be recorded if they occur at any time after securing the informed consent through to Day 28 post-T0. 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 associated with AEs will be documented in the eCRF.

6.4.8.1. 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 anesthesia induction for surgery, and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 36, 48, 60, 72, 96, and at 120 hours after study medication administration (± 15 minutes for all draws from 1 hour through 72 hours and ± 2 hours at 96 and at 120 hours).

6.4.8.2. Bioanalysis of Bupivacaine and Meloxicam

The concentrations of bupivacaine and meloxicam in plasma will be determined by 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.

6.5. Assessments by Visit

6.5.1. Screening Visit

Subjects meeting the eligibility criteria listed in Section 5.1 and Section 5.2 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
- ASA classification (see Appendix D)
- Review of medical history and inclusion/exclusion criteria for study eligibility
- Measurement of resting vital signs

- 12-lead ECG
- Physical examination including height and weight
- Clinical laboratory tests
- Urine drug screen and alcohol breath test
- Serum pregnancy test for women of childbearing potential
- Assessment of PONV risk factors (see Appendix C-3)
- Training on reporting pain intensity assessments
- Record prior and concomitant medications
- Record SAEs after informed consent signature

6.5.2. 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 (if screening ECG was > 7 days prior to Day 0)
- Physical examination, including weight only
- Neurologic Exam
- Clinical laboratory tests
- Urine drug screen and alcohol breath test
- Urine pregnancy test for women of childbearing potential
- Training reminders on reporting pain intensity assessments
- Blood draw for PK analysis of bupivacaine and meloxicam ('baseline' PK sample)
- Record prior and concomitant medications
- Record SAEs
- Photograph of surgical intervention site (immediately after surgery end) (see Appendix F)
- Study drug administration (closed wound/open wound)

Subjects who continue to meet eligibility criteria will undergo primary unilateral bunionectomy. Subjects who don't experience a clinically significant event during surgery (eg, 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.

6.5.3. Day 0 (Treatment) – Day 5

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

- PI assessments (see Appendix C-1)
- PGA for pain control (see Appendix C-2)
- Assessment of NRS for nausea (see Appendix C-4)

- Measurement of resting vital signs
- 12-lead ECG
- Blood samples for PK analysis of bupivacaine and meloxicam
- Physical examination (weight not required at the 72-hour exam)
- Clinical laboratory tests (72-hour only)
- Record AEs/SAEs and concomitant medications
- Monitor and record use of analgesia rescue medication
- Assessment of wound healing (48 and 72 hours, if the institutional standard post-surgical recovery procedure permits this) (see Appendix E)
- Photograph of surgical intervention site (48, 72, and 96 hours, if the institutional standard post-surgical recovery procedure permits this) (see Appendix F)
- Neurologic assessment

One hour after administration of study medication (T1), PI assessments will be completed if the subject is awake and alert.

Rescue analgesia medication will be available to subjects with inadequately controlled pain symptoms during the period from T0 to T72. After T72, subjects may resume standard of care pain medication as advised by their surgeon.

6.5.4. Day 10 ± 2 and Day 28 ± 2 (Follow-Up/End of Study Procedures)

The following end of study procedures will be conducted for all subjects during the Day 10 and/or Day 28 visits.

- Physical examination (Day 10 only)
- Vital signs (Day 10 only)
- 12-Lead ECG (Day 10 only)
- Record analgesic medications usage
- Record AEs/SAEs and concomitant medications
- Assessment of wound healing (see Appendix E)
- Photograph of surgical intervention site (see Appendix F)

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

6.5.5. Day 28 through Day 42 (Routine Surgical Follow-Up Visit)

An X-ray of the surgical intervention area will be performed for all subjects within Day 28 to Day 42 timeframe.

6.5.6. Follow Up Phone Call (Day 60 ± 7)

A follow up phone call will occur at Day 60 ± 7. The following questions will be asked:

- Are you having any pain related to the operation? Yes/No

- 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
- Thinking about the past 24 hours, have you taken any medication(s) to treat pain related to the operation? Yes/No
- If you answered yes to Question 3, what medications (name, dose, and route) have you taken?

6.5.7. Early Termination (ET) Procedures

Subjects who discontinue participation or who are discontinued prior to completing study participation will be asked to complete ET procedures, which will include:

- PI assessment (only if the subject discontinued prior to 96 hours) (see Appendix C-1)
- PGA assessment (only if the subject discontinued prior to 96 hours) (see Appendix C-2)
- Assessment of nausea NRS (see Appendix C-4)
- 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 (see Appendix E)
- Neurologic Assessment (only if the subject discontinued prior to 72 hours)

6.5.8. 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.

6.6. 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.

7. ADVERSE EVENTS (AEs), SERIOUS AEs, 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 (SSAR) 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.

7.1. 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 (eg, abnormal physical examination finding)
- signs, symptoms, or clinical sequelae of a suspected interaction
- signs, symptoms, or clinical sequelae of a suspected overdose of the study 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 (eg, endoscopy, appendectomy), although the condition that leads to the procedure is an AE
- anticipated day to day fluctuations of preexisting disease(s) or condition(s) (including laboratory values) present or detected at the start of the study that do not worsen
- the disease or disorder being studied, or expected progression, signs, or symptoms of the disease or disorder being studied, unless they become more severe or occur with a greater frequency than expected for the subject's condition
- transient paresthesia that 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 study completion or resolution of AE, whichever comes first.

7.2. 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 (ie, 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.

7.2.1. 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 (ie, related to study procedures or a change in existing therapy) will be transcribed onto the SAE reporting form and reported to the sponsor.

7.2.2. 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 30 days after 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 7.7.

7.3. 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.

7.4. Definition of a Serious Suspected Adverse Reaction (SSAR)

A SSAR is any SAR that is determined to be serious, based on the outcomes of a SAE described in Section 7.2; ie, 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.

7.5. 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.

7.5.1. 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 7.1 and Section 7.2).

7.5.2. 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:

- 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.
- Unlikely Related: An SE does not follow a temporal relationship to study drug. The AE can be explained due to study factors.
- 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.

7.5.3. 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

7.6. 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 7.7.

7.7. 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 S. Gordon, MD, MBA
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 for notification of 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.

7.8. Regulatory Reporting Requirements

The investigator must promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 7.7, "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 SSARs 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 SAR 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.

7.9. 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 7.7 for contact information).

8. STATISTICAL METHODOLOGY

8.1. Determination of Sample Size

The sample size up to 430 subjects in this study was selected empirically without a formal statistical assumption. This study comprises up to 34 cohorts. Subjects will receive HTX-011-49, HTX-011-56, HTX-002, HTX-009, or normal saline via three different administration techniques or Marcaine. The primary efficacy endpoint for this study is the summed pain intensity scores over the first 24 hours (SPI_{0-24}). The primary analysis will be via an Analysis of Variance with contrasts to test for differences between the cohorts and for differences between linear combinations of the cohorts.

8.2. Study Endpoints

See Section 3 for the efficacy, safety, and PK endpoints.

8.3. General Considerations for Statistical Analysis

8.3.1. Software and General Statistical Methods

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher) for Windows. If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

For continuous variables, summary statistics including number of subjects with data, mean, standard deviation (SD), median, minimum, and maximum will be provided. For categorical variables, the number of subjects and percentage for each category will be presented.

8.3.2. Analysis Datasets

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

Efficacy Set: The efficacy analysis set will include all subjects who are assigned randomly to receive study medication and who have recorded at least one PI score post study drug administration. This analysis set is identified 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.

8.3.3. Test Hypothesis and *P* Value Justification

This is a study designed to look at differences between the pairs of treatments or pooled treatments and linear combinations of the treatments or pooled treatments. The null hypothesis for each comparison made in this study is that there is no difference between the

groups being compared. The alternative hypothesis is that the treatment groups being compared are different.

The primary analysis will be via an Analysis of Variance with pre-defined contrasts for all the comparisons. The comparisons will be made using 2-sided test at the 0.05 level of significance. Nominal p-value will be reported without adjustment for multiplicity.

8.3.4. Procedures for Handling Missing Data

Unless indicated otherwise (see Section 8.3.4.1 and 8.3.4.2), no imputation will be done for missing data.

8.3.4.1. 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 (eg, the analgesic window for one oxycodone 10 mg oral 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.

8.3.4.2. 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, then 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.

8.3.5. Derived Variables

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

8.3.5.1. Study Population Summaries

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

8.3.6. 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.

8.3.7. Demographics

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

8.3.8. Protocol Violations

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

8.3.9. Treatment Compliance

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

8.3.10. 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 01 June 2015.

8.4. Efficacy Analysis

8.4.1. SPI and PI Analyses

The analyses of the primary and all secondary endpoints will be described in the statistical analysis plan. This basic analysis will be an Analysis of Variance with contrasts to test for differences between the cohorts.

8.4.2. 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.

8.4.3. Patient Global Assessment (PGA) of Pain Control

Number and percentage 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.

8.4.4. Proportion of Subjects Requiring Rescue Medication

The analysis will evaluate the relative risk between the treatment groups to require rescue medications during the treatment phase of the study. Proportion of subjects who used rescue medications at least once will be tabulated by treatment group; difference between the cohorts will be assessed as described in the statistical analysis plan.

8.4.5. 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.

8.4.6. 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. All Adverse Events will be reviewed by the medical monitor, and opioid related AE(s) will be identified and summarized.

8.4.7. Subgroup Analyses for Efficacy

No subgroup analysis for efficacy endpoints is planned.

8.5. Safety and Tolerability Evaluations

8.5.1. 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.

8.5.2. Clinical Laboratory Tests

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

8.5.3. Vital Sign Measurements

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

8.5.4. Electrocardiograms

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

8.5.5. Subgroup Analyses for Safety Endpoints

No subgroup analysis is planned for safety endpoints.

8.6. Interim Evaluation

An interim analysis is planned after Part 1 completes the T72 evaluation to support formulation and technique decisions. An interim analysis will also be conducted after Part 2 completes the T72 evaluation to support fixed combination dosing decisions, and a third interim analysis will be conducted after Part 3 completes the T72 evaluation to support dose ranging decisions and inform design of potential future studies looking at the contribution of the individual components.

9. STUDY ADMINISTRATION

9.1. Regulatory and Ethical Considerations

9.1.1. 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.

9.1.2. 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).

9.1.2.1. 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 (eg, 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.

9.1.2.2. 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-C2016-208. 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-002.

9.1.3. 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.

9.1.4. 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.

9.2. 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.

9.3. 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.

9.4. 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 (eg, 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

9.5. Records Retention

9.5.1. 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.

9.5.2. Financial Disclosure

Financial disclosure is required for this study.

9.5.3. 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 9.1.4) 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.

9.5.4. 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.

9.6. 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.

9.7. Information Disclosure and Inventions

9.7.1. 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.

9.7.2. 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 9.7.3. 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.

9.7.3. 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 9.7.1.

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.

9.7.4. 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.

9.7.5. Data Security

Access to the data will be strictly controlled.

9.8. 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.

10. REFERENCES

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11. APPENDICES

Appendix A: OVERVIEW OF STUDY SCHEDULE

Appendix A Table 1: Screening

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

[a] Results will determine subject eligibility for the study.
[b] Resting vital signs: blood pressure, pulse, respiration rate, oral temperature and SpO_2. Resting tests must be obtained after resting (seated/reclined) for ≥ 5 minutes
[c] Concomitant medications taken within 30 days before dosing will be recorded on the eCRF.
[d] SAEs will be reported if considered related to study participation.

Appendix A: OVERVIEW OF STUDY PROCEDURES

Appendix A Table 2: Day 0 Prior To Surgery and Surgery

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

[a] Used as 'baseline' reference, and not for determining subject eligibility.
[b] Resting vital signs: blood pressure, resting pulse, respiration rate, oral temperature and SpO_2. Resting tests must be obtained after resting (seated/reclined) for ≥ 5 minutes.
[c] Physical examination will include weight only but not height.
[d] Blood samples must be collected prior to first surgical incision.
[e] If screening 12-lead ECG was done > 7 days prior to Day 0.
[f] Immediately after surgery ends.
[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 PROCEDURES

Appendix A Table 3: Post Study Medication Administration

	Day 0 to 5																									Early Termination Assessments
	Post Study Drug Administration Time Points (hours)																									
	0.5	1	1.5	2	2.5	3	4	5	6	8, 10, 12	14	18	24	30	36	42	48	54	60	72	78	84	96[h]	120	Days 10 and 28 (± 2)	Days 60 (± 7)	
Subject confined at the study center	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							X
Physical Examination[c]																				X[g]					X (Day 10)		X
Clinical Laboratory Tests[a]																				X							X
Vital Signs (±15 min window)[b]		X		X			X		X	X (12h only)		X	X		X		X		X	X			X		X (Day 10)		X
12-lead ECG													X				X			X			X		X (Day 10)		X
Pain Intensity (±15 min window) *in a dependent position*							X		X	X	X	X	X	X	X	X	X	X	X	X							X[i]
Pain Intensity (±15 min window) in an elevated position *at rest*		X[f]		X																	X	X	X				X[i]
PGA of Pain Control													X				X			X			X				X[i]
Use of Rescue Medication	X	X[f]	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 Samples (±15 min window)	X[j]	X	X	X	X	X	X	X	X	X		X	X	X	X		X		X	X			X	X[h]			
Numerical Rating Scale for Nausea (±15 min window)									X				X				X			X							X[i]
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		X		X
Assessment of Wound Healing																	X[n]			X[n]					X		X
Photograph of foot undergoing surgery																	X[m]			X[m]			X[m]		X		X
Neurologic Assessment (±15 min window)										X (12h only)			X		X		X		X	X			X				X[k]
X-ray (surgical intervention site)																									X[l] (D28-42)		
Phone Call																										X	
Adverse Event 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		X		X

[a] Laboratory tests will include hematology and chemistry.
[b] Resting vital signs: blood pressure, pulse, respiration rate, oral temperature and SpO_2. Resting tests must be obtained after resting (seated/supine) for ≥ 5 minutes.
[c] Physical examination will include weight only, but not height. Weight not required at 72 hour exam.
[d] AEs will be monitored after administration of study medication through completion of the study or resolution of AE, whichever comes first.. SAEs will be monitored through Day 28 post-treatment. Toxicities thought to be associated with bupivacaine will be reported as AEs.
[e] Subjects may resume standard of care pain medication as advised by their surgeon after the T96 study visit.
[f] 1 hour assessments to be completed if subject is awake and alert.
[g] ±30 minutes window
[h] ±2 hours window
[i] assessed only if early termination for subject is prior to T96
[j] 15-minute window for sample collection not applicable to this timepoint
[k] assessed only if early termination for subject is prior to T72
[l] Day 28 to Day 42 timeframe, as part of the routine surgical follow-up.
[m] If the institutional standard post-surgical recovery procedure does not warrant removal of the bandage at the specified timepoint, then it is acceptable to forgo the photograph at that visit.
[n] If the institutional standard post-surgical recovery procedure does not facilitate this assessment to be conducted at 48 and at 72 hours, then is acceptable to forgo this assessment at both these timepoints.

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 (eg, 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 Section 7.7 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 (ie, 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

Check one Time-point:

☐ 24 Hours ☐ 48 Hours ☐ 72 Hours ☐ 96 Hours

☐ Early Termination

Assessment Not Done ☐

"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
- Nonsmoking status
- Female gender
- Expected to receive opioid analgesia postoperatively

Appendix C-4: Nausea Numerical Rating Scale

Check one Time-point:

☐ 6 Hours ☐ 24 Hours ☐ 48 Hours ☐ 72 Hours

☐ Early Termination

Assessment Not Done ☐

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: AMERICAN SOCIETY OF ANESTHESIOLOGISTS PHYSICAL STATUS CLASSIFICATION SYSTEM

I Normal healthy patient

II Patient with mild systemic disease; no functional limitation – eg, smoker with well-controlled hypertension

III Patient with severe systemic disease; definite functional impairment – eg, diabetes and angina with relatively stable disease, but requiring therapy

IV Patient with severe systemic disease that is a constant threat to life – eg, diabetes and angina and congestive heart failure; patients with dyspnea on mild exertion and chest pain

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

VI Brain dead patient 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 E: WOUND SITE EVALUATION

Time-point: ☐ 48 Hours ☐ 72 Hours ☐ Day 10 (±2 days) ☐ Day 28 (±2 days)

WOUND SITE EVALUATION NOT DONE ☐ ☐ Early Termination

	Normal (Expected Post-Surgical Findings)	***Abnormal**	***Abnormal findings are to be recorded as Adverse Events on the CRF** If observations are of mild severity, then they should **not** be recorded on the CRF as Adverse Events. Please describe below any other wound abnormalities that are not listed in boxes below.
Wound Site	☐	☐	
Other, *specify in the boxes below*	☐	☐	

Wound Description	**Normal**	***Abnormal**	**Not present**
Wet	☐	☐	☐
Dehiscence	☐	☐	☐
Erythema	☐	☐	☐
Drainage ☐ **Blood** ☐ **Serous** ☐ **Purulent** ☐ **Other (specify)** _____	☐	☐	☐
Bruising	☐	☐	☐
Swelling	☐	☐	☐

Investigator's Signature Date

Appendix F: PHOTOGRAPHY INSTRUCTIONS OF THE SURGICAL FOOT MATERIALS

- Camera (specify type and model).
- Identify camera settings
- Memory card
- Background cloth
- ID tag: Complete for **Protocol#, Subject #, Study Hour or Day, Date, Time and what is being photographed (ie, left foot)**
- 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. Place the subject's memory card in the camera.
3. Expose the foot to be photographed and place the background cloth under the area to be photographed.
4. Remove any dressing and place the completed ID tag adjacent to the area to be photographed, taking care not to obscure any area of the wound itself to be photographed.
5. Apply the adhesive backed ruler decal in an area of the foot, not obscuring the wound area itself.
6. Between the information entered on the ID tag and the ruler decal, ensure that **Protocol #, Subject #, Study Hour or Day, Date, Time and what is being photographed (ie, left foot)** is documented for reference purposes in the photograph.
7. At each photograph timepoint, take 3 photographs with the camera looking down at the surgical foot and 3 photographs with a lateral view of the surgical foot, 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.

Signature Manifest

Document Number: PRT-0035 **Revision:** 07

Title: A Phase 2, Randomized, Controlled, Multicenter, Evaluation of the Efficacy and Safety of Locally Administered HTX-011 for Postoperative Analgesia Following Bunionectomy (PRT-0035)

All dates and times are in Pacific Standard Time .

PRT-0035 V7

Document Approval

Name/Signature	Title	Date	Meaning/Reason
[redacted]	VP, Clinical Operations	24 Jan 2017, 10:37:44 AM	Approved

Final Approval

Name/Signature	Title	Date	Meaning/Reason
[redacted]	V.P. Clinical Research	24 Jan 2017, 01:13:09 PM	Approved