Document Type:	Study Protocol
Official Title:	A Phase 3, Randomized, Double-Blind, Saline Placebo- and Active Controlled, Multicenter Study of HTX-011 via Local Administration for Postoperative Analgesia and Decreased Opioid Use Following Unilateral Simple Bunionectomy
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CLINICAL STUDY PROTOCOL: HTX-011-301

Protocol Title:	A Phase 3, Randomized, Double-Blind, Saline Placebo- and Active-Controlled, Multicenter Study of HTX-011 via Local Administration for Postoperative Analgesia and Decreased Opioid Use Following Unilateral Simple Bunionectomy
Brief Title:	Phase 3 bunionectomy study for postoperative analgesia (EPOCH 1)
Investigational Product:	HTX-011 (bupivacaine and meloxicam extended-release solution) 2.5%/0.075%
Phase of Development:	3
EudraCT number:	2017-001637-81
Sponsor:	Heron Therapeutics, Inc. 4242 Campus Point Court, Suite 200 San Diego, CA 92121 1-858-251-4400
Medical Monitors:	Primary: [redacted] Secondary: [redacted]
Medical Project Leader:	[redacted]
Protocol Version:	Version 3 — 24 September 2017 Version 2 — 29 June 2017 Version 1 — 21 April 2017

INVESTIGATOR AGREEMENT

CLINICAL STUDY PROTOCOL: HTX-011-301

TITLE: A Phase 3, Randomized, Double-Blind, Saline Placebo- and Active-Controlled, Multicenter Study of HTX-011 via Local Administration for Postoperative Analgesia and Decreased Opioid Use Following Unilateral Simple 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 herein.

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

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

Principal Investigator: _____

Address: _____

Signature: _____

Date: _____

PROTOCOL SYNOPSIS

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Name of Active Ingredients: bupivacaine and meloxicam	**Phase of Development:** 3

Study Objectives:

Primary Objective:

- To compare the efficacy and duration of analgesia following local administration of HTX-011 with that of saline placebo during the first 72 hours following unilateral simple bunionectomy.

Secondary Objectives:

- To compare the efficacy and duration of analgesia for HTX-011 with bupivacaine HCl without epinephrine during the first 72 hours following surgery in this study population.
- To compare the effect of HTX-011 with saline placebo and bupivacaine HCl without epinephrine on opioid load during the first 72 hours following surgery in this study population.
- To assess the safety and tolerability of HTX-011 in this study population.
- To further establish the pharmacokinetic (PK) parameters of bupivacaine and meloxicam in HTX-011 in this study population.

Methodology: This is a Phase 3, randomized, double-blind, saline placebo- and active-controlled, multicenter study in subjects undergoing unilateral simple bunionectomy.

Subjects will be screened within 28 days prior to surgery. Subjects who meet the Screening eligibility criteria will be randomized. Randomization may be done up to 1 business day prior to surgery. On the day of surgery (Day 1), subjects who continue to meet the eligibility criteria will undergo a unilateral simple bunionectomy under regional anesthesia with no more than 20 mL of 1% lidocaine without epinephrine administered as a Mayo block. Epidural or spinal anesthesia is not permitted. During surgery, the use of intravenous (IV) fentanyl up to 4 μg/kg will be permitted for intraoperative pain control. Intraoperative administration of other opioids or any other analgesics (including ketamine), local anesthetics, or anti-inflammatory agents (except as specified by the protocol) is prohibited, unless needed to treat an adverse event (AE) that occurs after signing the Informed Consent Form (ICF), for pretreatment prior to a needle placement, or to decrease venous irritation (eg, caused by propofol, in which case no more than a single administration of lidocaine 1% 20 mg IV may be administered).

Near the completion of surgery and after irrigation and suction have been completed, a single dose of study drug (HTX-011, saline placebo, or bupivacaine HCl without epinephrine) will be given intraoperatively via local administration into the surgical site.

Following surgery and immediate postoperative recovery, subjects will be transferred to the postanesthesia care unit (PACU). Subjects will remain in the hospital/research facility for a minimum of 72 hours after the start of study drug administration to undergo postoperative assessments. After the 72-hour assessments have been completed, subjects may be discharged. Subjects will return to the study

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site on Days 10 and 28 to complete follow-up assessments. In addition, subjects will return for a Safety Follow-Up on Day 42.

Treatment Groups

Approximately 400 subjects will be randomized to 1 of the following 3 treatment groups in a 3:3:2 ratio:

- HTX-011, 60 mg/1.8 mg (bupivacaine/meloxicam doses), 2.1 mL, via instillation into the surgical site (150 subjects)
- Bupivacaine HCl without epinephrine 0.5%, 50 mg (10 mL), via injection into the surgical site (150 subjects)
- Saline placebo, 2.1 mL, via instillation into the surgical site (100 subjects)

Blinding

The study will use a double-blind design. The site's pharmacy staff and surgical staff will not be blinded to the treatment assignments because HTX-011 is a colored and viscous liquid whereas saline placebo and bupivacaine HCl are not, and the volume of study drug to be administered varies by treatment group. However, subjects will not be aware of the study drug they are receiving, and once surgery is complete and the subject is transferred to the PACU, the assessor and all staff involved in efficacy and safety assessments will be blinded to treatment assignments until after database lock.

Postoperative Rescue Medications

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

Postoperative rescue medication will consist of oral (PO) immediate-release oxycodone (no more than 10 mg within a 4-hour period as needed), IV morphine (no more than 10 mg within a 2-hour period as needed), and/or oral acetaminophen (no more than 1 gram [1000 mg] in a 6-hour window). For subjects administered any acetaminophen-containing product, the total combined daily dose must not exceed 4 grams (4000 mg) as severe liver damage may occur. No other analgesic agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), are permitted during the 72-hour postoperative observation period.

Subjects who are not medically ready for discharge at 72 hours may receive the same rescue medication as above to treat postoperative pain until discharge.

For subjects who are medically ready for discharge at 72 hours, oral acetaminophen (no more than 1000 mg every 6 hours as needed) should be recommended for postoperative pain. If a subject received 10 mg or more of oxycodone in the 12 hours prior to discharge, the subject should be provided with a prescription for oxycodone (up to 10 mg PO q4h as needed). Subjects will complete a daily diary to record if they take an opioid medication between 72 hours and Day 28.

Number of Planned Subjects: Approximately 400 subjects will be randomized and dosed.

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Study Sites: Up to approximately 25 sites.	

Study Population:

Inclusion Criteria

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

1. Is able to provide written informed consent, adhere to the study visit schedule, and complete all study assessments.
2. Is male or female, and ≥18 years of age at screening.
3. Is scheduled to undergo a primary unilateral, distal, first metatarsal bunionectomy with osteotomy and internal fixation under regional anesthesia.
4. Has an American Society of Anesthesiologists Physical Status of I, II, or III.
5. Female subjects are eligible only if all of the following apply:
    a. Not pregnant (female subjects of child-bearing potential must have a negative urine pregnancy test at screening and on Day 1 before surgery).
    b. Not lactating.
    c. Not planning to become pregnant during the study.
    d. Is surgically sterile; or is at least 2 years post-menopausal; or is in a monogamous relationship with a partner who is surgically sterile; or is practicing abstinence or agrees to use double-barrier contraception in the event of sexual activity; or is using an insertable, injectable, transdermal, or combination oral contraceptive approved by applicable regulatory authorities for greater than 2 months prior to screening and commits to the use of an acceptable form of birth control for the duration of the study and for 30 days after study drug administration. Note: women in only a same-sex relationship do not need to meet this criterion.

Exclusion Criteria

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

1. Has had a contralateral foot bunionectomy in the past 3 months.
2. Has a planned concurrent surgical procedure (eg, bilateral bunionectomy or collateral procedures on the surgical foot).
3. Has a pre-existing concurrent acute or chronic painful physical/restrictive condition expected to require analgesic treatment in the postoperative period for pain that is not strictly related to the bunionectomy and which may confound the postoperative assessments.
4. Has a contraindication or a known or suspected history of hypersensitivity or clinically significant idiosyncratic reaction to bupivacaine (or other local anesthetics), meloxicam (or other NSAIDs), oxycodone, morphine, or acetaminophen.

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5. Has known or suspected daily use of opioids for 7 or more consecutive days within the previous 6 months.
6. Has taken any NSAIDs (including meloxicam) within at least 10 days prior to the scheduled surgery with the exception of subjects on low-dose (≤100 mg) daily acetylsalicylic acid for cardioprotection.
7. Has taken long-acting opioids within 3 days prior to the scheduled surgery.
8. Has taken any opioids within 24 hours prior to the scheduled surgery.
9. Has been administered bupivacaine within 5 days prior to the scheduled surgery.
10. Has been administered any local anesthetic within 72 hours prior to the scheduled surgery, other than for pretreatment prior to a needle placement, to treat an AE that occurs after signing the ICF, or to decrease venous irritation (eg, caused by propofol, in which case no more than a single administration of lidocaine 1% 20 mg IV may be administered).
11. Has initiated treatment with any of the following medications within 1 month prior to study drug administration or is taking any of these medications to control pain: selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin, or cyclooxygenase-2 (COX-2) inhibitors. (Note: If a subject is taking one of these medications for a reason other than pain control, the subject must be on a stable scheduled dose [ie, not "as needed"] for at least 1 month prior to study drug administration.) Anxiolytics prior to surgery are permitted, if necessary.
12. Has been administered systemic steroids within 5 half-lives or 10 days prior to administration of study drug (whichever is longer).
13. Has a medical condition such that, in the opinion of the Investigator, participating in the study would pose a health risk to the subject or confound the postoperative assessments. Conditions may include, but are not limited to, any of the following:
    a. History of clinically significant cardiac abnormality such as myocardial infarction within 6 months prior to signing the ICF, New York Heart Association class III or IV, or clinically significant abnormalities in cardiac function or on electrocardiogram (ECG; including but not limited to a PR interval >200 msec, a QT corrected by Fridericia's formula [QTcF] >480 msec, or 3rd degree heart block).
    b. History of coronary artery bypass graft surgery within 12 months prior to signing the ICF.
    c. History of severe liver function impairment as defined by Child-Pugh Class C, having an aspartate aminotransferase >3 × the upper limit of normal (ULN), or having an alanine aminotransferase >3 × ULN.
    d. History of severe kidney function impairment as defined by creatinine clearance (Cockcroft-Gault) <30 mL/min, being on dialysis, and/or having a serum creatinine

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>2 × ULN.

e. History of known or suspected coagulopathy or uncontrolled anticoagulation.
f. Loss of sensation in extremities or significant peripheral neuropathy.

14. As per subject history and/or medical records, has active infection or is currently undergoing treatment for Hepatitis B, Hepatitis C, or human immunodeficiency virus (HIV).
15. Has uncontrolled anxiety, psychiatric, or neurological disorder that, in the opinion of the Investigator, might interfere with study assessments.
16. Had a malignancy in the last year, with the exception of nonmetastatic basal cell or squamous cell carcinoma of the skin or localized carcinoma in situ of the cervix.
17. Has a known or suspected history of drug abuse, a positive drug screen on the day of surgery, or a recent history of alcohol abuse. Note: Subjects with a positive drug screen who are taking an allowed, prescribed medication that is known to result in a positive drug test (eg, amphetamine and dextroamphetamine for attention-deficit/hyperactivity disorder, benzodiazepine for anxiety disorder) may be eligible for participation in the study. Subjects taking medical marijuana are not allowed to participate in the study.
18. Previously participated in an HTX-011 study.
19. Received an investigational product or device in a clinical trial within 30 days or within 5 elimination half-lives (whichever is longer) prior to surgery, or is planning to take part in another clinical trial while participating in this study.
20. Has undergone 3 or more surgeries within 12 months prior to signing the ICF, other than for diagnostic procedures (eg, colonoscopy).
21. Has a body mass index (BMI) >39 kg/m^2.

Investigational Product, Dose, and Mode of Administration:

HTX-011 is an extended-release, fixed-ratio combination product that contains bupivacaine (a long-acting, immediate-release local anesthetic as the free base) and low-dose meloxicam (an NSAID) incorporated in a proprietary bioerodible polymer (termed Biochronomer®). HTX-011 will be supplied by the Sponsor as a sterile, viscous liquid in 10 mL or 20 mL clear glass vials.

A single dose of HTX-011 60 mg/1.8 mg (bupivacaine/meloxicam doses) will be administered via instillation into the surgical site using a Luer-lock applicator. The Luer-lock applicator will also be supplied by the Sponsor.

Reference Therapy, Dose, and Mode of Administration:

A single dose of saline placebo (0.9% sodium chloride solution) or bupivacaine HCl without epinephrine 0.5% (50 mg) will be administered into the surgical site. Saline placebo will be administered by instillation using the same method as for HTX-011. Bupivacaine HCl will be administered via injection

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evenly throughout the tissue planes to ensure equal distribution across the surgical field. Saline placebo and bupivacaine HCl will be supplied by the Sponsor.	
Duration of Treatment: Subjects will receive a single dose of study drug. The total duration of study participation for each subject (from Screening through the Safety Follow-Up on Day 42) will be up to 77 days. The overall duration of the study is anticipated to be approximately 7 months.	
Criteria for Evaluation: Efficacy, safety, and PK assessments will be performed. The start of study drug administration will be considered as Time 0 for all efficacy, safety, and PK timepoints. <u>Efficacy Assessments:</u> • Pain intensity scores using NRS-R and NRS-A at 1, 2, 4, 8, 12, 24, 36, 48, 60, 72 hours, and on Day 10 and Day 28. – NRS-R: Subjects should be seated/recumbent with the surgically attended leg elevated or lying supine. Measurements should be obtained after the subject is in the resting position for at least 5 minutes. – NRS-A: Subjects should be seated with the plantar surface of the ball of the surgically attended foot touching the floor (no weight-bearing). • Date, time of administration, and amount of all opioid rescue medication taken through 72 hours. • Subject daily diary to record if any opioids were taken from 72 hours through Day 28. • Discharge readiness assessment per the Modified Postanaesthetic Discharge Scoring System (MPADSS) criteria at 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours. (Note: This study instrument assesses a subject's potential readiness to be discharged and should be repeated at all scheduled timepoints. It is not meant to be used to decide on whether or not to discharge a subject from the study, as subjects are required to remain in the hospital/research facility for at least 72 hours.) • Patient Global Assessment (PGA) of pain control at 24, 48, and 72 hours and on Day 28. <u>Safety Assessments:</u> • AEs from the time the subject signs the ICF through the Safety Follow-Up on Day 42. • Local Anesthetic Systemic Toxicity (LAST) assessments at 30 minutes (±5 min), 1 hour (±5 min), 2 hours (±15 min), 4 hours (±15 min), 18 hours (±30 min), 24 hours (±1 h), and 72 hours (±4 h). If symptoms are present at 30 minutes, 1 hour, or 2 hours, an unscheduled blood sample will be collected for PK and a 12-lead ECG will be performed. If symptoms are present at 72 hours, an unscheduled blood sample will be collected for PK. • Clinical safety laboratory tests (hematology and serum chemistry) at the Screening Visit, at	

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24 hours (hematology only), at 72 hours, and on Day 10.

- Physical examination at Screening Visit and 72 hours; the Screening Visit will also include height, weight, and BMI calculation.
- Wound healing assessment at 72 hours, on Day 10 and Day 28, and at the Safety Follow-Up on Day 42.
- X-ray for bone healing assessment on Day 28 and at the Safety Follow-Up on Day 42.
- Vital signs (resting heart rate, blood pressure, respiration rate, and body temperature) at the Screening Visit, on Day 1 before surgery, and post-treatment at 30 minutes and at 1, 1.5, 2, 4, 8, 12, 18, 24, 36, 48, 60, and 72 hours.
- ECG at the Screening Visit and at 4, 18, 24, 48, and 72 hours.

PK Assessments:

- Blood samples for bupivacaine and meloxicam PK analysis will be collected at 4, 18, 24, and 48 hours post-treatment. (Note: when PK and NRS pain intensity assessments coincide, the NRS pain intensity assessments should be conducted before the blood draw.)

Study Endpoints:

Primary Efficacy Endpoint:

- Mean area under the curve (AUC) of the Numeric Rating Scale of pain intensity scores with activity (NRS-A) through 72 hours (AUC_{0-72}) for HTX-011 compared with saline placebo.

Key Secondary Efficacy Endpoints (Hierarchical Testing):

1. Mean AUC_{0-72} of the NRS-A pain intensity scores for HTX-011 compared with bupivacaine HCl.
2. Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with saline placebo.
3. Proportion of subjects who are opioid-free through 72 hours for HTX-011 compared with bupivacaine HCl.
4. Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with bupivacaine HCl.

[redacted]

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- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Safety Endpoints

- Incidence of treatment-emergent AEs (TEAEs), serious TEAEs (SAEs), and opioid-related AEs (ORAEs) through the Safety Follow-Up on Day 42.
- Change from baseline in clinical laboratory results.
- Change from baseline in ECG data.
- Change from baseline in vital signs.
- Wound healing assessment at 72 hours, on Day 10 and Day 28, and at the Safety Follow-Up on Day 42.
- Bone healing assessment on Day 28 and at the Safety Follow-Up on Day 42.

PK Endpoints

- Calculated maximum plasma concentration (C_{max}).
- Calculated time to reach maximum plasma concentration (T_{max}).

Statistical Methods:

Efficacy Analyses

The primary estimand to address the efficacy objectives is the mean AUC of NRS-A pain intensity scores through 72 hours (AUC_{0-72}) adjusted for use of opioid rescue medication via windowed worst observation carried forward (wWOCF), comparing the estimated treatment difference between HTX-011 and saline placebo using analysis of variance (ANOVA) with missing data imputed via last observation carried forward (LOCF) for interval censored pain intensity scores and worst observation carried forward (WOCF) for right-censored pain intensity scores in the Intent-to-Treat Population.

The primary analysis of AUC_{0-72} of the NRS-A pain intensity scores will be carried out using an ANOVA model with treatment as the main effect, comparing HTX-011 with saline placebo at a significance level of 5%. Results will be expressed as mean AUCs and SDs, least-squares mean differences and SEs with associated 95% CIs, and p-values. To account for the duration effect of opioid rescue medication, the

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wWOCF method will be implemented as the primary analysis method for endpoints involving NRS pain intensity scores. In this method, pain intensity scores observed during the analgesic window (duration of effect) of any opioid rescue medication will be replaced with the worst (highest) postdose nonmissing NRS pain intensity score observed prior to the rescue medication window, with the following exception: if the NRS pain intensity score for a windowed observation is higher than the worst pre-window score, then it will not be replaced. Sensitivity analyses for endpoints involving NRS pain intensity scores will analyze the data without adjustment for the effect of opioid rescue medications.

To account for multiple hypothesis testing on the primary endpoint and on each of the 4 key secondary endpoints, a strict testing hierarchy will be applied to control study-wise alpha level at 0.05. If the primary endpoint is statistically significant ($p \leq 0.05$), then the first key secondary endpoint will be tested. If the first key secondary endpoint is statistically significant, then the second key secondary endpoint will be tested. Sequential testing will continue in this manner down the key secondary endpoint list until an endpoint fails to meet statistical significance, after which all subsequent key secondary endpoints will be considered exploratory. If the primary endpoint is not statistically significant, then all key secondary endpoints will be considered exploratory.

Continuous endpoints will be analyzed using an ANOVA model with treatment as the main effect. Results will be expressed as means and SDs, least-squares mean differences and SEs with associated 95% CIs, and p-values.

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

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

Handling of Missing Data

Due to the required 72-hour inpatient postoperative observation period, the amount of missing data is expected to be very low. For any missing data observed through 72 hours in subjects who complete the 72-hour postoperative observation period, NRS pain intensity scores will be imputed via LOCF, in which the most recent postdose value is used for a subsequent missing value. For subjects who do not have a postdose value prior to their first missing value, the median of the postdose values at the relevant timepoint from subjects with observed data in the same randomized treatment group will be used. Predose values will not be carried forward to postdose timepoints. In subjects who withdraw from the study prior to 72 hours, missing NRS pain intensity scores through 72 hours that were to be collected following withdrawal will be imputed via WOCF, in which the worst (highest) NRS pain intensity score observed prior to withdrawal will be used for post-withdrawal values through 72 hours. Analyses that adjust for the effect of opioid rescue medication will perform wWOCF following LOCF/WOCF (ie, perform LOCF/WOCF first, then apply wWOCF). The number and percentage of missing NRS pain intensity scores will be summarized.

Safety Analyses

All safety data will be listed and summarized by treatment group; no statistical hypothesis testing will be

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performed. All TEAEs will be coded and tabulated by System Organ Class and Preferred Term. Incidence of TEAEs, SAEs, and ORAEs will be summarized and presented in descending order of frequency according to the HTX-011 group. Associated laboratory parameters such as hepatic profile, renal function, and hematology values will be grouped and presented together in summary tables. Individual subject values will be listed and values outside of the standard reference range will be flagged. Changes in vital sign parameters and ECG results will be summarized. Wound healing assessment and bone healing assessment results will be summarized.

Determination of Sample Size

Based on a previous Phase 2 study of HTX-011 in subjects undergoing unilateral simple bunionectomy, estimates of the relevant parameters for each of the primary and key secondary endpoints are as follows:

Parameter	**Saline Placebo**	**Bupivacaine HCl**	**HTX-011 60 mg/1.8 mg**
Pain intensity $AUC_{0\text{-}72}$: Mean (SD)	425 (175)	425 (175)	325 (175)
Opioid consumption (mg): Mean (SD)	30 (25)	30 (25)	20 (20)
Proportion of opioid-free subjects	5%	10%	25%

Assuming these estimates and using Satterthwaite's t-test with $\alpha = 0.05$, 2-sided for the continuous endpoints and Fisher's exact test with $\alpha = 0.05$, 2-sided for the categorical endpoints, 150 subjects in the HTX-011 group, 150 subjects in the bupivacaine HCl active control group, and 100 subjects in the saline placebo control group provide at least 90% power to detect a statistically significant difference between the HTX-011 group and each of the control groups for each of the primary and key secondary endpoints.

SCHEDULE OF EVENTS

Assessments	Time Window	Screening ≤28 days	Screening ≤1 day	Preop	OR	Time After Study Drug Administration* D1 30 min ±5 min	D1 1h ±5 min	D1 1.5 h ±10 min	D1 2h ±15 min	D1 4h ±15 min	D1 8h ±30 min	D1 12h ±30 min	D1 18h ±30 min	D1 24h ±1h	D2 36h ±2h	D2 48h ±2h	D3 60h ±4h	D3 72h ±4h	D10 ±3d	D28 ±4d	F/Up D42 ±7d	ET[a]
Obtain informed consent		X																				
Urine drug screen[b]		X		X																		
Urine pregnancy test (WOCBP only)[b]		X		X																		
Assess/confirm eligibility		X		X																		
Medical history		X																				
Demographics		X																				
Physical examination		X[c]																X				X[d]
Vital signs[e]		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X				X[d]
12-lead ECG (triplicate)[e]		X								X			X	X		X		X				X[d]
Subject training for pain assessments		X		X																		
Randomize subject[f]			X																			
Hematology and serum chemistry tests		X												X[g]				X	X			X[d]
Surgery[h]					X																	
Administer study drug					X																	
LAST assessment						X	X		X	X			X	X				X				X[d]
Pain intensity assessment (NRS-R)[i]							X[j]		X	X	X	X		X	X	X	X	X	X	X		X[k]
Pain intensity assessment (NRS-A)[l]							X[j]		X	X	X	X		X	X	X	X	X	X	X		X[k]
Record any rescue medication						←	-	-	-	-	-	-	-	-	-	-	-	→				
Record opioid use (Diary)[m]																		←	-	→		
PGA of pain control														X		X		X		X		X[k]
Discharge readiness per MPADSS[n]									X	X	X	X		X	X	X	X	X				
Wound healing assessment																		X	X	X	X	X
Bone healing assessment (X-ray)[o]																				X	X	X[p]
PK blood sample[e]										X			X	X		X						
Concomitant medications[q]		←	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	→	X
Adverse events[e, r]		←	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	→	X

Abbreviations: D, day; ECG, electrocardiogram; ET, Early Termination; F/up, follow-up; h, hour; LAST, Local Anesthetic Systemic Toxicity; min, minutes; MPADSS, Modified Postanaesthetic Discharge Scoring System; NRS-A, Numeric Rating Scale with activity; NRS-R, Numeric Rating Scale at rest; OR, operating room; PGA, Patient Global Assessment; PK, pharmacokinetic; Preop, preoperative assessments; WOCBP, women of childbearing potential; D10, Day 10; D28, Day 28; D42, Day 42.

* The start of study drug administration will be considered as Time 0 for all efficacy, safety, and PK assessments. For assessments at timepoints when the subject is asleep, an attempt should be made to wake the subject. If there is no response, the assessments at these timepoints may be recorded as "Not Done." Assessments that can be done without waking the subject (eg, blood collection for PK) should be completed. When PK and NRS pain intensity assessments coincide, the NRS pain intensity assessments should be conducted before the blood draw. See Section 6 for more information on study procedures and assessments.

[a] Subjects who withdraw from the study will be asked to complete Early Termination procedures based on the timing of withdrawal (ie, prior to the Day 28 Visit, or after the Day 28 Visit and prior to the Safety Follow-Up on Day 42).

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

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

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

[e] If early neurologic and cardiac signs and symptoms of LAST are observed, unscheduled vital sign measurements, 12-lead ECG, and blood sample collection for PK must be performed.

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

[g] Hematology only.

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

[i] NRS-R should be assessed while the subject is seated/recumbent with the surgically attended leg elevated or lying supine. Measurements should be obtained after the subject is in the resting position for at least 5 minutes.

[j] If a subject requires rescue medication before the 1-hour pain intensity assessments, then an unscheduled NRS-R pain score followed by an NRS-A pain score must be obtained before administering the first dose of rescue medication. These do not replace the 1-hour NRS-R and NRS-A assessments.

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

[l] The prescribed activity for NRS-A is sitting with the plantar surface of the ball of the surgically attended foot touching the floor (no weight-bearing).

[m] Subjects will complete a daily diary from 72 hours through Day 28 to record if they take any opioid medication. Subject diary results will be reviewed at each site visit up to and including the Day 28 Visit.

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

[o] An X-ray finding of delayed healing should be followed with a repeat X-ray every 2 to 4 weeks until resolution (ie, signs of normal healing are evident).

[p] Only if the subject withdrew from the study after 72 hours.

[q] At the Screening Visit, ensure subject is not taking any prohibited medications. Record all medications taken from the time the subject signs the Informed Consent Form (ICF) through the Safety Follow-Up on Day 42.

[r] Adverse events will be collected from the time the subject signs the ICF through the Safety Follow-Up on Day 42.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ANOVA	Analysis of variance
API	Active pharmaceutical ingredient
AUC	Area under the curve
BMI	Body mass index
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
COX-2	Cyclooxygenase-2
CPMP	Committee for Proprietary Medicinal Products
CTM	Clinical trial material
CV	Cardiovascular
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPP	Good Publication Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
h	Hour(s)
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IRB	Institutional Review Board

IRT	Interactive response technology
ITT	Intent-to-Treat
IV	Intravenous(ly)
LAST	Local Anesthetic Systemic Toxicity
LOCF	Last observation carried forward
min	Minute
MPADSS	Modified Postanaesthetic Discharge Scoring System
NONMEM	Non-linear mixed effects modeling
NRS	Numeric Rating Scale
NRS-A	NRS scores with activity
NRS-R	NRS scores at rest
NSAID	Nonsteroidal anti-inflammatory drug
ORAE	Opioid-related adverse event
PACU	Postanesthesia care unit
PGA	Patient Global Assessment
PK	Pharmacokinetic(s)
PO	By mouth, orally
REB	Research Ethics Board
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SNRI	Selective norepinephrine reuptake inhibitor
SOP	Standard Operating Procedure
SSRI	Selective serotonin reuptake inhibitor
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum plasma concentration
ULN	Upper limit of normal
US	United States
WOCF	Worst observation carried forward
wWOCF	Windowed worst observation carried forward

1. INTRODUCTION

1.1. Background Information and Study Rationale

Up to 70% of patients have moderate to severe pain after surgery, and the most severe pain occurs within the first 72 hours (Lynch, 1997; Svensson, 2000; Apfelbaum, 2003; Gan, 2014; Misiolek, 2014; Singla, 2014; Meissner, 2015). Administering a local anesthetic (eg, bupivacaine, ropivacaine, or levobupivacaine) is a relatively simple and safe means of providing postoperative pain relief. A major limitation of current local anesthetics is their short duration of effect (6 to 12 hours following surgery) (Kehlet, 2011). Consequently, many patients are given opioids for pain management. The requirement for opioids postoperatively is a serious manifestation of ineffective pain relief. Exposure to opioids can lead to opioid-related adverse events (ORAEs) resulting in worse patient outcomes and increased hospital costs (Coley, 2002; Wheeler, 2002; Stephens, 2003; Cashman, 2004; Shirakami, 2005; Jarzyna, 2011; Ramachandran, 2011; Chan, 2013; Kessler, 2013; Oderda, 2013; Lee, 2015; Lee, 2016). Furthermore, transition from acute opioid use to chronic use can occur quickly. A recent review of a random sample of records from patients who had at least 1 opioid prescription between 2006 and 2015 showed that the probability of chronic opioid use begins to increase after the third day supplied and rises rapidly thereafter (Shah, 2017). The United States (US) is facing a national opioid crisis that has led to a public health epidemic with multiple national and state responses. In 2015, 2 million Americans had a substance use disorder involving prescription pain relievers, and over 20,000 accidental overdose deaths were related to prescription pain relievers (Bose, 2016; Rudd, 2016). Reduced exposure to opioids and better pain management is associated with improved patient outcomes and reduced risk for the development of persistent pain and consequent opioid abuse (Barnett, 2017). Therefore, there is a medical need for clinical alternatives to prescription opioids to manage ambulatory nonmalignant pain. The development of an extended-release local anesthetic applicable for a broad range of surgeries that could significantly reduce both pain and opioid use after surgery and can be easily administered with a favorable safety profile would address an important public health need.

Heron Therapeutics, Inc. (Heron) is developing HTX-011 for local administration into the surgical site to reduce postoperative pain and the need for opioid analgesics through 72 hours. HTX-011 is an extended-release, fixed-ratio combination product that contains 2 active pharmaceutical ingredients (APIs), bupivacaine as the main or disease-active ingredient and low-dose meloxicam to enhance the effectiveness of bupivacaine, incorporated in a proprietary bioerodible polymer (termed Biochronomer®). When HTX-011 is administered, the polymer undergoes controlled hydrolysis in the tissue resulting in the extended release of bupivacaine and meloxicam over 3 days. Bupivacaine HCl is an amide-type, long-acting, immediate-release, local anesthetic and meloxicam is a nonsteroidal anti-inflammatory drug (NSAID). Both have been approved by the US Food and Drug Administration (FDA) and in many countries outside the US and have a long history of clinical use. Bupivacaine is available as a solution for injection and is approved for surgical anesthesia and for acute pain management (nerve block) in adults and children (MARCAINE, SENSORCAINE®, and VIVACAINE™). Meloxicam is available as a tablet for oral use and approved for short-term symptomatic treatment of exacerbations of osteoarthrosis and long-term symptomatic treatment of rheumatoid arthritis or ankylosing

spondylitis in adults. The extended release is achieved using a proprietary vehicle formulation consisting of the novel tri[ethylene glycol]-based poly[orthoester] polymer (AP135) in combination with different excipients approved for human use (dimethyl sulfoxide, glycerol triacetate [triacetin], and maleic acid).

This is a Phase 3, randomized, double-blind, saline placebo- and active-controlled, multicenter study in subjects undergoing unilateral simple bunionectomy to evaluate the analgesic efficacy, safety, and pharmacokinetics (PK) of HTX-011 administered via local administration into the surgical site.

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

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

The study will compare HTX-011 via local administration into the surgical site with 2 controls: a saline placebo control and an active control, bupivacaine HCl without epinephrine. The study will employ a randomized and double-blind design to minimize potential bias in subject selection as well as efficacy and safety assessments. The site's pharmacy staff and surgical staff will not be blinded to the treatment assignments because HTX-011 is a colored and viscous liquid whereas bupivacaine HCl and saline placebo are not, and the volume of study drug to be administered varies by treatment group. However, subjects will not be aware of the study drug they are receiving, and once surgery is complete and the subject is transferred to the postanesthesia care unit (PACU), the Investigator and all staff involved in efficacy and safety assessments will be blinded to treatment assignments until after database lock.

One dose level of HTX-011 will be evaluated in this study, 60 mg/1.8 mg (bupivacaine/meloxicam doses) administered via instillation. The dose and administration technique were selected based on a previous Phase 2, dose-finding study in bunionectomy (Study 208). In Study 208, HTX-011 doses ranging from 30 mg/0.9 mg to 200 mg/6 mg administered via different local administration techniques (injection, injection using a Mayo block, instillation) were evaluated. The 60 mg/1.8 mg dose was determined to be the minimally effective dose for producing postoperative analgesia through 72 hours. An evaluation of pain intensity scores by local administration technique for HTX 011 60 mg/1.8 mg demonstrated a significant reduction in mean pain intensity over 72 hours when HTX-011 was administered via instillation compared with saline placebo and bupivacaine HCl. HTX-011 60 mg/1.8 mg had a favorable safety profile. No serious adverse events (SAEs) were observed for this dose. Based on these findings, 60 mg/1.8 mg administered via instillation was selected for this Phase 3 study.

The primary endpoint for this study, mean area under the curve (AUC) of the Numeric Rating Scale of pain intensity scores with activity (NRS-A) through 72 hours (AUC_{0-72}) for HTX-011 compared with saline placebo, was selected based on FDA and Committee for Medicinal Products for Human Use (CHMP) guidances as well as regulatory precedent. Draft FDA *Guidance for Industry on Analgesic Indications: Developing Drug and Biological Products* (February 2014) states that "pain intensity is the fundamental measure that defines the efficacy of an analgesic drug." In addition, the FDA agreed to a primary endpoint of AUC of the NRS pain intensity scores over the first 24-hour period in a bony model (bunionectomy) for EXPAREL® (EXPAREL USPI, 2016). The timepoint of 72 hours selected for this study is considered

clinically relevant for patients as literature shows that the most severe postoperative pain occurs within the first 72 hours after surgery (Lynch 1997; Svensson 2000; Apfelbaum 2003; Gan 2014; Misiolek 2014; Singla 2014; Meissner 2015). NRS-A was selected for the primary endpoint because activity is known to be a more sensitive measure of pain control (Breivik, 2008), and the prescribed activity reflects a simple daily activity for patients (sitting with the plantar surface of the ball of the surgically attended foot touching the floor [no weight-bearing]).

The primary comparator is saline placebo, as recommended in the February 2014 FDA draft *Guidance for Industry on Analgesic Indications: Developing Drug and Biological Products* and the Committee for Proprietary Medicinal Products (CPMP's) *Note for Guidance on Clinical Investigation of Medicinal Products For Treatment of Nociceptive Pain* (Doc. Ref. CPMP/EWP/612/00). Bupivacaine HCl is included as an active comparator. Bupivacaine HCl is the widely accepted standard for local analgesia. Bupivacaine is the disease-active ingredient in the HTX-011 fixed-ratio combination product with low-dose meloxicam included to enhance the effectiveness of bupivacaine. Discussions with experts confirmed that bupivacaine doses commonly used for bunionectomy range from 8 to 10 mL using 0.25% or 0.5% solution delivered into the wound. The dose of bupivacaine solution selected for this Phase 3 study, 50 mg (10 mL of 0.5% solution), reflects the maximum dose and maximum concentration that is commonly used and allows for appropriate comparisons within the study. This dose is within the range of dosing provided in bupivacaine labeling (MARCAINE USPI, 2011; MARCAIN SmPC, 2016) and is further supported by a clinical study of EXPAREL in bunionectomy, which used a volume of 8 mL for both EXPAREL and placebo (Golf, 2011), and by published literature with active comparators (Ptaszek, 1999; Baxter, 2013). All subjects with inadequately controlled pain will have access to prespecified rescue medication, including both non-opioid (acetaminophen) and opioid (morphine and/or oxycodone) options.

The study includes 4 prespecified key secondary endpoints with a strict statistical hypothesis testing hierarchy to preserve the study-wise alpha level at 5%. Given the importance of comparison to the bupivacaine active control arm in order to satisfy the Combination Rule, 21 Code of Federal Regulations (CFR) 300.50 *Fixed-Combination Prescription Drugs for Humans*, the first key secondary endpoint will evaluate the mean $AUC_{0\text{-}72}$ of the NRS-A pain intensity scores compared with an active control, bupivacaine HCl. The 2nd, 3rd, and 4th key secondary endpoints will evaluate opioid consumption through 72 hours compared with saline placebo, proportion of subjects who are opioid-free through 72 hours compared with bupivacaine HCl, and opioid consumption through 72 hours compared with bupivacaine HCl, respectively. Given the concern for misuse and abuse of opioids, a reduction in opioid load and an increase in the number of subjects who are opioid free are considered clinically meaningful endpoints and are in alignment with the February 2014 FDA draft *Guidance for Industry* on *Analgesic Indications: Developing Drug and Biological Products*. Opioid sparing endpoints were also included in recently approved labels for EXPAREL, OFIRMEV®, and CALDOLOR®, and NAROPIN®.

1.3. Potential Risks and Benefits

As of 23 March 2017, 665 subjects have been exposed to 1 of the 3 different formulations of HTX-011 in 6 clinical studies. This includes 2 Phase 1 studies in healthy volunteers (subcutaneous study drug administration [Studies 02 and 102]) and 4 Phase 2 local

administration studies (bunionectomy [Studies 201 and 208], herniorrhaphy [Study 202], and abdominoplasty [Study 203]). A total of 400 subjects received a single dose of the HTX-011 formulation for Phase 3. Study drug was given via subcutaneous injection or via local administration into the surgical site (injection, instillation, a combination of injection and instillation, or injection using a Mayo block) at doses ranging from 30 mg/0.9 mg to 600 mg/18 mg (bupivacaine/meloxicam doses).

Preliminary results from Phase 2 demonstrated that HTX-011 is generally well tolerated. The majority of treatment-emergent adverse events (TEAEs) were mild or moderate in severity and resolved without sequelae. The 2 most common TEAEs were nausea and constipation. [redacted] 2 SARs were reported in subjects who received the Phase 3 HTX-011 formulation. One SAR of non-healing postoperative wound was reported in a subject who received 200 mg/6 mg in the bunionectomy study (Study 208), and 1 SAR of wound dehiscence was reported in a subject who received 300 mg/9 mg in the abdominoplasty study (Study 203).

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

Potential risks for bupivacaine include dose-related cardiovascular (CV) and central nervous system toxicity (MARCAINE USPI, 2011; MARCAIN SmPC, 2016). Close attention should be given to conditions that may represent reported toxicities associated with bupivacaine including, but not limited to, perioral tingling, metallic taste, visual and auditory disturbances, muscle twitching, seizure, acidosis, shortness of breath, bradycardia (heart rate <50 beats per minute with symptoms), hypotension (systolic blood pressure <90 mmHg or symptomatic decrease from baseline), low oxygen saturation (≤90% for ≥1 minute), and cardiac arrest.

Potential risks for meloxicam include CV adverse reactions, gastrointestinal bleeding, and liver tests elevations (MOBIC SmPC, 2015; MOBIC Tablets USPI, 2016). NSAIDs may cause an increased risk of serious CV thrombotic events, myocardial infarction, and stroke, which can be fatal, and this risk may increase with duration of use. Patients with CV disease or risk factors for CV disease may be at greater risk. NSAIDs may also cause an increased risk of serious gastrointestinal AEs including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. Elderly patients are at greater risk for serious gastrointestinal events. Borderline elevations of 1 or more liver tests may occur in patients taking NSAIDs, including meloxicam, which may worsen. It is unclear how applicable these potential risks are for meloxicam when given as single dose via local administration (a novel administration method for meloxicam) for postoperative pain as part of a fixed-ratio combination (eg, HTX-011). Any subject in this study with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction.

Use of HTX-011 in subjects with hypersensitivity to bupivacaine, meloxicam, or any of the components of HTX-011 is contraindicated.

The analgesic efficacy of HTX-011 has been evaluated in Phase 2. In a Phase 2 study in subjects undergoing unilateral simple bunionectomy, single-dose administration of the Phase 3 HTX-011 formulation ranging from 60 mg/1.8 mg to 200 mg/6 mg resulted in a significant reduction in mean AUC of pain intensity scores through 72 hours. HTX-011 was also associated with decreased total opioid consumption, and resulted in more subjects who were opioid-free and a longer time to first opioid use compared with saline placebo. Similar efficacy results were observed in a second Phase 2 study in subjects undergoing unilateral open inguinal herniorrhaphy, where single-dose administration of the current HTX-011 formulation at doses of 200 mg/6 mg to 400 mg/12 mg also significantly decreased the mean AUC of pain intensity scores through 72 hours compared with saline placebo.

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

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to compare the efficacy and duration of analgesia following local administration of HTX-011 with saline placebo during the first 72 hours following unilateral simple bunionectomy.

2.2. Secondary Objectives

The secondary objectives are as follows:

- To compare the efficacy and duration of analgesia for HTX-011 with bupivacaine HCl without epinephrine during the first 72 hours following surgery in this study population.
- To compare the effect of HTX-011 with saline placebo and bupivacaine HCl without epinephrine on opioid load during the first 72 hours following surgery in this study population.
- To assess the safety and tolerability of HTX-011 in this study population.
- To further establish the PK parameters of bupivacaine and meloxicam in HTX-011 in this study population.

3. INVESTIGATIONAL PLAN AND ENDPOINTS

3.1. Description of the Study Design

3.1.1. Overall Study Design

This is a Phase 3, randomized, double-blind, saline placebo- and active-controlled, multicenter study to evaluate the analgesic efficacy, safety, and PK of HTX-011 administered via local administration into the surgical site in subjects undergoing unilateral simple bunionectomy.

All subjects will be screened within 28 days prior to surgery. Subjects who meet the Screening eligibility criteria will be randomized. Randomization may be done up to 1 business day prior to the day of surgery. On the day of surgery (Day 1), subjects who continue to meet the eligibility criteria will undergo a unilateral simple bunionectomy under regional anesthesia with no more than 20 mL of 1% lidocaine without epinephrine administered as a Mayo block. Epidural or spinal anesthesia is not permitted. During surgery, the use of intravenous (IV) fentanyl up to 4 µg/kg will be permitted for intraoperative pain control. Intraoperative administration of other opioids or other analgesics, local anesthetics, or anti-inflammatory agents (except as specified by the protocol) is prohibited, unless needed to treat an adverse event (AE) that occurs after signing the Informed Consent Form (ICF), for pretreatment prior to a needle placement, or to decrease venous irritation (eg, caused by propofol, in which case no more than a single administration of lidocaine 1% 20 mg IV may be administered).

Near the completion of surgery and after irrigation and suction have been completed, a single dose of study drug (HTX-011, saline placebo, or bupivacaine HCl without epinephrine) will be given intraoperatively via local administration into the surgical site, as described in Section 5.5.

Following surgery and immediate postoperative recovery, subjects will be transferred to the PACU. Subjects will remain in the hospital/research facility for a minimum of 72 hours after the start of study drug administration to undergo postoperative assessments. After the 72-hour assessments have been completed, subjects may be discharged. Subjects will return to the study site on Days 10 and 28 to complete follow-up assessments. In addition, subjects will return for a Safety Follow-Up on Day 42.

3.1.2. Treatment Groups

Approximately 400 subjects will be randomized to 1 of the following 3 treatment groups in a 3:3:2 ratio:

- HTX-011, 60 mg/1.8 mg (bupivacaine/meloxicam doses), 2.1 mL, via instillation into the surgical site (150 subjects)
- Bupivacaine HCl without epinephrine 0.5%, 50 mg (10 mL), via injection into the surgical site (150 subjects)
- Saline placebo, 2.1 mL, via instillation into the surgical site (100 subjects)

3.1.3. Postoperative Rescue Medications

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

Postoperative rescue medication will consist of oral (PO) immediate-release oxycodone (no more than 10 mg within a 4-hour period as needed), IV morphine (no more than 10 mg within a 2-hour period as needed), and/or oral acetaminophen (no more than 1 gram [1000 mg] in a 6-hour window). For subjects administered any acetaminophen-containing product, the total combined daily dose must not exceed 4 grams (4000 mg) as severe liver damage may occur. No other analgesic agents, including NSAIDs, are permitted during the 72-hour postoperative observation period.

Subjects who are not medically ready for discharge at 72 hours may receive the same rescue medication as above to treat postoperative pain until discharge.

For subjects who are medically ready for discharge at 72 hours, oral acetaminophen (no more than 1000 mg every 6 hours as needed) should be recommended for postoperative pain. If a subject received 10 mg or more of oxycodone in the 12 hours prior to discharge, the subject should be provided with a prescription for oxycodone (up to 10 mg PO q4h as needed). See Appendix G for instructions on postoperative pain management for subjects medically ready for discharge.

Subjects will complete a daily diary to record if they take an opioid medication between 72 hours and Day 28.

3.1.4. Postoperative Assessments

Efficacy assessments will include pain intensity scores using NRS-R and NRS-A, use of opioid medication, discharge readiness as assessed by the Modified Postanaesthetic Discharge Scoring System (MPADSS), and Patient Global Assessment (PGA) of pain control.

Safety assessments will include AE recording, local anesthetic systemic toxicity (LAST) assessments, physical examinations, vital signs, electrocardiograms (ECGs), hematology and serum chemistry, wound healing, and bone healing (X-ray) assessments.

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

See Section 6 for more information on the study procedures and assessments. For the timing of procedures and assessments, see Section 7 and the Schedule of Events table.

3.2. Study Endpoints

3.2.1. Efficacy Endpoints

3.2.1.1. Primary Efficacy Endpoint

- Mean area under the curve (AUC) of the Numeric Rating Scale of pain intensity scores with activity (NRS-A) through 72 hours (AUC_{0-72}) for HTX-011 compared with saline placebo.

3.2.1.2. Key Secondary Efficacy Endpoints (Hierarchical Testing)

1. Mean AUC_{0-72} of the NRS-A pain intensity scores for HTX-011 compared with bupivacaine HCl.
2. Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with saline placebo.
3. Proportion of subjects who are opioid-free through 72 hours for HTX-011 compared with bupivacaine HCl.
4. Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with bupivacaine HCl.

3.2.1.3. [redacted]

3.2.2. Safety Endpoints

- Incidence of TEAEs, SAEs, and ORAEs through the Safety Follow-Up on Day 42.
- Change from baseline in clinical laboratory results.
- Change from baseline in ECG data.
- Change from baseline in vital signs.
- Wound healing assessment at 72 hours, on Day 10 and Day 28, and at the Safety Follow-Up on Day 42.
- Bone healing assessment on Day 28 and at the Safety Follow-Up on Day 42.

3.2.3. Pharmacokinetic Endpoints

- Calculated maximum plasma concentration (C_{max}).
- Calculated time to reach maximum plasma concentration (T_{max}).

3.3. Study Duration

The overall duration of the study is anticipated to be approximately 7 months. The total duration of study participation for each subject (from Screening through the Safety Follow-Up on Day 42) will be up to 77 days.

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

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1. Study Population

Approximately 400 subjects will be randomized in this study at up to approximately 25 study sites.

4.1.1. Inclusion Criteria

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

1. Is able to provide written informed consent, adhere to the study visit schedule, and complete all study assessments.
2. Is male or female, and ≥18 years of age at screening.
3. Is scheduled to undergo a primary unilateral, distal, first metatarsal bunionectomy with osteotomy and internal fixation under regional anesthesia.
4. Has an American Society of Anesthesiologists Physical Status of I, II, or III.
5. Female subjects are eligible only if all of the following apply:
    a. Not pregnant (female subjects of child-bearing potential must have a negative urine pregnancy test at screening and on Day 1 before surgery).
    b. Not lactating.
    c. Not planning to become pregnant during the study.
    d. Is surgically sterile; or is at least 2 years post-menopausal; or is in a monogamous relationship with a partner who is surgically sterile; or is practicing abstinence or agrees to use double-barrier contraception in the event of sexual activity; or is using an insertable, injectable, transdermal, or combination oral contraceptive approved by applicable regulatory authorities for greater than 2 months prior to screening and commits to the use of an acceptable form of birth control for the duration of the study and for 30 days after study drug administration. Note: women in only a same-sex relationship do not need to meet this criterion.

4.1.2. Exclusion Criteria

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

1. Has had a contralateral foot bunionectomy in the past 3 months.
2. Has a planned concurrent surgical procedure (eg, bilateral bunionectomy or collateral procedures on the surgical foot).
3. Has a pre-existing concurrent acute or chronic painful physical/restrictive condition expected to require analgesic treatment in the postoperative period for pain that is not strictly related to the bunionectomy and which may confound the postoperative assessments.

4. Has a contraindication or a known or suspected history of hypersensitivity or clinically significant idiosyncratic reaction to bupivacaine (or other local anesthetics), meloxicam (or other NSAIDs), oxycodone, morphine, or acetaminophen.
5. Has known or suspected daily use of opioids for 7 or more consecutive days within the previous 6 months.
6. Has taken any NSAIDs (including meloxicam) within at least 10 days prior to the scheduled surgery with the exception of subjects on low dose (≤100 mg) daily acetylsalicylic acid for cardioprotection.
7. Has taken long-acting opioids within 3 days prior to the scheduled surgery.
8. Has taken any opioids within 24 hours prior to the scheduled surgery.
9. Has been administered bupivacaine within 5 days prior to the scheduled surgery.
10. Has been administered any local anesthetic within 72 hours prior to the scheduled surgery, other than for pretreatment prior to a needle placement, to treat an AE that occurs after signing the ICF, or to decrease venous irritation (eg, caused by propofol, in which case no more than a single administration of lidocaine 1% 20 mg IV may be administered).
11. Has initiated treatment with any of the following medications within 1 month prior to study drug administration or is taking any of these medications to control pain: selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin, or cyclooxygenase-2 (COX-2) inhibitors. (Note: If a subject is taking one of these medications for a reason other than pain control, the subject must be on a stable scheduled dose [ie, not "as needed"] for at least 1 month prior to study drug administration.) Anxiolytics prior to surgery are permitted, if necessary.
12. Has been administered systemic steroids within 5 half-lives or 10 days prior to administration of study drug (whichever is longer).
13. Has a medical condition such that, in the opinion of the Investigator, participating in the study would pose a health risk to the subject or confound the postoperative assessments. Conditions may include, but are not limited to, any of the following:
    a. History of clinically significant cardiac abnormality such as myocardial infarction within 6 months prior to signing the ICF, New York Heart Association class III or IV, or clinically significant abnormalities in cardiac function or on ECG (including but not limited to a PR interval >200 msec, a QT corrected by Fridericia's formula [QTcF] >480 msec, or 3rd degree heart block).
    b. History of coronary artery bypass graft surgery within 12 months prior to signing the ICF.
    c. History of severe liver function impairment as defined by Child-Pugh Class C, having an aspartate aminotransferase >3 × the upper limit of normal (ULN), or having an alanine aminotransferase >3 × ULN.
    d. History of severe kidney function impairment as defined by creatinine clearance (Cockcroft-Gault) <30 mL/min, being on dialysis, and/or having a serum creatinine >2 × ULN.
    e. History of known or suspected coagulopathy or uncontrolled anticoagulation.

f. Loss of sensation in extremities or significant peripheral neuropathy.

14. As per subject history and/or medical records, has active infection or is currently undergoing treatment for Hepatitis B, Hepatitis C, or human immunodeficiency virus (HIV).
15. Has uncontrolled anxiety, psychiatric, or neurological disorder that, in the opinion of the Investigator, might interfere with study assessments.
16. Had a malignancy in the last year, with the exception of nonmetastatic basal cell or squamous cell carcinoma of the skin or localized carcinoma in situ of the cervix.
17. Has a known or suspected history of drug abuse, a positive drug screen on the day of surgery, or a recent history of alcohol abuse. Note: Subjects with a positive drug screen who are taking an allowed, prescribed medication that is known to result in a positive drug test (eg, amphetamine and dextroamphetamine for attention-deficit/hyperactivity disorder, benzodiazepine for anxiety disorder) may be eligible for participation in the study. Subjects taking medical marijuana are not allowed to participate in the study.
18. Previously participated in an HTX-011 study.
19. Received an investigational product or device in a clinical trial within 30 days or within 5 elimination half-lives (whichever is longer) prior to surgery, or is planning to take part in another clinical trial while participating in this study.
20. Has undergone 3 or more surgeries within 12 months prior to signing the ICF, other than for diagnostic procedures (eg, colonoscopy).
21. Has a body mass index (BMI) >39 kg/m^2.

4.2. Method of Assigning Subjects to Treatment Groups

Subjects who meet the Screening eligibility criteria will be randomized. Randomization may be done up to 1 business day prior to the day of surgery. Subjects will be randomized using a centralized computer-generated blocked randomization algorithm created by an interactive response technology (IRT) provider. All randomization information will be kept in a secure location accessible only by the randomization personnel, the assigned Pharmacist(s) and his/her verifier, and the unblinded clinical monitor. No subject may receive study drug prior to randomization.

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

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

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

4.3. Blinding

The study will use a double-blind design to minimize potential bias in subject selection as well as efficacy and safety assessments. The site's pharmacy and surgical staff will not be blinded to the treatment assignments because HTX-011 is a colored and viscous liquid whereas bupivacaine HCl and saline placebo are not, and the volume of study drug to be administered varies by treatment group. However, subjects will not be aware of the study drug they are receiving, and once surgery is completed and the subject is transferred to the PACU, the Investigator and all site staff involved in safety and efficacy assessments will be blinded to the treatment assignment until after database lock. The Sponsor's study team will also be blinded to the treatment assignments with the exception of the clinical trial material (CTM) and clinical observer staff.

4.3.1. Breaking the Blind

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

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

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

4.4. Subject Withdrawal and Replacement

4.4.1. Subject Withdrawal

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

Possible reasons for early withdrawal include the following:

- Adverse event
- Consent withdrawal
- Death
- Lost to follow up
- Investigator's decision
- Sponsor's decision
- Ineligible at Day 1

The date and the primary reason for early withdrawal will be recorded on the electronic case report form (eCRF). At the time of withdrawal from the study, every attempt should be made to complete the Early Termination Visit assessments (see Section 7.3.1.3).

4.4.2. Subject Replacement

Randomized subjects who withdraw from study will not be replaced. To account for withdrawal of subjects who are ineligible at Day 1 or are otherwise randomized but not dosed, enrollment will continue until at least 400 subjects have been randomized and dosed.

5. STUDY TREATMENT

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

HTX-011, saline placebo, and bupivacaine HCl will be supplied by the Sponsor.

5.1. Description of Investigational Product

HTX-011 is a slightly yellow, viscous, semi-solid gel liquid. HTX-011 is supplied in 10 mL or 20 mL clear glass vials. The vials serve only as a closed container for the drug product. For administration of study drug, the formulation in the vials will be aseptically transferred to sterile syringes.

5.2. Manufacturing, Packaging, and Labeling

HTX-011 will be manufactured according to Good Manufacturing Practices.

Study drug will be packaged and labeled by the Sponsor or designee and will be packed and dispatched to comply with shipping and storage conditions. Study drug labeling will comply with all applicable national and local laws and regulations.

5.3. Storage

At the study site, HTX-011 should be stored at a controlled room temperature of 20 to 25°C (with excursions permitted from 15 to 30°C). The room should be locked with restricted access. A temperature log must be maintained to monitor the room's temperature.

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

5.4. Preparation

Study drug will be prepared at the study site. HTX-011 and saline placebo will be prepared in a group of syringes without a needle. Bupivacaine HCl will be prepared in a group of syringes with a needle. Refer to the Pharmacy Manual for details on study drug preparation.

5.5. Study Drug Administration

Study drug will be given via local administration into the surgical wound prior to wound closure, after irrigation and suction of each layer are complete. "Infiltration" is a regulatory term for product labels to describe local administration via instillation or injection.

5.5.1. Instillation: HTX-011 and Saline Placebo

HTX-011 and saline placebo will be administered via instillation using a Luer-lock applicator supplied by the Sponsor.

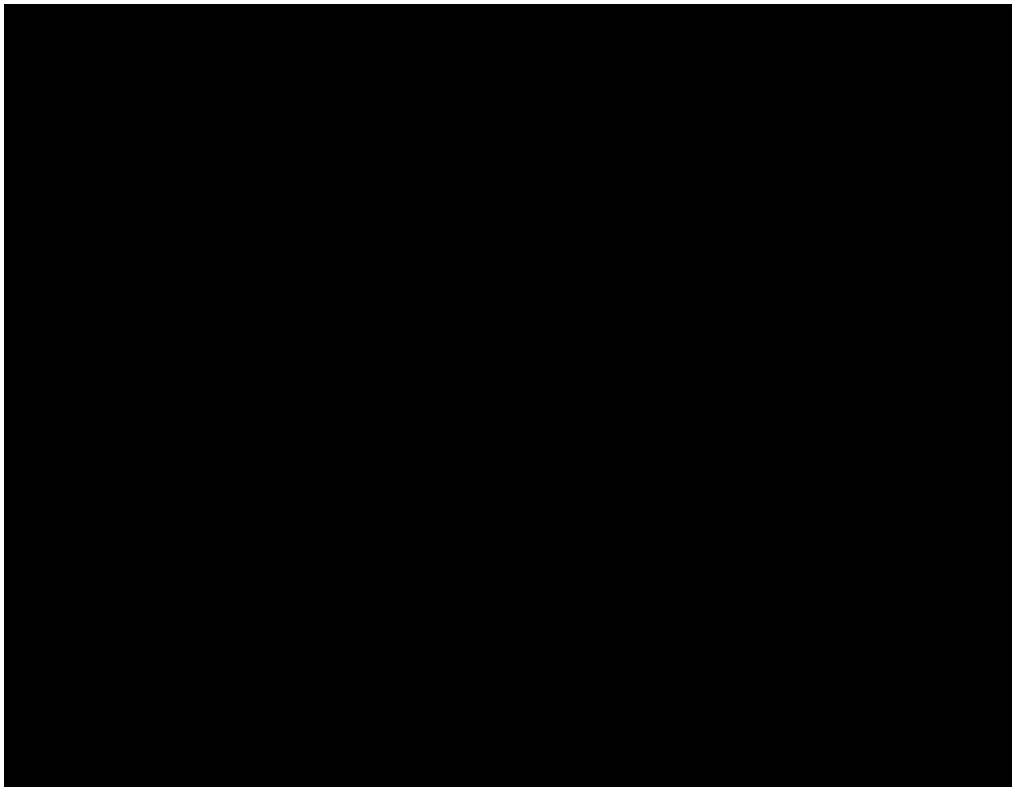
Following irrigation and suction of each fascial layer, study drug will be administered evenly so that all tissues receive adequate coverage. Care should be taken to ensure adequate exposure of the proximal and distal ends (ie, beyond the bony incision) of the wound to study drug. Study

drug should form rings of anesthetic around both the proximal and distal aspects of the metatarsal. To ensure adequate saturation of all exposed tissues in the surgical field, study drug may be administered in layers. Note that the shallow subdermal layer is to be avoided and that all study drug should be utilized (ie, there should be no residual study drug left). Thereafter, skin closure will commence to complete the surgical procedure (ie, there should be no betadine wash until after skin closure at the end of the case).

5.5.2. Injection: Bupivacaine HCl

Bupivacaine HCl will be administered via injection. Study drug should 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 syringe distally past the bony incision (blue arrows in photo below).
- Repeat the procedure with the rest of the syringe but now start distally and inject proximally (red arrows in photo below).
- Ensure adequate saturation of all exposed tissues in the surgical field.
- Thereafter, commence skin closure to complete the surgical procedure (ie, there should be no betadine wash until after skin closure at the end of the case).



5.6. Study Drug Compliance

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

5.7. Study Drug Accountability

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

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

6. STUDY PROCEDURES AND ASSESSMENTS

The following sections describe the study procedures and assessments that will be performed during the study. See Section 7 and the Schedule of Events table.

6.1. Medical History and Demographics

6.1.1. Medical History

A complete medical history will be obtained before randomization to ensure subjects qualify for the study. Medical history will be obtained through subject interview. A review of the subject's medical records from their primary care physician is recommended. Data collected will include medical and surgical history.

6.1.2. Demographics

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

6.2. Prior and Concomitant Therapy

All medications taken by subjects between signing the ICF and the Safety Follow-Up on Day 42 will be recorded in the subject's eCRF. The dosing regimen of "prn" should not be recorded on the eCRF.

During the 72-hour postoperative period, the name, dose, and route, as well as the start date and time, of concomitant medications must be recorded. Medications include prescription or over-the-counter medications (including herbal products and vitamins). For subjects entering on a stable dose of permitted medication, any change in dose should also be recorded. Note: All medications received during this period must have a start time recorded, except for IV fluids and oxygen during surgery, which do not need to be recorded unless being used to treat an AE.

After the 72-hour period until the Safety Follow-Up on Day 42, at least the start date of each concomitant medication should be recorded.

6.2.1. Allowed Concomitant Medications

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

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

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

See Section 3.1.3 for information on rescue medications permitted.

See Appendix G for information on postoperative pain management for subjects who are medically ready for discharge.

6.2.2. Prohibited Medications

6.2.2.1. Medications Prohibited Prior to Surgery

Refer to exclusion criteria 5 through 11 and 17 for medications that are prohibited prior to the scheduled surgery (Section 4.1.2). Of note, for exclusion criterion 12, oral, parenteral, and topical steroids are considered systemic steroids, but inhaled and ophthalmic steroids are not considered systemic steroids.

6.2.2.2. Medications Prohibited During Surgery

Epidural or spinal anesthesia is not permitted.

Intraoperative administration of opioids or any other analgesics (including ketamine), local anesthetics, or anti-inflammatory agents except as specified by the protocol (ie, HTX-011, bupivacaine HCl, and fentanyl) is prohibited, unless needed to treat an AE that occurs after signing the ICF, for pretreatment prior to a needle placement, or to decrease venous irritation (eg, caused by propofol, in which case no more than a single administration of lidocaine 1% 20 mg IV may be administered).

6.2.2.3. Medications Prohibited From Time 0 Through 72 Hours

With the exception of rescue medications specified in Section 3.1.3, no other analgesic agents, including NSAIDs, are permitted during the 72-hour postoperative observation period.

6.3. Efficacy Assessments

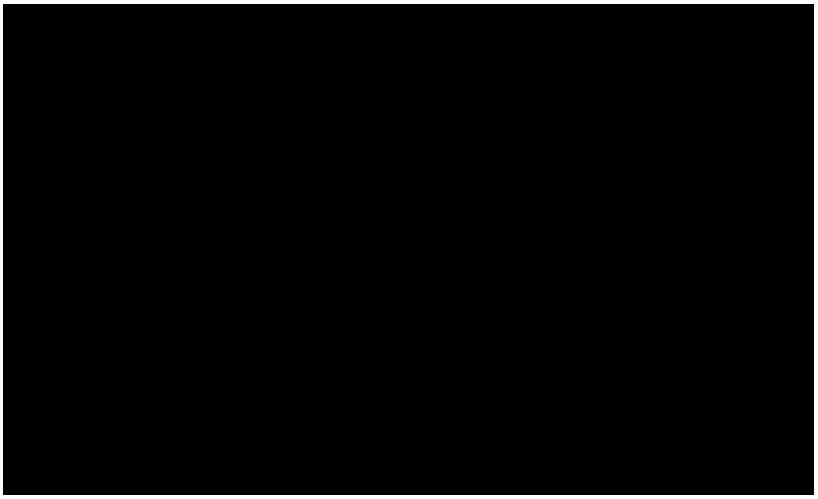
6.3.1. Pain Intensity Assessment

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

Pain intensity scores will be assessed using an 11-point NRS (0–10) where 0 represents “no pain” and 10 represents “worst pain imaginable” (Breivik 2008). NRS scores will be recorded first at rest (NRS-R) and then with activity (NRS-A).

For NRS-R assessments, subjects should be seated/recumbent with the surgically attended leg elevated or lying supine. Measurements should be obtained after the subject is in the resting position for at least 5 minutes.

For NRS-A assessments, subjects should be seated with the plantar surface of the ball of the surgically attended foot touching the floor (no weight-bearing; see photo below).



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

6.3.2. Use of Opioid Medications

6.3.2.1. Opioid Rescue Medication Through 72 Hours

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

6.3.2.2. Subject Daily Diary of Opioid Use From 72 Hours Through Day 28

Subjects will be provided a daily diary to record if they take any opioid medication from 72 hours through Day 28 (yes or no).

6.3.3. Discharge Readiness

Discharge readiness will be assessed using the MPADSS criteria (Chung, 1995). See Appendix E.

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

6.3.4. Patient Global Assessment (PGA) of Pain Control

Subjects will be asked to evaluate their pain control over the preceding 24 hours using a 4-point PGA scale where 0 represents "poor" and 3 represents "excellent" (Rothman, 2009). See Appendix D for the PGA scale.

6.4. Safety Assessments

6.4.1. Adverse Events

All AEs regardless of causality or seriousness will be recorded from the time the subject signs the ICF through the Safety Follow-Up on Day 42. See Section 8 for details. Clinically significant post-treatment findings for laboratory results, vital signs, ECGs, or X-rays should be recorded as AEs. LAST signs or symptoms, abnormal physical examination findings and wound healing abnormalities should also be recorded as AEs.

6.4.2. Local Anesthetic Systemic Toxicity Assessment

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

Subjects should be assessed with this questionnaire on a regular basis to identify early stages of toxicity to determine whether treatment should be initiated. If a subject has signs or symptoms that may be attributed to LAST, vital sign measurements, 12-lead ECG, and blood sample collection for PK must be performed. If symptoms are present at a timepoint when 1 of these assessments is not scheduled, an unscheduled assessment must be performed.

6.4.3. Physical Examinations

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

Baseline height and weight measurements, and calculation of BMI (see Appendix B) will be conducted.

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

6.4.4. Vital Signs

Vital signs will include systolic and diastolic blood pressure, resting heart rate, respiration rate, and body temperature. Subjects should be in a supine position (includes sitting in a recliner chair) for at least 5 minutes before taking vital signs.

6.4.5. 12-Lead Electrocardiograms

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

The ECG tracings will be reviewed by a central reader. Refer to the Cardiac Safety Study Manual for instructions on collecting and transmitting results.

6.4.6. Wound Healing Assessment

A wound healing assessment questionnaire is provided (see Appendix F). Surgical wound healing will be evaluated by the Investigator or other medically qualified clinical site personnel; every attempt should be made by the site to use the same assessor for individual subject assessments. Any abnormality of wound healing should be followed to resolution.

6.4.7. Bone Healing Assessment

An X-ray of the surgical site will be obtained to evaluate the status of the bone healing process. X-rays should be evaluated by a physician with training and expertise in X-ray evaluations, including assessment of bone healing. The results should be reported as normal healing, delayed healing, or mal-union. The X-ray reports of anything other than normal healing will be provided to the Sponsor.

An X-ray finding of delayed healing should be followed with a repeat X-ray every 2 to 4 weeks until resolution (ie, signs of normal healing are evident).

6.4.8. Clinical Laboratory Tests

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

Laboratory results will be reviewed by the Investigator. Any laboratory values outside of the normal reference range will be evaluated for clinical significance.

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

Table 1: Clinical Laboratory Tests

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

	Glucose Lactate dehydrogenase Magnesium Phosphorus Potassium Sodium Total bilirubin Total protein Uric acid

6.5. Pharmacokinetic Assessments

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

7. TIMING OF PROCEDURES AND ASSESSMENTS

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

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

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

- NRS-R pain intensity assessment (subjects should be seated/recumbent with the surgically attended leg elevated or lying supine; measurements should be obtained after the subject is in the resting position for at least 5 minutes)
- PGA of pain control assessment
- Vital signs
- 12-lead ECG
- NRS-A pain intensity assessment (subjects should be seated with the plantar surface of the ball of the surgically attended foot touching the floor [no weight bearing])
- LAST assessment
- Blood sample collection
- Physical examination
- Wound healing assessment
- Bone healing assessment (X-ray)

7.1. Screening Period

After providing written informed consent, potential study subjects will undergo Screening procedures to confirm eligibility to participate in the study. Screening procedures must be performed within 28 days prior to surgery. The Investigator must evaluate the subject's medical history and the results of all Screening assessments to determine study eligibility before the subject is randomized.

Screening procedures and assessments will include the following:

- Urine drug screen
- Urine pregnancy test (female subjects of child-bearing potential only)
- Medical history
- Demographic recording

- Physical examination (including weight, height, and BMI calculation)
- Vital signs measurements
- 12-lead ECG (in triplicate)
- Blood sample collection for the hematology and serum chemistry
- Subject training for pain intensity assessments
- AE recording (from the time the subject signs the ICF)
- Prior and concomitant medication recording (from the time the subject signs the ICF)

The urine drug screen and urine pregnancy test should be performed first, and the results should be confirmed as negative prior to performing any additional assessments. A subject who fails the drug test may be rescreened at the discretion of the Investigator. Subjects with a positive drug screen who are taking an allowed, prescribed medication that is known to result in a positive drug test (eg, amphetamine and dextroamphetamine for attention-deficit/hyperactivity disorder, benzodiazepine for anxiety disorder) may be eligible for participation in the study. Any other screening laboratory test result that does not meet the eligibility criteria may not be repeated without the Sponsor's approval.

All subjects who meet the Screening eligibility criteria will be randomized. Randomization may be done up to 1 business day prior to the day of surgery. Subjects do not need to be present for randomization to occur.

7.2. Treatment and Postoperative Observation Period

7.2.1. Day of Surgery (Day 1)

7.2.1.1. Prior to Surgery

On Day 1, subjects will be reassessed for study eligibility. This includes a urine drug screen test (all subjects) and urine pregnancy test (female subjects of child-bearing potential only). Results should be confirmed as negative prior to performing any additional assessments.

Subjects who continue to meet the eligibility criteria can continue on study and will be admitted to the surgical unit. The following additional study procedures and assessments will be performed before surgery:

- Vital signs measurements
- Subject training for pain intensity assessments (refresher training)
- AE recording
- Prior and concomitant medication assessment

7.2.1.2. Surgery and Study Drug Administration

Subjects will undergo a unilateral simple bunionectomy under regional anesthesia (no more than 20 mL of 1% lidocaine without epinephrine administered as a Mayo block; epidural or spinal anesthesia is not permitted). Sites should follow intraoperative safety monitoring in accordance

with ASA Standards for Basic Anesthetic Monitoring (American Society of Anesthesiologists, 2015), which is consistent with the European Board of Anaesthesiology (EBA) recommendations for minimal monitoring during Anaesthesia and Recovery (for review in 2018) (EBA UEMS, 2016). The start and stop time of surgery and additional surgical details (including the length of the surgical incision) should be recorded in the eCRF.

Subjects will be administered study drug unless they experience a clinically significant event during surgery (eg, excessive bleeding, hemodynamic instability) that would render the subject medically unstable or complicate their postoperative course. Study drug will be administered via local administration into the surgical site at the end of the surgical procedure, but prior to wound closure. See Section 5.5 for complete details on the study drug administration technique.

The start and stop times of study drug dosing will be recorded in the eCRF. Details of administration will be recorded on a worksheet, which will be used in the dictation of the surgical notes and will become part of the source document. **Note: The start of study drug administration will be considered as Time 0 for all efficacy, safety, and PK assessments.** Placement of the last suture will be considered the end of surgery.

Concomitant medications used during surgery will be recorded (note that IV fluids and oxygen are not required to be recorded unless being used to treat an AE). AEs will also be recorded.

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

7.2.2. Postoperative Assessment Period (Up to 72 Hours)

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

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

- **NRS-R and NRS-A pain intensity assessments:** at 1 hour (±5 min), 2 and 4 hours (±15 min), 8 and 12 hours (±30 min), 24 hours (±1 h), 36 and 48 hours (±2 h), 60 and 72 hours (±4 h)
  - Note: If a subject requires rescue medication before the 1-hour pain intensity assessments, then an unscheduled NRS-R pain score followed by an NRS-A pain score must be obtained before administering the first dose of rescue medication. These do not replace the 1-hour NRS-R and NRS-A assessments.
- **PGA of pain control assessment:** 24 hours (±1 h), 48 hours (±2 h), and 72 hours (±4 h)
- **Vital signs measurements:** 30 minutes (±5 min), 1 hour (±5 min), 1.5 hours (±10 min), 2 hours (±15 min), 4 hours (±15 min), 8 hours (±30 min), 12 hours (±30 min), 18 hours (±30 min), 24 hours (±1 h), 36 hours (±2 h), 48 hours (±2 h), 60 hours (±4 h), and 72 hours (±4 h)
- **LAST assessments**: 30 minutes (±5 min), 1 hour (±5 min), 2 hours (±15 min), 4 hours (±15 min), 18 hours (±30 min), 24 hours (±1 h), and 72 hours (±4 h). If symptoms are present at 30 minutes, 1 hour, or 2 hours, an unscheduled blood sample

will be collected for PK and a 12-lead ECG will be performed. If symptoms are present at 72 hours, an unscheduled blood sample will be collected for PK.

- **12-lead ECG (in triplicate)**: 4 hours (±15 min), 18 hours (±30 min), 24 hours (±1 h), 48 hours (±2 h), and 72 hours (±4 h)
- **Physical examination:** 72 hours (±4 h; height and weight not required)
- **Blood sample for hematology and serum chemistry tests:** 24 hours (±1 h; hematology only) and 72 hours (±4 h; hematology and serum chemistry)
- **Blood sample collection for PK**: 4 hours (±15 min), 18 hours (±30 min), 24 hours (±1 h), and 48 hours (±2 h)
- **Wound healing assessment:** 72 hours (±4 h)
- **Discharge readiness assessment per the MPADSS criteria:** 2 and 4 hours (±15 min), 8 and 12 hours (±30 min), 24 hours (±1 h), 36 and 48 hours (±2 h), 60 and 72 hours (±4 h)
- **AE recording:** (Note: the start date and time of all AEs during this timeframe must be recorded)
- **Concomitant medication recording:** (Note: the start date and time of all concomitant medications during this timeframe must be recorded)
- **Use of rescue medication recording:** Any time between study drug administration and 72 hours (Note: the start date and time of all rescue medications during this timeframe must be recorded.)

7.2.3. End of the Postoperative Assessment Period

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

Subjects who are not medically ready for discharge at 72 hours may receive the same rescue medication as outlined in Section 3.1.3 to treat postoperative pain until discharge.

For subjects who are medically ready for discharge at 72 hours, oral acetaminophen (no more than 1000 mg every 6 hours as needed) should be recommended for postoperative pain. If a subject received 10 mg or more of oxycodone in the 12 hours prior to discharge, the subject should be provided with a prescription for oxycodone (up to 10 mg PO q4h as needed, #15, no substitutions). See Appendix G for instructions on postoperative pain management for subjects medically ready for discharge.

Subjects will be given a diary to complete daily and record if they take any opioid medication from 72 hours through Day 28.

7.3. Follow-Up Period

7.3.1.1. Day 10 Visit (±3 Days)

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

- NRS-R pain intensity assessment
- NRS-A pain intensity assessment
- Wound healing assessment
- Blood sample collection for the hematology and serum chemistry
- Review subject diary results
- AE recording
- Concomitant medication recording

7.3.1.2. Day 28 Visit (±4 Days)

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

- NRS-R pain intensity assessment
- NRS-A pain intensity assessment
- PGA of pain control assessment
- Wound healing assessment
- Review subject diary results
- AE recording
- Concomitant medication recording
- Bone healing assessment (X-ray)

7.3.1.3. Safety Follow-Up (Day 42 ±7 Days)

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

- Wound healing assessment
- AE recording
- Concomitant medication recording
- Bone healing assessment (X-ray)

7.4. Early Termination Visit

Subjects who withdraw from the study before their Day 28 Visit will be asked to complete Early Termination procedures, which will include the items listed in Section 7.4.1. Subjects who withdraw from the study after the Day 28 Visit but prior to the Safety Follow-Up on Day 42 will

be asked to complete Early Termination procedures, which will include the items listed in Section 7.4.2.

7.4.1. Withdrawal Prior to the Day 28 Visit

- NRS-R pain intensity assessment
- NRS-A pain intensity assessment
- PGA of pain control assessment
- Vital signs (if withdrew prior to 72 hours)
- Blood sample collection for hematology and serum chemistry (if withdrew prior to 72 hours)
- 12-lead ECG (triplicate) (if withdrew prior to 72 hours)
- Physical examination (if withdrew prior to 72 hours [height and weight not required])
- Wound healing assessment
- Bone healing assessment (X-ray; if clinically indicated and withdrew after 72 hours)
- LAST assessment (if withdrew prior to 72 hours)
- Review subject diary results
- AE recording
- Concomitant medication recording

7.4.2. Withdrawal After the Day 28 Visit and Prior to the Safety Follow-Up on Day 42

- AE recording
- Concomitant medication recording
- Wound healing assessment
- Bone healing assessment (X-ray)

7.5. Unscheduled Visits and Assessments

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

- Vital signs
- Physical examination
- ECG
- Wound healing assessment

- AE recording
- Concomitant medication recording
- Blood sample collection to determine plasma bupivacaine concentration (if the unscheduled visit is potentially related to a cardiac or neurological TEAE)
- Blood sample collection for hematology and chemistry
- X-ray of the surgical site (if clinical concern)

8. SAFETY MONITORING AND REPORTING

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

Investigators must review the HTX-011 IB so as to be aware of the safety-related events, which may be anticipated with its use. Investigators will also be versed in the latest standard of care guidelines.

8.1. Definition of Safety Parameters

8.1.1. Definition of an Adverse Event

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

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

Examples of AEs include the following:

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

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

The following examples are not considered AEs:

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

8.1.2. Definition of a Serious Adverse Event

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

- Death.
- A life-threatening AE (ie, presented an immediate risk of death from the event as it occurred. This criterion is not intended to include an AE that, had it occurred in a more severe form, might have caused death.)
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

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

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

8.1.3. Definition of a Suspected Adverse Reaction

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

8.1.4. Definition of a Serious Suspected Adverse Reaction

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

8.1.5. Definition of Unanticipated Problems

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

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

An unanticipated adverse device effect is defined in Section 8.1.2.

8.2. Classification of Adverse Events

8.2.1. Severity of Adverse Events

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

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

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

8.2.2. Relationship to Study Drug

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

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

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

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

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

8.3.1. Adverse Event and Serious Adverse Event Monitoring

All AEs regardless of causality or seriousness will be recorded from the time the subject signs the ICF through the Safety Follow-Up on Day 42. Note: the AE start time, as well as the date, must be recorded during the 72-hour postoperative period. After this period, only the start date must be recorded.

For subjects who received study drug, if an Investigator becomes aware of an SAE that occurs after the subject's study participation and the Investigator considers the event to be possibly related to the study drug, the Investigator needs to report the SAE to the Sponsor as described in Section 8.4.1.

8.3.2. Follow-Up of Events

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

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

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

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

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

8.4. Reporting Procedures

8.4.1. Reporting Serious Adverse Events to the Sponsor

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

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

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

Email Address: Heron_PV@ubc.com

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

- AE record
- Medical history
- Prior and concomitant medications

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

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

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

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

8.4.2. Reporting Unanticipated Problems to the Sponsor

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

Email Address: Heron_PV@ubc.com

The following information will be included with unanticipated problem reporting:

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

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

8.4.3. Regulatory Reporting Requirements

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

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

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

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

8.4.4. Pregnancy Reporting

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

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

Email Address: Heron_PV@ubc.com

8.5. Safety Oversight

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

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

9. OTHER STUDY RESTRICTIONS

9.1. Contraception

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

10. STATISTICAL CONSIDERATIONS

10.1. General Considerations

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

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

10.2. Determination of Sample Size

Based on a previous Phase 2 study of HTX-011 in subjects undergoing unilateral simple bunionectomy, estimates of the relevant parameters for each of the primary and key secondary endpoints are as follows:

Parameter	Saline Placebo	Bupivacaine HCl	HTX-011 60 mg/1.8 mg
Pain intensity AUC_{0-72}: Mean (SD)	425 (175)	425 (175)	325 (175)
Opioid consumption (mg): Mean (SD)	30 (25)	30 (25)	20 (20)
Proportion of opioid-free subjects	5%	10%	25%

Assuming these estimates and using Satterthwaite's t-test with $\alpha = 0.05$, 2-sided for the continuous endpoints and Fisher's exact test with $\alpha = 0.05$, 2-sided for the categorical endpoints, 150 subjects in the HTX-011 group, 150 subjects in the bupivacaine HCl active control group, and 100 subjects in the saline placebo control group provide at least 90% power to detect a statistically significant difference between the HTX-011 group and each of the control groups for each of the primary and key secondary endpoints.

10.3. Analysis Populations

Intent-to-Treat (ITT) Population: All subjects who are randomized and receive study drug will be included in the ITT Population. This population will be used as the primary analysis population for all efficacy endpoints. The randomized treatment assignment will be used for analysis in this population.

Per Protocol Population: All subjects in the ITT Population who do not receive a prohibited rescue medication prior to 72 hours and who have no important protocol violations prior to 72 hours will be included in the Per Protocol Population. This population will be used for sensitivity analyses on the primary and key secondary endpoints.

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

10.4. Statistical Analysis Methods

10.4.1. Disposition and Demographics

The number and percentage of subjects in each analysis population will be summarized. Subject disposition, including the number of subjects screened, randomized, dosed, completing the 72-hour postoperative observation period, completing Day 28, completing the Safety Follow-up on Day 42, and not completing the Safety Follow-up on Day 42 by reason for withdrawal will be summarized for the ITT Population. Subject demographics and baseline characteristics will also be summarized for the ITT Population and will include age, age category, sex, race, ethnicity, height, weight, and BMI.

10.4.2. Efficacy Analysis

10.4.2.1. Primary Efficacy Analysis

The primary estimand to address the efficacy objectives is the mean AUC of NRS-A pain intensity scores through 72 hours (AUC_{0-72}) adjusted for use of opioid rescue medication via windowed worst observation carried forward (wWOCF), comparing the estimated treatment difference between HTX-011 and saline placebo using analysis of variance (ANOVA) with missing data imputed via last observation carried forward (LOCF) for interval censored pain intensity scores and worst observation carried forward (WOCF) for right-censored pain intensity scores in the ITT Population.

The primary analysis of AUC_{0-72} of the NRS-A pain intensity scores will be carried out using an ANOVA model with treatment as the main effect, comparing HTX-011 with saline placebo at a significance level of 5%. Results will be expressed as mean AUCs and SDs, least-squares mean differences (LSMD) and SEs with associated 95% CIs, and p-values. To account for the duration effect of opioid rescue medication, the wWOCF method will be implemented as the primary analysis method for endpoints involving NRS pain intensity scores. In this method, pain intensity scores observed during the analgesic window (duration of effect) of any opioid rescue medication will be replaced with the worst (highest) postdose nonmissing NRS pain intensity score observed prior to the rescue medication window, with the following exception: if the NRS pain intensity score for a windowed observation is higher than the worst pre-window score, then it will not be replaced. Sensitivity analyses for endpoints involving NRS pain intensity scores will analyze the data without adjustment for the effect of opioid rescue medications.

10.4.2.2. Key Secondary Efficacy Analyses

Key secondary endpoints involving AUC of NRS-A will be analyzed similarly to the methods described for the primary endpoint.

Total opioid consumption through 72 hours will be summarized using descriptive statistics. The Shapiro-Wilk test will be used to examine the assumption of normality. If this test is statistically significant (ie, $p \leq 0.05$) then the assumption of normality is violated and the total postoperative opioid consumption during period of interest will be analyzed using Wilcoxon rank sum test. Results will be expressed as median (range) and p-values. However, if assumption of normality holds (ie, Shapiro-Wilk p-value >0.05), then the total postoperative opioid consumption during period of interest will be analyzed using an ANOVA model with randomized treatment as the

main effect. Results will be expressed as means, SDs, and LSMD and SE with associated 95% CI, and p-values.

The proportion of subjects who are opioid-free through 72 hours will be analyzed using Fisher's exact test. Results will be expressed as the number and percentage of subjects meeting the relevant endpoint, differences in proportions with 95% CIs, and p-values.

10.4.2.3. Study-Wise Type I Error Control

To account for multiple hypothesis testing on the primary endpoint and on each of the 4 key secondary endpoints, a strict testing hierarchy will be applied to control study-wise alpha level at 0.05. If the primary endpoint is statistically significant ($p \leq 0.05$), then the first key secondary endpoint will be tested. If the first key secondary endpoint is statistically significant, then the second key secondary endpoint will be tested. Sequential testing will continue in this manner down the key secondary endpoint list until an endpoint fails to meet statistical significance, after which all subsequent key secondary endpoints will be considered exploratory. If the primary endpoint is not statistically significant, then all key secondary endpoints will be considered exploratory.

[redacted]

10.4.2.5. Handling of Missing Data

Due to the required 72-hour inpatient postoperative observation period, the amount of missing data is expected to be very low. For any missing data observed through 72 hours in subjects who complete the 72-hour postoperative observation period, NRS pain intensity scores will be imputed via LOCF, in which the most recent postdose value is used for a subsequent missing value. For subjects who do not have a postdose value prior to their first missing value, the median of the postdose values at the relevant timepoint from subjects with observed data in the same randomized treatment group will be used. Predose values will not be carried forward to postdose timepoints. In subjects who withdraw from the study prior to 72 hours, missing NRS pain intensity scores through 72 hours that were to be collected following withdrawal will be imputed via WOCF, in which the worst (highest) NRS pain intensity score observed prior to withdrawal will be used for post-withdrawal values through 72 hours. Analyses that adjust for the effect of opioid rescue medication will perform wWOCF following LOCF/WOCF (ie, perform LOCF/WOCF first, then apply wWOCF). The number and percentage of missing NRS pain intensity scores will be summarized.

10.4.3. Safety Analysis

All safety analyses will be carried out on the Safety Population. All safety data will be listed and summarized by treatment group.

AEs that occur between the time the subject signs the ICF and the start of study drug administration will be considered pretreatment AEs. AEs that start during or after study drug administration, or AEs with an onset prior to study drug administration that worsen after study

drug administration will be considered TEAEs. All TEAEs will be coded and tabulated by System Organ Class and Preferred Term. Incidence of TEAEs and SAEs will be summarized and presented in descending order of frequency according to the HTX-011 group. AEs leading to study withdrawal, if any, will be listed separately.

Associated laboratory parameters such as hepatic profile, renal function, and hematology values will be grouped and presented together in summary tables. For each laboratory test, individual subject values will be listed and values outside of the standard reference range will be flagged. Shift tables will be produced showing the frequency of shifts from Baseline to the lowest and to the highest on-study value in and out of the normal range as well as by visit. Laboratory parameters will also be summarized by visit.

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

Wound healing assessment results will be summarized at each timepoint. Bone healing assessment X-ray results will also be summarized.

10.4.4. Pharmacokinetic Analysis

Plasma bupivacaine and meloxicam concentrations will be determined using validated liquid chromatography tandem-mass spectrometry assays. Concentrations will be calculated by interpolation from a calibration curve. An estimated C_{max} and T_{max} will be calculated using population PK modeling, which will be developed in non-linear mixed effects modeling (NONMEM) using data from previous HTX-011 clinical studies.

10.5. Interim Analysis

No formal interim analyses are planned.

11. QUALITY ASSURANCE AND QUALITY CONTROL

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

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

12. REGULATORY AND ETHICAL CONSIDERATIONS

12.1. Regulatory Authority Approval

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

12.2. Ethical Conduct of the Study

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

12.3. Ethics Committee Approval

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

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

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

12.4. Informed Consent Process

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

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

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

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

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

12.5. Confidentiality

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

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

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

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

13. STUDY ADMINISTRATION

13.1. Clinical Monitoring

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

13.2. Source Documents and Record Retention

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

Study records must be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by applicable regulatory requirements or if agreed to in the Clinical Trial Agreement. It is the responsibility of the Sponsor to inform the site as to when these documents no longer need to be retained.

13.3. Management of Protocol Amendments and Deviations

13.3.1. Protocol Modification

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

13.3.2. Protocol Violations and Deviations

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

Protocol deviations fall into 2 categories: those with approval prior to the event (protocol exemptions) and those occurring during the course of the study without prior approval (protocol

violations). If an exemption from the protocol design (eg, a missed study visit or an unmet inclusion or exclusion criterion) is desired for an individual subject, other than those to eliminate immediate hazard, the Investigator must request an exemption from the Sponsor or designee. The Investigator will notify the EC of exemptions and deviations, as required by EC guidelines and site requirements. Exemptions (with rationale) will be documented at the site and in the Sponsor files. For any protocol violation, the site will document the protocol violation in the subject's source documents. In the event of a significant violation, the site will notify the Sponsor or designee. Significant violations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessments. The Sponsor is responsible for notifying the regulatory authorities, if required.

13.4. Financial Disclosure

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

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

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

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

13.5.1. Suspension of Study

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

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

13.5.2. Termination of Study or Investigational Site

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

- If there is a suspension of the study and further investigation shows that any death or 3 non-fatal SAEs are determined by the Sponsor to be related to study drug and pose an unacceptable risk to the study subjects, the study will be terminated.
- Discovery of an unexpected, significant, or unacceptable risk to the subjects.
- Failure of the Investigator to comply with the protocol, GCP regulations and guidelines, or local requirements.
- Insufficient adherence to protocol requirements or an unacceptably high rate of missing, erroneous, or improperly collected data.
- Data are not sufficiently complete and/or evaluable.
- Inadequate recruitment of subjects by the Investigator.
- Sponsor decision.

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

13.6. Publication and Information Disclosure Policy

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

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

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

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

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APPENDIX A. AMERICAN SOCIETY OF ANESTHESIOLOGISTS PHYSICAL STATUS CLASSIFICATION SYSTEM

ASA PS Classification	Definition	Examples, including, but not limited to:
ASA I	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use
ASA II	A patient with mild systemic disease	Mild diseases only without substantial functional limitations. Examples include, but not limited to: current smoker, social alcohol drinker, pregnancy, obesity (30 < BMI <40), well-controlled DM/HTN, mild lung disease
ASA III	A patient with severe systemic disease	Substantial functional limitations; one or more of moderate to severe diseases. Examples include, but not limited to: poorly controlled DM or HTN; COPD; morbid obesity (BMI ≥40); active hepatitis; alcohol dependence or abuse; implanted pacemaker; moderate reduction of ejection fraction; ESRD undergoing regularly scheduled dialysis; premature infant PCA <60 weeks; history (>3 months) of MI, CVA, TIA, or CAD/stents
ASA IV	A patient with severe systemic disease that is a constant threat to life	Examples include, but not limited to: recent (<3 months) of MI, CVA, TIA, or CAD/stents; ongoing cardiac ischemia or severe valve dysfunction; severe reduction of ejection fraction; sepsis; DIC; ARD or ESRD not undergoing regularly scheduled dialysis
ASA V	A moribund patient who is not expected to survive without the operation	Examples include, but not limited to: ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	

Abbreviations: ARD, acute renal disease; ASA, American Society of Anesthesiologists; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DIC, disseminated intravascular coagulation; DM, diabetes mellitus; ESRD, end stage renal disease; HTN, hypertension; MI, myocardial infarction; PCA, postconceptional age; PS, physical status; TIA, transient ischemic attack.
Note: The addition of "E" denotes Emergency surgery. (An emergency is defined as existing when delay in treatment of the patient would lead to a significant increase in the threat to life or body part.)
Source: ASA Physical Status Classification System approved by the ASA House of Delegates on October 15, 2014.

APPENDIX B. BMI CALCULATION

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

Meters = inches × 0.0254

Kilograms = pounds × 0.45

Example:

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

165 lbs. × 0.45 = 74.25 kg

71 in. × 0.0254 = 1.8 m

74.25 / (1.8 × 1.8) = 22.92 kg/m^2

APPENDIX C. PAIN INTENSITY ASSESSMENTS USING THE NUMERIC RATING SCALE (NRS)

The following question will be answered by the subject for all NRS with activity (NRS-A) and NRS at rest (NRS-R) pain intensity assessments:

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

The response must be one of the following:

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

Reference: Breivik, H., P. C. Borchgrevink, S. M. Allen, L. A. Rosseland, L. Romundstad, E. K. Hals, G. Kvarstein and A. Stubhaug (2008). "Assessment of pain." Br J Anaesth 101(1): 17-24.

APPENDIX D. PATIENT GLOBAL ASSESSMENT (PGA) OF PAIN CONTROL

The following question will be answered by the subject at each PGA assessment timepoint:

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

The response must be one of the following:

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

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

APPENDIX E. DISCHARGE READINESS ASSESSMENT – MODIFIED POSTANAESTHETIC DISCHARGE SCORING SYSTEM CRITERIA

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

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

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

Appendix F. WOUND HEALING ASSESSMENT

Record "Present" or "Absent" for each of the following symptoms in relationship to the wound. Signs and symptoms that are present should be entered on the electronic case report form (eCRF) as adverse events (AEs). Note that if an event qualifies as a serious adverse event (SAE; see Section 8.4.1), the Sponsor must be notified within 24 hours of when the Investigator is first aware of the event.

Bruising	Present ☐	Absent ☐
Erythema	Present ☐	Absent ☐
Edema	Present ☐	Absent ☐
Heat	Present ☐	Absent ☐
Drainage	Present ☐	Absent ☐
Cellulitis	Present ☐	Absent ☐
Delayed healing	Present ☐	Absent ☐
Dehiscence	Present ☐	Absent ☐

APPENDIX G. INSTRUCTIONS FOR POSTOPERATIVE PAIN MANAGEMENT FOR SUBJECTS MEDICALLY READY FOR DISCHARGE

The following text should be read by the Investigator or designee to the subject at the time of discharge:

You have completed the initial part of the study which required you to stay at the facility. You are now being discharged to go home. You will come back here again for check-up visits on Day 10 (approximately 1 week from now), Day 28 (approximately 3½ weeks from now), and for a Safety Follow-Up on Day 42 (approximately 5½ weeks from now).

While you are at home, if you experience any pain from your operation, please take up to 2 over-the-counter extra-strength (500 mg) acetaminophen tablets (eg, Tylenol) every 6 hours as needed. Do not take more than 8 tablets (4000 mg) in a 24-hour period. If this does not control your pain, please call <<insert name and contact information>> so that we can talk about providing you with a prescription for something stronger, if needed.

Do not take other acetaminophen-containing products that are available over the counter without first checking with your doctor. As an example, cold medicine over the counter may contain acetaminophen and may result in exceeding the daily dose limit of acetaminophen and can cause liver damage.

NOTE: If a subject required 10 mg or more of oxycodone in the 12 hours prior to discharge, the subject should be provided with a prescription for oxycodone up to 10 mg PO q4h, #15, as needed. Pharmacists should be instructed that substitutions for any other opioid-containing product are not permitted.

APPENDIX H. LOCAL ANESTHETIC SYSTEMIC TOXICITY ASSESSMENT

This Local Anesthetic Systemic Toxicity (LAST) questionnaire is provided to monitor for early neurologic and cardiac signs and symptoms of LAST. Subjects should be assessed with this questionnaire at the following timepoints: 30 minutes (±5 min), 1 hour (±5 min), 2 hours (±15 min), 4 hours (±15 min), 18 hours (±30 min), 24 hours (±1 h), and 72 hours (±4 h) following the start of study drug administration, and at the Early Termination Visit if the subject withdraws before 72 hours.

If a subject has signs or symptoms that may be attributed to LAST, vital sign measurements, 12-lead ECG, and blood sample collection for PK must be performed. In many cases, those assessments are already scheduled within that timepoint and do not need to be repeated (see the shaded areas in the table below). If symptoms are present at a timepoint when one of these assessments is not scheduled, an unscheduled assessment must be performed. These unscheduled assessments are shown by timepoint as the checked areas in the following table.

Signs or Symptoms of LAST: Unscheduled Assessments of ECGs and PK Blood Samples

	Time After Study Drug Administration							
Assessment	**30 min**	**1h**	**2h**	**4h**	**18h**	**24h**	**72h**	**ET[a]**
Vital signs	Scheduled assessments							
12-lead ECG (triplicate)	√	√	√	Scheduled assessments				
Blood sample for PK	√	√	√	Scheduled assessments			√	√

Abbreviations: ECG, electrocardiogram; ET, Early Termination; h, hour; min, minutes; LAST, Local Anesthetic Systemic Toxicity; PK, pharmacokinetics.
[a] Only if subject withdraws prior to 72 hours.
√ - obtain unscheduled 12-lead ECG and blood sample for PK if signs or symptoms that may be attributed to LAST are present.

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

Local Anesthetic Systemic Toxicity (LAST) Questionnaire

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

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

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

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Approval	[redacted] 25-Sep-2017 00:31:06 GMT+0000

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