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Official Title:	A Phase 3b, Open-Label Study of HTX-011 as Part of a Scheduled Non-Opioid Multimodal Analgesic Regimen in Subjects Undergoing Total Knee Arthroplasty
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CLINICAL STUDY PROTOCOL: HTX-011-306

Protocol Title:	A Phase 3b, Open-Label Study of HTX-011 as Part of a Scheduled Non-Opioid Multimodal Analgesic Regimen in Subjects Undergoing Total Knee Arthroplasty
Brief Title:	TKA Study of HTX-011 in an MMA Regimen
Investigational Product:	HTX-011 (bupivacaine and meloxicam) extended-release solution
Phase of Development:	3b
Sponsor:	Heron Therapeutics, Inc. 4242 Campus Point Court, Suite 200 San Diego, CA 92121 1-858-251-4400
Medical Monitor:	[redacted]
Medical Project Leader:	[redacted]

Protocol Version:		
	Version 6	02 July 2020
	Version 5	12 September 2019
	Version 4	07 August 2019
	Version 3	26 June 2019
	Version 2	29 May 2019
	Version 1	30 April 2019

SPONSOR SIGNATURE

Protocol Title:	A Phase 3b, Open-Label Study of HTX-011 as Part of a Scheduled Non-Opioid Multimodal Analgesic Regimen in Subjects Undergoing Total Knee Arthroplasty
Protocol Number:	HTX-011-306

This protocol Version 6 has been reviewed and approved by the Sponsor.

The electronic signature is appended.

[redacted]
Heron Therapeutics, Inc.

INVESTIGATOR AGREEMENT

CLINICAL STUDY PROTOCOL: HTX-011-306

TITLE: A Phase 3b, Open-Label Study of HTX-011 as Part of a Scheduled Non-Opioid Multimodal Analgesic Regimen in Subjects Undergoing Total Knee Arthroplasty

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

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

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

Principal Investigator: _____

Address: _____

Signature: _____

Date: _____

PROTOCOL SYNOPSIS

NAME OF SPONSOR:	Heron Therapeutics, Inc.
NAME OF FINISHED PRODUCT:	HTX-011 (bupivacaine and meloxicam) extended-release solution
NAME OF ACTIVE INGREDIENTS:	bupivacaine and meloxicam
PROTOCOL NUMBER:	HTX-011-306
PHASE OF DEVELOPMENT:	3b

PROTOCOL TITLE: A Phase 3b, Open-Label Study of HTX-011 as Part of a Scheduled Non-Opioid Multimodal Analgesic Regimen in Subjects Undergoing Total Knee Arthroplasty

STUDY SITES: Up to 6 sites in the United States (US).

STUDY OBJECTIVES:

Primary

- To assess pain control following HTX-011 as part of a scheduled non-opioid multimodal analgesic (MMA) regimen in subjects undergoing total knee arthroplasty (TKA).

Secondary

- To assess total opioid use following HTX-011 as part of a scheduled non-opioid MMA regimen in this study population.
- To assess the proportion of subjects who are opioid-free after receiving HTX-011 as part of a scheduled non-opioid MMA regimen in this study population.
- To assess the safety and tolerability of HTX-011 in a multimodal setting in this study population.
- To characterize the pharmacokinetic (PK) parameters of bupivacaine and meloxicam in this study population.

BACKGROUND AND RATIONALE FOR THE STUDY: Up to 70% of patients have moderate to severe pain after surgery, and as a result, many receive opioids. Poorly managed pain and opioid-related adverse reactions resulting in worse patient outcomes and increased hospital costs. Opioid use also increases the risk of long-term use and abuse. Therefore, there is a significant unmet need for a more effective non-opioid analgesic that provides sustained pain relief and reduces or eliminates the need for opioids, especially in the first 72 hours following surgery.

Heron Therapeutics, Inc. (Heron) has developed HTX-011 for application into the surgical site to reduce postoperative pain for 72 hours and the need for opioid analgesics. HTX-011 is a novel, non-opioid, fixed-dose, extended-release anesthetic containing bupivacaine and low-dose meloxicam formulated in a proprietary polymer that enables extended release of the products simultaneously for approximately 3 days. Bupivacaine is an amide-type local anesthetic and meloxicam is a nonsteroidal anti-inflammatory drug (NSAID). HTX-011 is administered as a single dose. In a prior Phase 2b study in TKA (Study 209), HTX-011 400 mg/12 mg with or without ropivacaine injected into the posterior capsule significantly reduced pain over 48 hours and 72 hours compared with saline placebo despite the absence of a background scheduled MMA regimen. Although almost all subjects required opioid rescue during the 72-hour postoperative period, HTX-011 reduced total opioid consumption.

This Phase 3b study will evaluate if HTX-011 administered as the foundation of a scheduled non-opioid MMA regimen can further improve pain control and lead to greater reduction or eliminate the need for opioids following primary unilateral TKA. Multimodal analgesia for the treatment of postoperative pain is

recommended in the American Pain Society guidelines. The analgesic regimen in Cohorts 1 to 3 in this study, acetaminophen and celecoxib, was selected based on published literature. Acetaminophen and celecoxib have different mechanisms of action and may therefore increase effectiveness without increasing risk. The study will also evaluate the contribution of bupivacaine HCl injection into the posterior capsule on the reduction of postoperative pain in Cohort 3.

An additional fourth cohort has been added to test the hypothesis that the postoperative nonspecific cyclooxygenase (COX) inhibition of ibuprofen will contribute more to postoperative analgesia and therefore work better with HTX-011, as opposed to the COX-2 specific inhibition gained from celecoxib, which contributes more to an anti-inflammatory effect and therefore may be duplicative to the impact of the local meloxicam applied as part of HTX-011.

METHODOLOGY: This is a Phase 3b, open-label, multicohort study in which all subjects will receive HTX-011 as part of a scheduled non-opioid MMA regimen.

Study Overview

Subjects will be screened within 28 days prior to the planned surgery date and eligibility will be confirmed on the day of surgery. Subjects who meet the eligibility criteria will be enrolled in the study and will undergo primary unilateral TKA under bupivacaine spinal anesthesia (≤20 mg).

All subjects will receive HTX-011 as part of a non-opioid MMA regimen consisting of acetaminophen, an NSAID, and a gabapentanoid prior to surgery, a single dose of HTX-011 during surgery, and scheduled acetaminophen and an NSAID for 7 days following surgery. Up to 115 subjects will be dosed in 4 sequential cohorts:

- Cohort 1: Approximately 50 subjects will be administered a single dose of HTX-011 400 mg/12 mg via periarticular application into the surgical site during surgery.
- Cohort 2: Approximately 15 subjects will be administered a single dose of HTX-011 400 mg/12 mg via periarticular application into the surgical site during surgery. Drains will be prohibited.
- Cohort 3: Approximately 30 subjects will be randomized into 2 groups. In Group A, subjects will be administered a single dose of HTX-011 300 mg/9 mg via periarticular application into the surgical site during surgery. In Group B, subjects will be administered a single dose of HTX-011 300 mg/9 mg via periarticular application into the surgical site and 100 mg bupivacaine HCl injected into the posterior capsule during surgery. Drains will be prohibited.
- Cohort 4: Up to approximately 20 subjects will be administered a single dose of HTX-011 400 mg/12 mg via periarticular application into the surgical site during surgery.

On the day of surgery (Day 1), subjects will be administered oral (PO) acetaminophen 1 g, PO celecoxib 200 mg, and PO pregabalin 300 mg just before being taken to the operating room. During surgery, a single dose of HTX-011 will be administered via periarticular application into the surgical site in all study cohorts. Bupivacaine HCl will be administered into the posterior capsule in Group B of Cohort 3. The use of intravenous (IV) fentanyl up to 4 μg/kg will be permitted during surgery for intraoperative pain control. Subjects will remain in the hospital/research facility for 72 hours from the start of study drug administration to undergo postoperative efficacy, safety, and PK assessments.

Subjects will receive a scheduled non-opioid MMA regimen over the 72-hour postoperative period consisting of PO acetaminophen 1 g every 8 hours and PO celecoxib 200 mg every 12 hours (Cohorts 1, 2, and 3) or PO acetaminophen 1 g every 8 hours and PO ibuprofen 600 mg every 6 hours (Cohort 4).

After the 72-hour assessments have been completed, subjects may be discharged. Subjects in all cohorts will continue a scheduled MMA regimen for 4 days after discharge consisting of PO ibuprofen alternating with PO acetaminophen. Thereafter, subjects may continue acetaminophen and/or ibuprofen as needed. Subjects will return to the study site on Days 11 and 29 for follow-up assessments.

Inpatient Postoperative Rescue Medication

During the 72-hour postoperative period, subjects should only receive rescue medication upon request for pain control. 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 pain intensity scores using the visual analogue scale (VAS) and numeric rating scale (NRS) must be obtained.

Postoperative rescue medication will consist only of any 1 or more of the following opioid medications, as needed: PO immediate-release oxycodone (≤10 mg within a 4-hour period), IV morphine (2.5 mg to 5 mg within a 4-hour period), and/or IV hydromorphone (0.5 mg to 1.0 mg within a 4-hour period). Combination products containing an opioid and non-opioid are not allowed. With the exception of the protocol-specified MMA medications, no other analgesic agents, including other NSAIDs, are permitted during the 72-hour postoperative period. Note: Acetaminophen is not to be given as a rescue medication as it is part of the postoperative scheduled MMA regimen.

Opioid Prescriptions at and After Discharge

If a subject did not receive any opioids or received <10 mg of oxycodone within 12 hours prior to discharge, the subject should not receive an opioid prescription at discharge. If a subject received ≥10 mg of oxycodone within 12 hours prior to discharge, the Investigator may provide the subject with a prescription for immediate-release PO oxycodone tablets: no more than thirty 5 mg immediate-release oxycodone, take 1 to 2 pills (5 mg to 10 mg) every 4 hours as needed. The prescription must indicate that substitutions with any other opioid-containing product are not permitted, including combination opioid/non-opioid products.

Sites will record if subjects are discharged with an opioid prescription and information about the opioid prescription. All subjects (whether or not they were discharged with an opioid prescription) will be provided a daily diary to record any opioid medication use from discharge through the Day 11 Visit. Sites will record all site- or subject-initiated contact between discharge and the Day 11 Visit and if any contact resulted in issuing an opioid prescription.

Postoperative Analgesia After Discharge

Upon discharge, subjects will be instructed to manage their pain while awake over the next 4 days with the following scheduled MMA regimen: PO ibuprofen 600 mg every 6 hours, alternating with PO acetaminophen 1 g every 6 hours, so that an analgesic is taken approximately every 3 hours. Thereafter, subjects may continue one or both of the MMA medications as needed, but should not exceed ibuprofen 600 mg every 6 hours or acetaminophen 1 g every 6 hours (maximum ibuprofen dose of 2.4 g/day and maximum acetaminophen dose of 4 g/day).

Other Scheduled Study Medications

All subjects will also receive IV tranexamic acid (TXA) and PO acetylsalicylic acid for antifibrinolysis and deep vein thrombosis (DVT) prophylaxis, respectively. TXA 1g IV will be administered within approximately 4 hours prior to the start of surgery and a second dose will be administered up to approximately 8 hours later. Subjects will receive acetylsalicylic acid 325 mg PO twice a day (BID) following surgery until discharge.

Prohibited Medications

Other than the protocol-required study medications, any drug formulation containing bupivacaine or meloxicam is prohibited before surgery (within 5 days for bupivacaine and within 10 days for meloxicam), during surgery, and following surgery through Day 11 Visit. Refer to exclusion criteria 4 through 13 for medications that are prohibited during the study.

NUMBER OF PLANNED SUBJECTS: Approximately 115 subjects will be enrolled and dosed.

STUDY POPULATION:

Inclusion Criteria

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

1. Is able to provide written informed consent.
2. Is able to adhere to the study visit schedule and complete all study assessments.
3. Is male or female, and ≥18 years of age at screening.
4. Is scheduled to undergo primary unilateral TKA under spinal anesthesia (all cohorts) and without drains in Cohorts 2 and 3.
5. Has not previously undergone TKA in either knee.
6. Has an American Society of Anesthesiologists Physical Status of I, II, or III.
7. Is able to walk at least 20 feet with optional use of a 4-legged walker for balance.
8. Female subjects are eligible only if all of the following apply:
    a. Not pregnant (female subject 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 double-barrier contraception; or practicing abstinence (must agree to use double-barrier contraception in the event of sexual activity); or is using an insertable, injectable, transdermal, or combination PO contraceptive approved by the US Food and Drug Administration (FDA) and commits to the use of an acceptable form of birth control from the Screening Visit until 30 days after study drug administration. Note: women in only a same-sex relationship do not need to meet this criterion.

Exclusion Criteria

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

1. Has a planned concurrent surgical procedure (eg, bilateral TKA) during the study.
2. 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 knee surgery and which may confound the postoperative assessments.
3. Has a contraindication or a known or suspected history of hypersensitivity or clinically significant idiosyncratic reaction (including methemoglobinemia) to bupivacaine (or other local anesthetics), NSAIDs (eg, meloxicam, ibuprofen, celecoxib), oxycodone, morphine, hydromorphone, TXA, fentanyl, pregabalin, acetaminophen, or acetylsalicylic acid.
4. Using or expected to use Factor IX Complex or anti-inhibitor coagulant concentrates during the study.
5. Has known or suspected daily use of opioids for 7 or more consecutive days within the previous 6 months.
6. Has taken NSAIDs (including meloxicam) within 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 adverse event (AE) that occurs after

signing the informed consent form (ICF), or to decrease venous irritation caused by propofol, if needed (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, duloxetine, or 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). Note that for purposes of this exclusion criterion, inhaled, ophthalmic, and over-the-counter steroids are not considered systemic.
13. Previously participated in a clinical study or received an investigational product or device in a clinical trial within 30 days or within 5 elimination half-lives (whichever is longer) prior to the scheduled surgery, or is planning to take part in another clinical trial while participating in this study.
14. Has a known or suspected history of drug abuse, a positive drug screen on the day of surgery, or a history of alcohol abuse (within 10 years). 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 with a positive drug screen for cannabinoids on the day of surgery will not be allowed to participate in the study.
15. 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 of electrocardiogram (ECG) or cardiac function.
    b. History of coronary artery bypass graft surgery within 12 months prior to signing the ICF.
    c. 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. Severe kidney function impairment as defined by creatinine clearance (Cockcroft-Gault) <30 mL/min or on dialysis.
    e. History of known or suspected coagulopathy or uncontrolled anticoagulation (platelet count <100,000/μL; hemoglobin <12 g/dL; or hematocrit <35%).
    f. Loss of sensation in extremities or significant peripheral neuropathy.
    g. Known history of glucose-6-phosphate dehydrogenase deficiency.
16. Is currently undergoing treatment for hepatitis B, hepatitis C, or HIV.
17. Has uncontrolled anxiety, psychiatric, or neurological disorder that, in the opinion of the Investigator, might interfere with study assessments.
18. Has acquired defective color vision or acute gastrointestinal ulcers, either of which could interfere with scheduled study medications.
19. Has any chronic neuromuscular deficit of either femoral nerve function or thigh musculature.
20. Has any chronic condition or disease that would compromise neurological or vascular

assessments.

21. 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.
22. Has undergone 3 or more surgeries within 12 months prior to signing the ICF, other than for diagnostic procedures (eg, colonoscopy).
23. Has a body mass index (BMI) >40 kg/m^2.

INVESTIGATIONAL PRODUCT, DOSE, AND MODE OF ADMINISTRATION:

HTX-011 is a fixed-dose, extended-release anesthetic that contains bupivacaine and low-dose meloxicam. Bupivacaine is an amide-type local anesthetic and meloxicam is an NSAID. [redacted].

HTX-011 will be supplied by the Sponsor as a clear, pale yellow to yellow, viscous liquid in single-dose 20 mL glass vials.

All subjects will receive a single dose of HTX-011. Subjects in Cohorts 1, 2, and 4 will receive 400 mg/12 mg (bupivacaine/meloxicam doses). Subjects in Cohort 3 will receive 300 mg/9 mg.

HTX-011 will be administered intraoperatively by periarticular application into the surgical site with a Luer lock applicator (without a needle) distributed to 3 areas: (1) the posterior capsule (except Group B of Cohort 3), (2) the anteromedial tissues and periosteum, and (3) the anterolateral tissues and periosteum.

REFERENCE THERAPY, DOSE, AND MODE OF ADMINISTRATION: None.

ADDITIONAL STUDY MEDICATION, DOSE, AND MODE OF ADMINISTRATION:

Additional study medication includes bupivacaine HCl, scheduled non-opioid MMA, and antifibrinolysis and DVT prophylaxis. Study sites will supply the additional study medication.

Bupivacaine HCl

All subjects will be administered bupivacaine HCl 0.5% or 0.75%, per institutional practice, as part of the spinal anesthesia during surgery. The dose of bupivacaine should not exceed a maximum of 20 mg (ie, maximum of 4 mL of bupivacaine 0.5% or maximum of 2.6 mL of bupivacaine 0.75%).

Subjects in Group B of Cohort 3 will be administered 100 mg of bupivacaine HCl 0.25% or 0.5% as a 40 mL injection into the posterior capsule during surgery just prior to placement of the prosthesis (ie, 40 mL of 0.25% or 20 mL of 0.5% diluted with 20 mL of 0.9% Normal Saline for a total of 40 mL).

Scheduled Non-Opioid Multimodal Analgesic Regimen

All subjects will follow a scheduled MMA regimen.

Preoperatively, all subjects will receive PO acetaminophen 1 g, PO celecoxib 200 mg, and PO pregabalin 300 mg just before being taken to the operating room.

After surgery, subjects will receive a scheduled non-opioid MMA regimen for 7 days. The first dose of the postoperative MMA regimen will be administered once the subject is able to tolerate PO intake. For the first 3 days after surgery, the MMA regimen will consist of PO acetaminophen 1 g every 8 hours and PO celecoxib 200 mg every 12 hours (Cohorts 1, 2, and 3) or PO acetaminophen 1 g every 8 hours and PO ibuprofen 600 mg every 6 hours (Cohort 4). For the next 4 days, the MMA regimen for all cohorts will consist of PO ibuprofen 600 mg every 6 hours alternating with PO acetaminophen 1 g every 6 hours (maximum ibuprofen dose of 2.4 g/day and maximum acetaminophen dose of 4 g/day) while the subject is awake, so that an analgesic is taken approximately every 3 hours.

Antifibrinolysis and DVT Prophylaxis

All subjects will be administered TXA and acetylsalicylic acid for antifibrinolysis and DVT prophylaxis, respectively, consistent with clinical practice for TKA. TXA 1g IV will be administered within approximately 4 hours prior to the start of surgery and a second dose will be administered up to approximately 8 hours later. Subjects will receive acetylsalicylic acid 325 mg PO BID following surgery

until discharge.

DURATION OF TREATMENT: Subjects will receive a single dose of study drug (HTX-011) during surgery and 7 days of a scheduled non-opioid MMA regimen. Subjects in Group B of Cohort 3 will also receive bupivacaine HCl via injection into the posterior capsule during surgery. The total duration of study participation for each subject (from Screening through the Day 29 Visit) will be up to 61 days. The overall duration of the study is anticipated to be approximately 16 months.

STUDY ASSESSMENTS:

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

Efficacy Assessments

- VAS and NRS of pain intensity at rest (NRS-R) assessments. Assessments should be performed when the subject is in the resting position (either seated comfortably or lying down) for at least 5 minutes prior to obtaining the pain scores.
- Opioid rescue medications: Date, time of administration, amount, and type of all opioid rescue medication taken from study drug administration through 72 hours.
- Discharge readiness assessment per the Modified Postanaesthetic Discharge Scoring System (MPADSS) criteria. (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 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.
- Overall benefit of analgesia score (OBAS).
- Treatment Satisfaction Questionnaire for Medication (TSQM-9).
- Time to ambulation (defined as the ability to walk at least 20 feet with optional use of a 4-legged walker for balance. All subjects will be encouraged to ambulate as early as possible during the 72-hour postoperative period.
- Ability to participate in scheduled rehabilitation sessions.
- Whether the subject is discharged home or to a skilled nursing facility.
- Opioid prescription at discharge.
- Site- or subject-initiated postdischarge contact through the Day 11 Visit.
- Opioid prescription after discharge through the Day 11 Visit.
- Subject daily diary to record whether opioids were taken from discharge through the Day 11 Visit.

Safety Assessments

- AEs from the time the subject signs the ICF through the Day 29 Visit.
- Physical examination.
- Vital signs, including blood pressure, resting heart rate, respiratory rate, and temperature.
- Wound healing assessment using the Southampton Wound Scoring Scale.
- Clinical laboratory tests (hematology and serum chemistry).

Pharmacokinetic Assessments

Blood samples will be collected to measure the plasma concentrations of bupivacaine and meloxicam (all cohorts) and alpha-1-acid glycoprotein (Cohort 4 only). Blood samples may also be used to evaluate other study drug components.

STUDY ENDPOINTS:

Primary Efficacy Endpoint

- Mean area under the curve (AUC) of VAS scores from 12 through 48 hours (AUC_{12-48}).

Secondary Efficacy Endpoints

- Mean AUC of VAS scores through 72 hours.
- Mean AUC of the NRS-R scores through 72 hours.
- Proportion of subjects with severe pain at each timepoint and through 72 hours.
- Mean total postoperative opioid consumption (in IV morphine milligram equivalents [MME]) through 72 hours.
- Proportion of subjects who are opioid-free through 72 hours and through Day 11.
- Proportion of subjects who are opioid-free through 72 hours who remain opioid-free through Day 11.
- Median time to first opioid rescue medication through 72 hours.
- Proportion of subjects who do not receive an opioid prescription at discharge.
- Proportion of subjects who do not receive an opioid prescription between discharge and the Day 11 Visit.
- Proportion of subjects achieving a score of "good" or better (>1) pain control based on PGA at each timepoint.
- Median time to first ambulation through 72 hours.
- Proportion of subjects unable to participate in each rehabilitation session because of pain.
- Proportion of subjects who first achieve an MPADSS score ≥9 at each timepoint.
- Proportion of subjects who are discharged home vs to a skilled nursing facility.
- Mean OBAS at each timepoint.
- Mean TSQM-9 score.

Safety Endpoints

- Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and opioid-related adverse events (ORAEs).
- Change from baseline in clinical laboratory results.
- Change from baseline in vital signs.
- Wound healing assessment results at each assessed timepoint.

PK Endpoints (Cohorts 1, 2, and 4)

- Maximum concentration (C_{max}).
- Time of occurrence of maximum concentration (T_{max}).

PK Endpoints (Cohort 3)

- C_{max}.
- T_{max}.
- Area under the concentration-time curve from Time 0 to the time of the last quantitative concentration (AUC_{last}).
- Area under the concentration-time curve from Time 0 extrapolated to infinity (AUC_{inf}).
- Apparent terminal elimination rate constant (λ_z).

- Apparent terminal half-life ($t_{1/2}$).

STATISTICAL METHODS:

Determination of Sample Size

The sample size of 115 subjects was selected empirically without formal statistical assumptions.

Efficacy Analyses

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

Handling of Missing Data

For any missing pain scores observed in subjects who complete the 72-hour observation period, VAS and NRS-R scores will be imputed via last observation carried forward (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 will be used. In subjects who withdraw from the study prior to the end of 72-hour observation period, missing VAS and NRS scores through 72 hours that were to be collected following withdrawal will be imputed via worst observation carried forward (WOCF), in which the worst (highest) VAS and NRS-R scores 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 windowed worst observation carried forward (wWOCF) following LOCF/WOCF (ie, perform LOCF/WOCF first, then apply wWOCF). The number and percentage of missing pain intensity scores will be summarized.

Safety Analyses

All safety data will be listed and summarized by cohort and by treatment group. TEAEs will be coded and tabulated by System Organ Class and Preferred Term. Incidence of TEAEs, SAEs, and ORAEs will be summarized. 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 will be summarized.

PK Analyses

Plasma bupivacaine and meloxicam concentrations will be determined using validated liquid chromatography tandem-mass spectrometry assays. Concentrations will be calculated by interpolation from a calibration curve. PK parameters for bupivacaine and meloxicam will be calculated using noncompartmental analysis, as appropriate. Additional exploratory analyses may be performed, as appropriate, to facilitate cross-study comparisons and to fully characterize the concentration-time profiles of each analyte or other study drug components.

In Cohort 4, concentrations of alpha-1-acid glycoprotein will be summarized using descriptive statistics. As an exploratory analysis, ex-vivo protein binding of bupivacaine will be determined using equilibrium dialysis. PK parameters for free bupivacaine will be calculated using noncompartmental analysis, as appropriate.

Interim Analysis

No formal interim analyses are planned.

SCHEDULE OF EVENTS

		Screening	3-Day Inpatient Period															Out patient	Site Visits		
			D1										D2		D3		D4				
			Preop	OR	30 min	1h	2h	4h	6h	8h	12h	20h	24h	36h	48h	60h	72h	D5-D8	D11	D29	
Assessments	**Time Window**	**≤28 days**			**±5 min**	**±10 min**	**±15 min**	**±30 min**	**±30 min**	**±30 min**	**±30 min**	**±1h**	**±1h**	**±2h**	**±2h**	**±2h**	**±2h**		**±2d**	**±4d**	**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[d]
12-lead ECG (triplicate)[e]		X																			
Subject training for pain assessments		X	X																		
Hematology and serum chemistry tests		X															X		X		X[f]
Administer TXA IV[g]			X					X													
Administer preoperative MMA: PO acetaminophen, celecoxib, and pregabalin[h]			X																		
Surgery				X																	
Administer HTX-011				X																	
Administer bupivacaine HCl as injection into posterior capsule (Cohort 3 Group B only)				X																	
Administer acetylsalicylic acid[i]				X									X		X		X				
Administer scheduled postoperative MMA regimen[j]					◄----	----	----	----	----	----	----	----	----	----	----	----	----►	X			
Pain intensity assessment (VAS)			X			X[k]	X	X	X	X	X		X	X	X	X	X		X	X	X

		Screening	3-Day Inpatient Period															Out patient	Site Visits		
			D1										D2		D3		D4				
			Preop	OR	30 min	1h	2h	4h	6h	8h	12h	20h	24h	36h	48h	60h	72h	D5-D8	D11	D29	
Assessments	**Time Window**	**≤28 days**			**±5 min**	**±10 min**	**±15 min**	**±30 min**	**±30 min**	**±30 min**	**±30 min**	**±1h**	**±1h**	**±2h**	**±2h**	**±2h**	**±2h**		**±2d**	**±4d**	**ET[a]**
Pain intensity assessment (NRS-R)			X			X[k]	X	X	X	X	X		X	X	X	X	X		X	X	X
Ambulation assessment[l]		X			◄	-	-	-	-	-	-	-	-	-	-	-	►				
Rehabilitation assessment[m]								X						X		X					
Discharge readiness per MPADSS[n]							X	X	X	X	X		X	X	X	X	X				
PGA of pain control													X		X		X		X		
OBAS assessment													X		X		X		X		
TSQM-9 questionnaire																	X		X		
Wound healing assessment																	X		X	X	X
PK blood sample[e] (Cohorts 1+2)			X[o]					X				X	X		X						
PK blood sample[e] (Cohort 3)			X[o]		X	X	X	X	X	X	X	X	X	X	X	X	X				
PK blood sample[e] (Cohort 4)			X[o]		X	X	X	X	X	X	X	X	X		X		X				
Blood sample for alpha-1-acid glycoprotein[e] (Cohort 4)			X[o]					X			X	X	X		X		X				
Discharge subject																	X				
Record if opioid prescription at discharge																	X				
Provide opioid daily diary to all subjects[p]																	X				
Record site or subject contact																		◄	-	►	
Subjects record opioid use in daily diary[q]																		◄	-	►	
Review subject diary at site[r]																			X		X[f]
Concomitant medications[s]		◄	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	►
Adverse events[e, t]		◄	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	►

Abbreviations: AE, adverse event; D or d, day; ECG, electrocardiogram; eCRF, electronic Case Report Form; ET, Early Termination; h, hour; min, minutes; ICF, informed consent form; IV, intravenous; LAST, local anesthetic systemic toxicity; MMA, multimodal analgesic; MPADSS, Modified Postanaesthetic Discharge Scoring System; NRS-R, Numeric Rating Scale of pain intensity score at rest; OBAS, overall benefit of analgesia score; OR, operating room; PGA, Patient Global Assessment of pain control; PK, pharmacokinetic; PO, oral; Preop, preoperative; TSQM-9, Treatment Satisfaction Questionnaire for Medication; TXA, tranexamic acid; VAS, Visual Analogue Scale; WOCBP, women of childbearing potential.

Notes: The start of HTX-011 administration will be considered 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 pain intensity assessments coincide, the pain intensity assessments should be conducted before the blood draw. See Section 6 for more information on study assessments and procedures.

[a] Subjects who withdraw from the study early will be asked to complete ET procedures based on the timing of their withdrawal.

[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. Subjects with a positive drug screen who are taking an allowed, prescribed medication that is known to result in a positive drug test may be eligible for participation in the study. Subjects who fail the drug test may be rescreened at the discretion of the Investigator.

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

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

[e] If signs and symptoms of suspected LAST are observed, unscheduled vital sign measurements, 12-lead ECGs, and blood sample collection for PK (all cohorts) and alpha-1-acid glycoprotein analysis (Cohort 4 only) must be promptly performed.

[f] Only if subject withdraws prior to the Day 11 Visit.

[g] TXA 1 g IV will be administered within approximately 4 hours prior to the start of surgery. A second dose will be administered up to approximately 8 hours after the initial dose.

[h] Administer PO acetaminophen 1 g, PO celecoxib 200 mg, and PO pregabalin 300 mg just before the subject is taken to the operating room.

[I] From study drug administration until hospital discharge, subjects should receive acetylsalicylic acid 325 mg PO twice a day.

[j] The first dose of the MMA regimen will be administered once the subject is able to tolerate PO intake. For the first 3 days, the scheduled MMA regimen will consist of PO acetaminophen 1 g every 8 hours and PO celecoxib 200 mg every 12 hours (Cohorts 1, 2, and 3) or PO acetaminophen 1 g every 8 hours and PO ibuprofen 600 mg every 6 hours (Cohort 4). For the next 4 days, the scheduled MMA regimen for all cohorts will consist of PO ibuprofen 600 mg every 6 hours, alternating with PO acetaminophen 1 g every 6 hours (maximum ibuprofen dose of 2.4 g/day and maximum acetaminophen dose of 4 g/day), so that an analgesic is taken approximately every 3 hours while the subject is awake.

[k] Prior to the administration of the first dose of opioid rescue medication, if the subject has not already had at least 1 postoperative pain score assessed, then VAS and NRS-R scores must be obtained.

[l] Defined as the ability to walk at least 20 feet with optional use of a 4-legged walker for balance. All subjects will be encouraged to ambulate as early as possible during the 72-hour postoperative period. The date and time of first ambulation must be recorded.

[m] Subjects will participate in rehabilitation on the evening of Day 1, and in the morning and evening of Days 2 and 3.

[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 whether or not to discharge a subject from the study.

[o] Preoperative blood samples must be collected before administering the spinal anesthesia.

[p] All subjects (whether or not they were discharged with an opioid prescription) must be provided a daily diary at discharge to record opioid use through the Day 11 Visit.

[q] Subjects will complete a daily diary to record if they take any opioid medication from discharge through Day 11 Visit.

[r] Subject diary results will be reviewed at the Day 11 Visit. If a subject recorded "yes" for taking an opioid, sites must record the medication on concomitant medication eCRF.

[s] Record all medications taken from the time the subject signs the ICF through the Day 29 Visit.

[t] Record all AEs from the time the subject signs the ICF through the Day 29 Visit.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ASA	American Society of Anesthesiologists
AUC	Area under the curve
BID	Twice a day
BMI	Body mass index
CFR	Code of Federal Regulations
C_{max}	Maximum concentration
COX	Cyclooxygenase
CV	Cardiovascular
DVT	Deep vein thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
h	Hour(s)
ICF	Informed consent form
ICH	International Conference on Harmonisation
IV	Intravenous(ly)
LAST	Local anesthetic systemic toxicity
LOCF	Last observation carried forward
min	Minute(s)
MMA	Multimodal analgesic
MME	Morphine milligram equivalents
MPADSS	Modified Postanaesthetic Discharge Scoring System
NRS	Numeric rating scale
NRS-R	NRS scores of pain intensity at rest
NSAID	Nonsteroidal anti-inflammatory drug
OBAS	Overall benefit of analgesia score

Abbreviation	Definition
ORAE	Opioid-related adverse event
PGA	Patient Global Assessment
PK	Pharmacokinetic(s)
PO	By mouth, orally
SAE	Serious adverse event
SAR	Serious adverse reaction
TEAE	Treatment-emergent adverse event
T_{max}	Time of occurrence of maximum concentration
TKA	Total knee arthroplasty
TSQM	Treatment Satisfaction Questionnaire for Medication
TXA	Tranexamic acid
ULN	Upper limit of normal
US	United States
VAS	Visual Analogue Scale
WOCF	Worst observation carried forward
wWOCF	Windowed worst observation carried forward

Note: Abbreviations defined in the text but not used again in the text are not included in this List of Abbreviations. Abbreviations used only in a table or figure are also excluded from this List of Abbreviations; they are defined in the table or figure footnotes.

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 (Apfelbaum 2003; Gan 2014; Lynch 1997; Meissner 2015; Misiolek 2014; Singla 2014; Svensson 2000). Administering a local anesthetic (eg, bupivacaine, ropivacaine, or levobupivacaine) perioperatively is a relatively simple and safe means of providing postoperative pain relief. A major limitation of most currently available local anesthetics is that their duration of effect is only 6 to 12 hours (Kehlet 2011). Consequently, many patients are given opioids to manage pain. The requirement for opioids postoperatively is a serious manifestation of ineffective pain control. Exposure to opioids can lead to opioid-related adverse reactions resulting in worse patient outcomes and increased hospital costs (Cashman 2004; Chan 2013; Coley 2002; Jarzyna 2011; Kessler 2013; Lee 2015; Lee 2016; Oderda 2013; Ramachandran 2011; Shirakami 2005; Stephens 2003; Wheeler 2002). Patients can quickly transition from acute opioid use to chronic use. Orthopedic surgery can be a point of first exposure to opioids for patients as it has one of the highest rates of opioid prescribing (Morris 2015). Reduced exposure to opioids and better pain management is associated with improved patient outcomes as well as reduced risk for the development of persistent pain and chronic opioid use and abuse (Barnett 2017). Therefore, there is a significant unmet need for a more effective non-opioid analgesic that provides sustained pain relief and reduces or eliminates the need for opioids, especially in the first 72 hours following surgery.

Heron Therapeutics, Inc. (Heron) has developed HTX-011 for application into the surgical site to reduce postoperative pain for up to 72 hours and the need for opioid analgesics. [redacted] Bupivacaine and meloxicam are approved in the United States (US), Europe, and other regions and have a long history of clinical use. Unlike other local anesthetics, HTX-011 is not injected; it is applied without a needle to coat the pain-generating tissues in the surgical site. After single-dose administration, the polymer enables extended release of bupivacaine and meloxicam simultaneously for approximately 3 days. Low-dose meloxicam in HTX-011 does not provide analgesic activity on its own (Viscusi 2017). Rather, meloxicam reduces the local inflammation caused by surgery and normalizes the local pH, which enhances penetration of bupivacaine into the nerves, thereby potentiating bupivacaine's analgesic effect (Dasta 2018).

In a prior adequate and well-controlled Phase 2b study in total knee arthroplasty (TKA; Study 209), HTX-011 400 mg/12 mg (bupivacaine/meloxicam doses) with or without ropivacaine injected into the posterior capsule significantly reduced pain over 48 hours and 72 hours compared with saline placebo despite the absence of a background scheduled multimodal analgesic (MMA) regimen and with only opioid rescue medication options. Although almost all subjects required opioid rescue during the 72-hour postoperative period, subjects who received HTX-011 demonstrated lower opioid consumption through 72 hours than subjects who received saline placebo or bupivacaine HCl. This Phase 3b study will evaluate if HTX-011 administered as the foundation of a scheduled non-opioid MMA regimen can further

improve pain control and lead to a greater reduction or eliminate the need for opioids following primary unilateral TKA. The study will also evaluate the contribution of bupivacaine HCl injection into the posterior capsule on the reduction of postoperative pain.

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

This is an open-label multicohort study. Cohorts 1, 2, and 4 will evaluate HTX-011 400 mg/12 mg via periarticular application into the surgical site. This dose and administration technique were evaluated in the prior Phase 2b TKA study (Study 209). Drains are no longer commonly used; therefore, Cohort 2 will prohibit the use of drains to evaluate the impact, if any, on postoperative analgesia.

Cohort 3 will evaluate HTX-011 300 mg/9 mg with or without bupivacaine HCl 100 mg, a local anesthetic commonly used in TKA. The use of drains will also be prohibited in Cohort 3. HTX-011 will be administered via periarticular application into the surgical site. Bupivacaine HCl will be injected into the posterior capsule to see if anesthetizing that area contributes to the reduction of initial postoperative pain. The 100 mg dose of bupivacaine HCl injection was selected as this dose has been used in combination with liposomal bupivacaine in TKA (Dysart 2016). As such, HTX-011 300 mg/9 mg was selected to use with 100 mg bupivacaine HCl to compare the efficacy of this cohort with Cohort 1 where HTX-011 400 mg/12 mg will be administered into the surgical site.

All subjects will follow a scheduled non-opioid MMA regimen. Multimodal analgesia for the treatment of postoperative pain is recommended in the American Pain Society guidelines (Chou 2016) and is supported by literature suggesting that using both acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), which have different mechanisms of action, can increase effectiveness without increasing risk (Ong 2010). The scheduled MMA regimen selected for Cohorts 1, 2, and 3 (acetaminophen, celecoxib, and pregabalin before surgery and acetaminophen and celecoxib for the first 72 hours after surgery) is the same as the PILLAR study, a randomized, controlled study that evaluated liposomal bupivacaine administered with a standardized MMA regimen in TKA (Dysart 2016; Mont 2018). The scheduled MMA regimen for Cohort 4 will be similar to Cohorts 1, 2, and 3, but includes ibuprofen instead of celecoxib during the first 72 hours after surgery. The hypothesis is that the postoperative non-specific cyclooxygenase (COX) inhibition of ibuprofen will contribute more to postoperative analgesia and therefore work better with HTX-011, as opposed to the COX-2-specific inhibition gained from celecoxib, which contributes more to an anti-inflammatory effect and therefore may be duplicative to the impact of the local meloxicam applied as part of HTX-011.

Pain will be assessed using 2 different validated pain rating scales, the visual analogue scale (VAS) and the numeric rating scale (NRS) (Breivik 2008; Haefeli 2006). The primary efficacy endpoint for this study, area under the curve (AUC) of the VAS pain intensity scores from 12 through 48 hours ($AUC_{12\text{-}48}$), is consistent with the study goal to assess pain control and is the same as the primary endpoint reported for the PILLAR study (Mont 2018). The primary endpoint is also consistent with Draft Food and Drug Administration (FDA) Guidance for Industry on *Analgesic Indications: Developing Drug and Biological Products* (February 2014), which states that "pain intensity is the fundamental measure that defines the efficacy of an analgesic drug."

Safety assessments in this study are considered standard for clinical studies and this surgical model. Evaluations will include adverse event (AE) and serious adverse event (SAE) recording,

hematology and serum chemistry, vital signs, physical examinations, and wound healing assessments.

The pharmacokinetic (PK) timepoints for this study were selected to characterize systemic exposure of bupivacaine and meloxicam to confirm that exposures are consistent with historical values obtained in Study 209. In addition, in Cohort 4 scheduled blood draws will also be performed to evaluate the impact of surgery on alpha-1-acid glycoprotein concentrations, which impacts the free fraction of bupivacaine. If potential signs and symptoms of local anesthetic systemic toxicity (LAST) are observed, a blood sample for PK and alpha-1-acid glycoprotein analysis will also be collected.

1.3. Potential Risks and Benefits

1.3.1. HTX-011

As of 27 September 2019, a total of 1,362 adult subjects (1,352 undergoing surgery and 10 healthy volunteers) have received HTX-011 as a single dose ranging from 30 mg/0.9 mg to 600 mg/18 mg across 12 clinical studies.

1.3.1.1. Safety

Safety data from 504 subjects who received HTX-011 via instillation into the surgical site in two Phase 3 studies (Study 301 in bunionectomy and Study 302 in herniorrhaphy) and two Phase 2b studies (Study 209 in TKA and Study 211 in augmentation mammoplasty) were pooled for analysis. Results from these studies revealed that the safety profile of a single dose of HTX-011 was similar to the well-established safety profile of bupivacaine HCl. The types of treatment-emergent adverse events (TEAEs) reported for HTX-011 were generally similar across studies; the most common TEAEs were nausea, constipation, dizziness, vomiting, and headache. These TEAEs were also the most common TEAEs in the saline placebo and bupivacaine HCl groups. Of these 5 most common TEAEs, those with an incidence higher in the HTX-011 group than in the saline placebo group were constipation (17.3% vs 14.6%), vomiting (16.9% vs 15.0%), and headache (11.7% vs 8.9%). The majority of TEAEs were mild or moderate in severity. The incidence of severe TEAEs was low and similar across all treatment groups.

There were no clinically meaningful differences in laboratory results, vital sign measurements, or electrocardiogram (ECG) findings. There was no evidence of LAST based on a comprehensive review of potential LAST-related TEAEs, LAST assessment questionnaire responses, bupivacaine plasma concentrations, 12-lead ECG/Holter monitoring findings, and vital sign results. Finally, bone healing and wound healing were not affected by HTX-011.

Serious Adverse Events

As of 23 October 2019, no deaths were reported for subjects who received HTX-011. The incidence of SAEs in subjects who received HTX-011 was low (1.5%) and was similar to saline placebo (1.2%) and bupivacaine HCl (2.2%). [redacted]

1.3.1.2. Efficacy

In Phase 3 studies in bunionectomy and herniorrhaphy, a single dose of HTX-011 (60 mg/1.8 mg and 300 mg/9 mg, respectively) significantly reduced pain and opioid consumption through 72 hours compared with both bupivacaine HCl and saline placebo. The efficacy of HTX-011 has also been demonstrated in Phase 2 studies in subjects undergoing TKA, augmentation mammoplasty, and abdominoplasty at HTX-011 doses up to 400 mg/12 mg. The efficacy of HTX-011 was also evaluated when administered as the foundation of a non-opioid MMA regimen. In completed studies in bunionectomy and herniorrhaphy, the regimens resulted in further reduction of pain and opioid consumption.

1.3.1.3. Potential Risks Associated With HTX-011

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. Use of HTX-011 in subjects with allergies to or hypersensitivity to bupivacaine, meloxicam, or any of the components of HTX-011 is contraindicated. For more information on HTX-011, refer to the HTX-011 Investigator's Brochure. For more information on the active ingredients, bupivacaine and meloxicam, refer to the local product labels.

1.3.1.3.1. Potential Risks Associated With Bupivacaine

Potential risks for bupivacaine include dose-related central nervous system and cardiovascular (CV) system toxicity, including, but not limited to, perioral tingling, metallic taste, visual and auditory disturbances, muscle twitching, seizure, acidosis, shortness of breath, bradycardia, hypotension, hypoxia, and cardiac arrest. Cases of methemoglobinemia have been reported in association with local anesthetic use (MARCAINE USPI 2018). Although all patients receiving a local anesthetic are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. Patients with a known history of glucose-6-phosphate dehydrogenase deficiency or with congenital or idiopathic

methemoglobinemia are excluded from this study. Close monitoring for symptoms and signs of methemoglobinemia is recommended.

1.3.1.3.2. Potential Risks Associated With Meloxicam

Potential risks for meloxicam include the common AEs (≥5% and greater than placebo) of diarrhea, upper respiratory tract infections, dyspepsia, and influenza-like symptoms (MOBIC USPI 2018). Other potential risks include CV adverse reactions, gastrointestinal bleeding, and abnormal liver tests . NSAIDs may cause an increased risk of serious CV thrombotic events, myocardial infarction, and stroke, which can be fatal. Patients with known 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 inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, or intestines, which can be fatal. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a gastrointestinal bleed compared to patients without these risk factors. Elderly patients are at greater risk for serious gastrointestinal events. Elevations of one or more liver tests may occur in patients taking NSAIDs, including meloxicam. Exacerbation of asthma related to aspirin sensitivity, reduction in renal blood flow, and renal toxicity are reported risks after exposure to NSAIDs. Serious skin AEs such as exfoliative dermatitis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis, which can be fatal, can occur without warning. It is unclear how applicable these potential risks are for meloxicam when given as single dose via instillation into the surgical site (a novel administration method for meloxicam) for postoperative pain as part of a fixed-dose combination (eg, HTX-011).

1.3.2. Other Scheduled Study Medications

Common, as well as uncommon but severe, adverse drug reactions that are associated with the other study medications are listed below. The Investigator should refer to the respective package inserts for detailed information on risks associated with the scheduled study medications (bupivacaine, pregabalin, celecoxib, acetaminophen, ibuprofen, fentanyl, tranexamic acid [TXA], acetylsalicylic acid) and any other approved medications that may be administered while a subject participates in this study (eg, anesthetics, antibiotics).

1.3.2.1. Bupivacaine

Potential risks associated with bupivacaine are addressed in Section 1.3.1.3.1.

1.3.2.1.1. Pregabalin

Common adverse drug reactions with pregabalin include dizziness, sleepiness, dry mouth, swelling of hands and feet, blurred vision, weight gain, and trouble concentrating. An uncommon but severe adverse drug reactions, reported in a small number of people, was suicidal thoughts.

1.3.2.1.2. Celecoxib

Common adverse drug reactions with celecoxib include headache, upper respiratory tract infections, dyspepsia, and diarrhea. Uncommon but severe adverse drug reactions include gastrointestinal ulceration, bleeding, and perforation. Other uncommon but serious adverse reactions which occur in <0.1% of subjects include syncope, congestive heart failure, ventricular

fibrillation, cerebrovascular accident, peripheral gangrene, thrombophlebitis, pancreatitis, cholelithiasis, thrombocytopenia, aseptic meningitis, suicide, acute renal failure, sepsis, and sudden death.

1.3.2.1.3. Acetaminophen

Common adverse drug reactions with acetaminophen include nausea, vomiting, headache, and insomnia. An uncommon but severe adverse drug reaction may include severe skin rash and liver failure.

1.3.2.1.4. Ibuprofen

Common adverse drug reactions with ibuprofen are gastrointestinal (nausea, epigastric pain, heartburn, diarrhea, abdominal distress cramps or pain, nausea and vomiting, indigestion, constipation, bloating and flatulence, decreased appetite), dizziness, headache, nervousness, tinnitus, rash, pruritus, fluid retention, and elevated liver function tests. Less common but severe adverse drug reactions which can be fatal include myocardial infarction and stroke, serious gastrointestinal bleeding, ulceration, and perforation of the stomach or intestines, serious allergic reactions, new or worsening of high blood pressure, congestive heart failure and edema, renal toxicity including papillary necrosis, and serious skin reactions (such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis).

1.3.2.1.5. Tranexamic Acid

Common adverse drug reactions with TXA include visual abnormalities, nausea, vomiting, diarrhea, allergic dermatitis, and thromboembolic events. An uncommon but severe adverse drug reaction, hypotension, has been reported when the intravenous (IV) injection rate is too rapid.

1.3.2.1.6. Acetylsalicylic Acid

Common adverse drug reactions of aspirin include vomiting, stomach pain, heartburn, drowsiness, and nausea. Uncommon but severe risks include stomach ulcers, stomach bleeding, and worsening asthma.

1.3.2.1.7. Opioid Medications

Common adverse drug reactions associated with opioids include nausea, constipation, vomiting, headache, itchiness, dizziness, drowsiness, excessive sweating, and impaired concentration and reaction abilities. Drinking alcohol may further decrease mental functions and increase the risk of liver damage. Uncommon but severe adverse drug reactions include hypoxia, respiratory arrest, cardiac arrest, hypotension, and/or shock. Opioids have the risk of addiction, abuse, and misuse, which can lead to overdose and death.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to assess pain control following HTX-011 as part of a scheduled non-opioid MMA regimen in subjects undergoing TKA.

2.2. Secondary Objectives

The secondary objectives are as follows:

- To assess total opioid use following HTX-011 as part of a scheduled non-opioid MMA regimen in this study population.
- To assess the proportion of subjects who are opioid-free after receiving HTX-011 as part of a scheduled non-opioid MMA regimen in this study population.
- To assess the safety and tolerability of HTX-011 in a multimodal setting in this study population.
- To characterize the PK parameters of bupivacaine and meloxicam 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 3b, open-label, multicohort study in which subjects undergoing a primary unilateral TKA will receive HTX-011 as part of a scheduled non-opioid MMA regimen. Subjects will be screened within 28 days prior to the planned surgery date and eligibility will be confirmed on the day of surgery. Subjects who meet the eligibility criteria will be enrolled and will undergo primary unilateral TKA under bupivacaine spinal anesthesia (≤20 mg). All subjects will receive HTX-011 as part of a non-opioid MMA regimen consisting of acetaminophen, an NSAID, and a gabapentanoid prior to surgery, a single dose of HTX-011 during surgery, and scheduled acetaminophen and an NSAID for 7 days following surgery. Up to 115 subjects will be dosed in 4 sequential cohorts:

- Cohort 1: Approximately 50 subjects will be administered a single dose of HTX-011 400 mg/12 mg via periarticular application into the surgical site during surgery.
- Cohort 2: Approximately 15 subjects will be administered a single dose of HTX-011 400 mg/12 mg via periarticular application into the surgical site during surgery. Drains will be prohibited.
- Cohort 3: Approximately 30 subjects will be randomized into 2 groups. In Group A, subjects will be administered a single dose of HTX-011 300 mg/9 mg via periarticular application into the surgical site during surgery. In Group B, subjects will be administered a single dose of HTX-011 300 mg/9 mg via periarticular application into the surgical site and 100 mg bupivacaine HCl injected into the posterior capsule during surgery. Drains will be prohibited.
- Cohort 4: Up to approximately 20 subjects will be administered a single dose of HTX-011 400 mg/12 mg via periarticular application into the surgical site during surgery.

On the day of surgery (Day 1), subjects will be administered oral (PO) acetaminophen 1 g, PO celecoxib 200 mg, and PO pregabalin 300 mg just before being taken to the operating room. During surgery, a single dose of HTX-011 will be administered via periarticular application into the surgical site in all study cohorts, as described in Section 5.1.5. Bupivacaine HCl will be administered into the posterior capsule in Group B of Cohort 3. The use of IV fentanyl up to 4 µg/kg will be permitted during surgery for intraoperative pain control. Subjects will receive antifibrinolysis and deep vein thrombosis (DVT) prophylaxis medications as described in Section 3.1.3.

Subjects will remain in the hospital/research facility for 72 hours from the start of study drug administration to undergo postoperative efficacy, safety, and PK assessments. The study staff will follow standard safety precautions to prevent postoperative falls. Subjects will receive a scheduled non-opioid MMA regimen over the 72-hour postoperative period consisting of PO acetaminophen 1 g every 8 hours and PO celecoxib 200 mg every 12 hours (Cohorts 1, 2, and 3)

or PO acetaminophen 1 g every 8 hours and PO ibuprofen 600 mg every 6 hours (Cohort 4). The first dose of the MMA regimen will be administered once the subject is able to tolerate PO intake.

After the 72-hour assessments have been completed, subjects may be discharged. Subjects will be discharged with instructions to follow a scheduled MMA regimen for 4 days after discharge consisting of PO ibuprofen alternating with PO acetaminophen (all cohorts), as described in Section 3.1.2.3. Thereafter, subjects may continue acetaminophen and/or ibuprofen as needed. Subjects will return to the study site on Days 11 and 29 for follow-up assessments.

3.1.2. Postoperative Analgesia Medications

3.1.2.1. Inpatient Postoperative Rescue Medication

During the 72-hour postoperative period, subjects should only receive rescue medication upon request for pain control. 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 pain intensity scores using the VAS and NRS must be obtained.

Postoperative rescue medication will consist only of any 1 or more of the following opioid medications, as needed: PO immediate-release oxycodone (≤10 mg within a 4-hour period), IV morphine (2.5 mg to 5 mg within a 4-hour period), and/or IV hydromorphone (0.5 mg to 1.0 mg within a 4-hour period). Combination products containing an opioid and non-opioid are not allowed. With the exception of the protocol-specified MMA medications, no other analgesic agents, including other NSAIDs, are permitted during the 72-hour postoperative period. Note: Acetaminophen is not to be given as a rescue medication as it is part of the postoperative scheduled MMA regimen.

3.1.2.2. Opioid Prescriptions at and After Discharge

If a subject did not receive any opioids or received <10 mg of oxycodone within 12 hours prior to discharge, the subject should not receive an opioid prescription at discharge. If a subject received ≥10 mg of oxycodone within 12 hours prior to discharge, the Investigator may provide the subject with a prescription for immediate-release PO oxycodone tablets: no more than thirty 5 mg immediate-release oxycodone, take 1 to 2 pills PO (5 mg to 10 mg) every 4 hours as needed. The prescription must indicate that substitutions with any other opioid-containing product are not permitted, including combination opioid/non-opioid products.

Sites will record if subjects are discharged with an opioid prescription and information about the opioid prescription. All subjects (whether or not they were discharged with an opioid prescription) will be provided a daily diary to record any opioid medication use from discharge through the Day 11 Visit. Sites will record all site- or subject-initiated contact between discharge and the Day 11 Visit and if any contact resulted in issuing an opioid prescription.

3.1.2.3. Postoperative Analgesia After Discharge

Upon discharge, subjects will be instructed to manage their pain while awake over the next 4 days with the following scheduled MMA regimen: PO ibuprofen 600 mg every 6 hours, alternating with PO acetaminophen 1 g every 6 hours, so that an analgesic is taken approximately

every 3 hours. Thereafter, subjects may continue one or both of the MMA medications as needed, but should not exceed ibuprofen 600 mg every 6 hours or acetaminophen 1 g every 6 hours (maximum ibuprofen dose of 2.4 g/day and maximum acetaminophen dose of 4 g/day).

3.1.3. Antifibrinolysis and Deep Vein Thrombosis Prophylaxis

All subjects will receive IV TXA and PO acetylsalicylic acid for antifibrinolysis and DVT prophylaxis, respectively, consistent with clinical practice for TKA. TXA 1g IV will be administered within approximately 4 hours prior to the start of surgery and a second dose will be administered up to approximately 8 hours later (Themistoklis 2017). Subjects will receive acetylsalicylic acid 325 mg PO twice a day (BID) following surgery until discharge. Surgeons may also use additional DVT prophylaxis as per their standard of care.

3.1.4. Postoperative Assessments

Efficacy assessments will include pain intensity assessments using the VAS and the NRS; the use of opioid rescue medication; discharge readiness and discharge information; Patient Global Assessment (PGA) of pain control; the subject's assessment of overall benefit of analgesia score (OBAS); the subject's satisfaction with their scheduled non-opioid MMA regimen; and ambulation and rehabilitation assessments.

Safety assessments will include AE recording, physical examinations, vital signs, clinical safety laboratory tests (hematology and serum chemistry), and wound healing assessments.

Blood samples will be collected for bupivacaine and meloxicam PK analysis (all cohorts) and for alpha-1-acid glycoprotein (Cohort 4 only). Blood samples may be used to evaluate other study drug components.

More information on study procedures and assessments is provided in Section 6. The timing of procedures and assessments is provided in Section 7 and the SCHEDULE OF EVENTS table.

3.2. Study Endpoints

3.2.1. Primary Efficacy Endpoint

The primary endpoint of this study is the mean $AUC_{12\text{-}48}$ of VAS scores.

3.2.2. Secondary Efficacy Endpoints

The secondary endpoints of this study are as follows:

- Mean AUC of VAS scores through 72 hours.
- Mean AUC of NRS-R scores through 72 hours.
- Proportion of subjects with severe pain at each timepoint and through 72 hours.
- Mean total postoperative opioid consumption (in IV morphine milligram equivalents [MME]) through 72 hours.
- Proportion of subjects who are opioid-free through 72 hours and through Day 11.
- Proportion of subjects who are opioid-free through 72 hours who remain opioid-free through Day 11.

- Median time to first opioid rescue medication through 72 hours.
- Proportion of subjects who do not receive an opioid prescription at discharge.
- Proportion of subjects who do not receive an opioid prescription between discharge and the Day 11 Visit.
- Proportion of subjects achieving a score of "good" or better (>1) pain control based on PGA at each timepoint.
- Median time to first ambulation through 72 hours.
- Proportion of subjects unable to participate in each rehabilitation session because of pain.
- Proportion of subjects who first achieve a Modified Postanaesthetic Discharge Scoring System (MPADSS) score ≥9 at each timepoint.
- Proportion of subjects who are discharged home vs to a skilled nursing facility.
- Mean OBAS at each timepoint.
- Mean Treatment Satisfaction Questionnaire for Medication (TSQM-9) score.

3.2.3. Safety Endpoints

The safety endpoints of this study are as follows:

- Incidence of TEAEs, SAEs, and opioid-related adverse events (ORAEs).
- Change from baseline in clinical laboratory results.
- Change from baseline in vital signs.
- Wound healing assessment results at each assessed timepoint.

3.2.4. PK Endpoints (Cohorts 1, 2, and 4)

The PK endpoints for Cohorts 1 and 2 of this study are as follows:

- Maximum concentration (C_{max}).
- Time of occurrence of maximum concentration (T_{max}).

3.2.5. PK Endpoints (Cohort 3)

The PK endpoints for Cohort 3 of this study are as follows:

- C_{max}.
- T_{max}.
- Area under the concentration-time curve from Time 0 to the time of the last quantitative concentration (AUC_{last}).
- Area under the concentration-time curve from Time 0 extrapolated to infinity (AUC_{inf}).

- Apparent terminal elimination rate constant (λ_z).
- Apparent terminal half-life ($t_{1/2}$).

3.3. Study Duration

The overall duration of the study is anticipated to be approximately 16 months. The total duration of study participation for each subject (from Screening through the Day 29 Visit) will be up to 61 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 115 subjects will be enrolled and dosed in the study at up to approximately 6 study sites in the US.

4.1.1. Inclusion Criteria

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

1. Is able to provide written informed consent.
2. Is able to adhere to the study visit schedule and complete all study assessments.
3. Is male or female, and ≥18 years of age at screening.
4. Is scheduled to undergo primary unilateral TKA under spinal anesthesia (all cohorts) and without drains in Cohorts 2 and 3.
5. Has not previously undergone TKA in either knee.
6. Has an American Society of Anesthesiologists (ASA) Physical Status of I, II, or III.
7. Is able to walk at least 20 feet with optional use of a 4-legged walker for balance.
8. Female subjects are eligible only if all of the following apply:
    a. Not pregnant (female subject 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 double-barrier contraception; or practicing abstinence (must agree to use double-barrier contraception in the event of sexual activity); or is using an insertable, injectable, transdermal, or combination PO contraceptive approved by the US FDA and commits to the use of an acceptable form of birth control from the Screening Visit until 30 days after study drug administration. Note: women in only a same-sex relationship do not need to meet this criterion.

4.1.2. Exclusion Criteria

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

1. Has a planned concurrent surgical procedure (eg, bilateral TKA) during the study.
2. 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 knee surgery and which may confound the postoperative assessments.

3. Has a contraindication or a known or suspected history of hypersensitivity or clinically significant idiosyncratic reaction (including methemoglobinemia) to bupivacaine (or other local anesthetics), NSAIDs (eg, meloxicam, ibuprofen, celecoxib), oxycodone, morphine, hydromorphone, TXA, fentanyl, pregabalin, acetaminophen, or acetylsalicylic acid.
4. Using or expected to use Factor IX Complex or anti-inhibitor coagulant concentrates during the study.
5. Has known or suspected daily use of opioids for 7 or more consecutive days within the previous 6 months.
6. Has taken NSAIDs (including meloxicam) within 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 informed consent form (ICF), or to decrease venous irritation caused by propofol, if needed (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, duloxetine, or 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). Note that for purposes of this exclusion criterion, inhaled, ophthalmic, and over-the-counter steroids are not considered systemic.
13. Previously participated in a clinical study or received an investigational product or device in a clinical trial within 30 days or within 5 elimination half-lives (whichever is longer) prior to the scheduled surgery, or is planning to take part in another clinical trial while participating in this study.
14. Has a known or suspected history of drug abuse, a positive drug screen on the day of surgery, or a history of alcohol abuse (within 10 years). 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 with a positive drug screen for cannabinoids on the day of surgery will not be allowed to participate in the study.

15. 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 of ECG or cardiac function.
    b. History of coronary artery bypass graft surgery within 12 months prior to signing the ICF.
    c. 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. Severe kidney function impairment as defined by creatinine clearance (Cockcroft-Gault) <30 mL/min or on dialysis.
    e. History of known or suspected coagulopathy or uncontrolled anticoagulation (platelet count <100,000/μL; hemoglobin <12 g/dL; or hematocrit <35%).
    f. Loss of sensation in extremities or significant peripheral neuropathy.
    g. Known history of glucose-6-phosphate dehydrogenase deficiency.
16. Is currently undergoing treatment for hepatitis B, hepatitis C, or HIV.
17. Has uncontrolled anxiety, psychiatric, or neurological disorder that, in the opinion of the Investigator, might interfere with study assessments.
18. Has acquired defective color vision or acute gastrointestinal ulcers, either of which could interfere with scheduled study medications.
19. Has any chronic neuromuscular deficit of either femoral nerve function or thigh musculature.
20. Has any chronic condition or disease that would compromise neurological or vascular assessments.
21. 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.
22. Has undergone 3 or more surgeries within 12 months prior to signing the ICF, other than for diagnostic procedures (eg, colonoscopy).
23. Has a body mass index (BMI) >40 kg/m^2.

4.2. Method of Assigning Subjects to Treatment Groups

The study is an open-label, multicohort study.

In Cohorts 1, 2, and 4, subjects who meet the eligibility criteria will be enrolled.

In Cohort 3, subjects who meet the eligibility criteria will be randomized in a 1:1 ratio to 2 treatment groups. Randomization should be done within 1 business day prior to the day of

surgery. Subjects will be randomized using a computer-generated randomization scheme. No subject may receive study drug prior to randomization.

4.2.1. Procedures for Handling 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. In the event a subject does not meet the eligibility criteria, but 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

Not applicable because this is an open-label study.

4.4. Subject Withdrawal and Replacement

4.4.1. Subject Withdrawal

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

Possible reasons for early withdrawal include the following:

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

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

4.4.2. Subject Replacement

Subjects enrolled in Cohorts 1, 2, or 4 who withdraw early from the study for any reason will not be replaced.

Any subject who is randomized in Cohort 3 but withdraws from the study prior to study drug administration will be replaced by the next eligible study subject. The replacement subject will be assigned to the same treatment group as the subject who withdrew.

5. STUDY TREATMENT

All subjects will receive a single dose of study drug intraoperatively while undergoing TKA. Study drug is defined as HTX-011 (investigational product). HTX-011 will be supplied by the Sponsor.

Subjects in Group B of Cohort 3 will also be administered bupivacaine HCl via injection into the posterior capsule during surgery. Bupivacaine HCl will be supplied by study sites.

5.1. Study Drug (HTX-011)

5.1.1. Description of Investigational Product

HTX-011 is a clear, pale yellow to yellow, viscous liquid supplied in single-dose, 20 mL 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 as described in the Pharmacy Manual.

5.1.2. Manufacturing, Packaging, and Labeling

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

HTX-011 will be packaged and labeled by the Sponsor or designee and will be packed and dispatched to comply with shipping and storage conditions. HTX-011 labeling will comply with all applicable national and local laws and regulations.

5.1.3. Study Drug Storage

At the study site, HTX-011 should be stored at a controlled room temperature of 20°C to 25°C (with excursions permitted from 15°C to 30°C). To protect from light, HTX-011 should be stored in the original packaging until time of use. The study drug storage area should be locked with restricted access. A temperature log must be maintained to monitor the storage area's temperature.

5.1.4. Study Drug Preparation

HTX-011 will be prepared at the study site. HTX-011 cannot be mixed with water, saline, or other local anesthetics because the product will become very viscous and difficult to administer.

Refer to the Pharmacy Manual for details on the study drug preparation.

5.1.5. Study Drug Administration

HTX-011 will be administered by periarticular application into the surgical site with a Luer lock applicator (without a needle) to the following 3 areas:

1. Posterior capsule (except Group B of Cohort 3).
2. Anteromedial tissues and periosteum.
3. Anterolateral tissues and periosteum.

The goal of this method of application is even distribution of the drug throughout the entire joint lining containing sensory nerve fibers including capsule, synovium, and periosteum.

Refer to the Pharmacy Manual for details on the study drug administration.

5.1.6. Study Drug Compliance

Because HTX-011 is being administered as a component of the surgical procedure, a lack of treatment compliance is not expected.

5.1.7. Study Drug Accountability

HTX-011 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 HTX-011 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 HTX-011 (ie, accountability or dispensing logs).

All HTX-011 records must be readily available for inspection by the site's Clinical Monitor and/or auditor. The Clinical Monitor is responsible for verifying the accuracy of the HTX-011 records at the study site. All returns, disposal, or destruction must be approved by the Sponsor in writing.

5.2. Injection of Bupivacaine HCl into the Posterior Capsule (Group B of Cohort 3 Only)

Bupivacaine HCl 100 mg 0.25% or 0.5% will be administered as a 40 mL injection into the posterior capsule just prior to placement of the prosthesis (ie, 40 mL of 0.25% or 20 mL of 0.5% diluted with 20 mL of 0.9% Normal Saline for a total of 40 mL). Bupivacaine HCl should be injected evenly with at least 10 to 15 injection points. Refer to the Pharmacy Manual for details on administration.

5.3. Additional Scheduled Concomitant Medications

Anesthesia: Bupivacaine 0.5% or 0.75%, per institutional practice, will be administered as part of the spinal anesthesia during surgery. The dose of bupivacaine should not exceed a maximum of 20 mg (ie, maximum of 4 mL of bupivacaine 0.5% or maximum of 2.6 mL of bupivacaine 0.75%).

Scheduled MMA Regimen: Just before being taken to the operating room, all subjects will receive PO acetaminophen 1 g, PO celecoxib 200 mg, and PO pregabalin 300 mg. For the first 3 days after surgery, all subjects will receive PO acetaminophen 1 g every 8 hours and PO celecoxib 200 mg every 12 hours (Cohorts 1, 2, and 3) or PO acetaminophen 1 g every 8 hours and PO ibuprofen 600 mg every 6 hours (Cohort 4). For the next 4 days, the MMA regimen for all cohorts will consist of PO ibuprofen 600 mg every 6 hours alternating with PO acetaminophen 1 g every 6 hours (maximum ibuprofen dose of 2.4 g/day and maximum acetaminophen dose of 4 g/day) while the subject is awake, so that an analgesic is taken approximately every 3 hours.

Antifibrinolysis and DVT prophylaxis: All subjects will also be administered TXA IV and acetylsalicylic acid PO for antifibrinolysis and DVT prophylaxis, respectively. TXA 1g IV will be administered within approximately 4 hours prior to the start of surgery and a second dose will be administered up to approximately 8 hours later. Subjects will receive acetylsalicylic acid 325 mg PO BID following surgery until discharge.

6. STUDY PROCEDURES AND ASSESSMENTS

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

6.1. Medical History and Demographics

6.1.1. Medical History

A complete medical history will be obtained 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 Day 29 Visit will be recorded. 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 Day 29 Visit, 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 in keeping with the standard of medical care.

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

During surgery, the use of fentanyl up to 4 μg/kg IV is permitted for intraoperative pain control; postoperative fentanyl use is not permitted.

Opioid rescue medications permitted to treat pain during the 72-hour postoperative period include of any 1 or more of the following opioid medications, as needed: PO immediate-release oxycodone (≤10 mg within a 4-hour period), IV morphine (2.5 mg to 5 mg within a 4-hour period), and/or IV hydromorphone (0.5 mg to 1.0 mg within a 4-hour period). Combination products containing an opioid and non-opioid are not allowed.

After 7 days of the schedule non-opioid MMA regimen, subjects may continue one or both of the MMA medications as needed, but should not exceed ibuprofen 600 mg every 6 hours or acetaminophen 1 g every 6 hours (maximum ibuprofen dose of 2.4 g/day and maximum acetaminophen dose of 4 g/day).

6.2.2. Prohibited Therapy

6.2.2.1. Medications Prohibited Prior to Surgery

Any drug formulation containing bupivacaine or meloxicam is prohibited before surgery (within 5 days for bupivacaine and within 10 days for meloxicam). Refer to exclusion criteria 4 through 13 for medications that are prohibited prior to the scheduled surgery (Section 4.1.2).

6.2.2.2. Medications Prohibited During Surgery

Intraoperative administration of opioids or any other analgesics (including ketamine), local anesthetics, or anti-inflammatory agents except as specified by the protocol (ie, HTX-011, bupivacaine, 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 During the Postoperative Period

With the exception of the scheduled non-opioid MMA regimen (Section 5.2) and permitted opioid rescue medications (Section 6.2.1), no other analgesic agents, including pregabalin and other NSAIDs, are permitted through Day 11.

6.3. Efficacy Assessments

6.3.1. Pain Intensity Assessments

Subjects will be asked to evaluate their current pain level at scheduled timepoints after surgery. The subject should be in the resting position (either seated comfortably or lying down) for at least 5 minutes prior to obtaining the pain scores. Pain intensity scores will be assessed using 2 different pain scales: VAS and NRS (Breivik 2008; Haefeli 2006). Subjects will receive training by the site on how to provide pain intensity assessments.

The VAS consists of a straight 10-cm line that represents pain ranging from “no pain” to “pain as bad as it could be” (see Appendix C). Subjects will be asked to mark their current pain level on the line. The distance between “no pain at all” and the subject’s mark defines the subject’s pain.

The NRS is an 11-point scale (0 to 10) where 0 represents “no pain” and 10 represents “worst pain imaginable” (see Appendix D). Subjects will be asked to rate their current pain level on this scale.

6.3.2. Use of Opioid Medications

6.3.2.1. Opioid Rescue Medication Prior to Discharge

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 during the 72-hour postoperative period. More information on opioid rescue medications permitted is provided in Section 3.1.2.

6.3.3. Opioid Medication After Discharge

All subjects (whether or not they were discharged with an opioid prescription) will be provided a daily diary to record any opioid medication use from discharge through the Day 11 Visit.

Sites will also record all site or subject-initiated contact between discharge and the Day 11 Visit and if any resulted in issuing an opioid prescription.

6.3.4. Discharge Readiness

Discharge readiness will be assessed using the MPADSS criteria, which considers a number of clinical variables: vital signs, ambulation, nausea/vomiting, pain, and surgical bleeding (Chung 1995). 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 whether or not to discharge a subject from the study. Subjects are required to remain in the hospital/research facility for 72 hours. See Appendix E for the MPADSS criteria.

6.3.5. Patient Global Assessment 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 F for the PGA scale.

6.3.6. Overall Benefit of Analgesia Assessment

Subjects will be questioned about their overall benefit of analgesia using a 7-item, multidimensional, quality assessment questionnaire (Lehmann 2010). The 7 items address pain, vomiting, itching, sweating, freezing, dizziness, and overall satisfaction with postoperative pain and make up the OBAS. See Appendix G for the OBAS scale.

6.3.7. Treatment Satisfaction

Subjects will be asked to evaluate their satisfaction with their scheduled non-opioid MMA regimen for the treatment of their TKA-related pain using the TSQM-9 (Bharmal 2009). Subjects will answer 9 questions related to effectiveness, convenience, and global satisfaction (see Appendix H).

6.3.8. Ambulation and Rehabilitation

Sites will assess the subject's time to ambulate. Ambulation is defined as the ability walk at least 20 feet with optional use of a 4-legged walker for balance. All subjects will be encouraged to ambulate as early as possible during the 72-hour postoperative period. The date and time of first ambulation must be recorded.

Sites will also assess the subject's ability to participate in scheduled rehabilitation sessions on the evening of Day 1 and in the morning and evening of Days 2 and 3 according to institution's guidelines.

6.3.9. Discharge Information

Sites will record when subjects are discharged and if subjects are discharged home or to a skilled nursing facility.

Sites will also record if subjects are discharged with an opioid prescription and information about the opioid prescription. See Section 3.1.2.2 for guidance on providing an opioid prescription at discharge.

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 Day 29 Visit. Additional safety information is provided in Section 8.

6.4.2. 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 will be conducted and BMI calculated (Appendix B).

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.

Any abnormal physical examination finding deemed clinically significant by the Investigator must be recorded as an AE.

6.4.3. Vital Signs

Vital sign measurements will include 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 measuring vital signs.

Any abnormal vital sign result deemed clinically significant by the Investigator must be recorded as an AE.

6.4.4. 12-Lead Electrocardiograms

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

Any abnormal ECG result deemed clinically significant by the Investigator must be recorded as an AE.

6.4.5. Wound Healing Evaluation

Surgical wound healing will be assessed using the Southampton Wound Scoring System (Appendix I). 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.

Only an abnormal wound healing finding deemed clinically significant by the Investigator must be recorded as an AE and should be followed to resolution.

6.4.6. Clinical Laboratory Tests

Blood and urine samples will be collected for diagnostic screening tests and for safety laboratory tests (hematology and serum chemistry). A list of clinical laboratory tests and parameters is provided in Table 1.

Scheduled hematology and serum chemistry tests will be performed by a central laboratory. Urine samples collected during the Screening period for pregnancy and drug screening will be tested at the study site using kits provided by the central laboratory.

Laboratory results will be reviewed by the Investigator. Laboratory values outside of the normal reference range will be evaluated for clinical significance. Only an abnormal laboratory value deemed clinically significant by the Investigator must be recorded as an AE. Results for any unscheduled local laboratory tests deemed abnormal and clinically significant must be recorded on an eCRF.

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

Table 1: Clinical Laboratory Tests

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

6.4.7. Local Anesthetic Systemic Toxicity (LAST) Assessment

If signs and symptoms of suspected LAST are observed, the following assessments must be promptly performed: vital sign measurements, 12-lead ECGs, and blood sample collection to measure bupivacaine plasma concentrations (all cohorts) and alpha-1-acid glycoprotein concentrations (Cohort 4 only).

6.5. Pharmacokinetic Assessments

Blood samples for bupivacaine and meloxicam PK analysis will be collected from all subjects. Blood samples for alpha-1-acid glycoprotein analysis will be collected from subjects in Cohort 4. Blood samples may also be used to evaluate other study drug components.

Blood samples may be drawn using a properly maintained indwelling cannula. Samples for bupivacaine and meloxicam PK analysis will be sent to a bioanalytical laboratory for analysis. In Cohort 4, ex vivo protein binding of bupivacaine will be determined to support PK analysis of free bupivacaine. Samples for alpha-1-acid glycoprotein, which impacts the free fraction of bupivacaine, will be sent to a central laboratory for analysis. Detailed instructions on sample collection, processing, storage, and shipping procedures are provided in the Laboratory Manual.

7. TIMING OF PROCEDURES AND ASSESSMENTS

This section lists the study procedures and assessments that will be performed at scheduled timepoints during the study. Information on study procedures and assessments is provided in Section 6.

Unless there is a safety concern, every effort should be made to avoid protocol deviations. For assessments at timepoints when the subject is asleep, an attempt should be made to wake the subject. If there is no response, the assessments at these timepoints may be recorded as "Not Done." Assessments that can be done without 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:

- Pain intensity assessment (VAS and NRS-R).
- PGA of pain control assessment.
- Vital sign measurements.
- 12-lead ECG recording (in triplicate).
- Blood sample collection.
- Physical examination.
- Wound healing assessment.

7.1. Screening Period (Within 28 Days Before Surgery)

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.

Results of the following tests should be confirmed as negative prior to performing any additional assessments:

- Urine drug screen test (all subjects): A subject who fails the drug test may be rescreened at the discretion of the Investigator after discussion with the Study Medical Monitor. 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.
- Urine pregnancy test (female subjects of child-bearing potential only).

Additional screening procedures and assessments will include the following:

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

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. Results of the following should be confirmed as negative prior to performing any additional assessments:

- Urine drug screen test (all subjects).
- Urine pregnancy test (female subjects of child bearing potential only).

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

- Vital sign measurements.
- Blood sample collection for PK (before administering the spinal anesthesia).
- Blood sample collection for alpha-1-acid glycoprotein (before administering the spinal anesthesia) (Cohort 4 only).
- Subject training for pain intensity assessments (refresher training).
- VAS pain intensity assessment.
- NRS-R assessment.
- AE recording.
- Prior and concomitant medication recording.

Within approximately 4 hours prior to the start of surgery, TXA 1 g IV will be administered.

Just before the subject is taken to the operating room, acetaminophen 1 g PO, celecoxib 200 mg PO, and pregabalin 300 mg PO will be administered.

7.2.1.2. Surgery and Study Treatment Administration

Subjects will undergo a primary unilateral TKA under bupivacaine spinal anesthesia. Sites should follow intraoperative safety monitoring in accordance with ASA Standards for Basic Anesthetic Monitoring (American Society of Anesthesiologists 2015). The use of drains is prohibited in Cohorts 2 and 3. The start and stop time of surgery and additional surgical details should be recorded in the eCRF. The start time of the skin incision will be considered the start of surgery. Placement of the last suture will be considered the end of surgery.

Subjects will be administered study drug (HTX-011; all cohorts) and bupivacaine HCl (Group B of Cohort 3 only) 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 and bupivacaine HCl will be applied into the surgical site prior to wound closure. More information on the administration techniques are provided in Section 5.1.5 and Section 5.2, respectively.

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 Time 0 for all efficacy, safety, and PK assessments.**

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 postanesthesia care unit.

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. During the inpatient period, subjects will be administered a scheduled non-opioid MMA regimen and medication for DVT prophylaxis (Section 7.2.2.1) and will undergo safety, efficacy, and PK assessments (Section 7.2.2.2).

7.2.2.1. Study Medication During Inpatient Period

As soon as subjects are able to tolerate oral intake, they will be started on a MMA regimen consisting of PO acetaminophen 1 g every 8 hours and PO celecoxib 200 mg every 12 hours (Cohorts 1, 2, and 3) or PO acetaminophen 1 g every 8 hours and PO ibuprofen 600 mg every 6 hours (Cohort 4).

Subjects will also receive TXA 1 g IV up to approximately 8 hours after the presurgery dose of TXA and acetylsalicylic acid 325 mg PO BID until hospital discharge. Surgeons may also use additional DVT prophylaxis as per their standard of care.

Subjects may be administered opioid rescue medication if needed to treat pain, as detailed in Section 3.1.2.1.

7.2.2.2. Study Procedures and Assessments During Inpatient Period

Study procedures and assessments that will be performed during the 72-hour postoperative period 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.

- **VAS and NRS-R assessments:** 1 hour (±10 min), 2 hour (±15 min), 4 hours (±30 min), 6 hours (±30 min), 8 hours (±30 min), 12 hours (±30 min), 24 hours (±1 h), 36 hours (±2 h), 48 hours (±2 h), 60 hours (±2 h), and 72 hours (±2 h).
  - Note: If a subject requires rescue medication before the 1-hour pain intensity assessments, then an unscheduled VAS and NRS-R score must be obtained before administering the first dose of rescue medication. These do not replace the 1-hour VAS and NRS-R assessments.
- **PGA of pain control assessment:** 24 hours (±1 h), 48 hours (±2 h), and 72 hours (±2 h).
- **Vital sign measurements:** 24 hours (±1 h), 48 hours (±2 h), and 72 hours (±2 h).
- **Blood sample for hematology and serum chemistry:** 72 hours (±2 h).
- **Blood sample collection for PK (Cohorts 1 and 2)**: 4 hours (±30 min), 20 hours (±1 h), 24 hours (±1 h), and 48 hours (±2 h).
- **Blood sample collection for PK (Cohort 3)**: 30 minutes (±5 min), 1 hour (±10 min), 2 hours (±15 min), 4 hours (±30 min), 6 hours (±30 min), 8 hours (±30 min), 12 hours (±30 min), 20 hours (±1 h), 24 hours (±1 h), 36 hours (±2 h), 48 hours (±2 h), 60 hours (±2 h), and 72 hours (±2 h).
- **Blood sample collection for PK (Cohort 4)**: 30 minutes (±5 min), 1 hour (±10 min), 2 hours (±15 min), 4 hours (±30 min), 6 hours (±30 min), 8 hours (±30 min), 12 hours (±30 min), 20 hours (±1 h), 24 hours (±1 h), 48 hours (±2 h), and 72 hours (±2 h).
- **Blood sample collection for alpha-1-acid glycoprotein (Cohort 4):** 4 hours (±30 min), 12 hours (±30 min), 20 hours (±1 h), 24 hours (±1 h), 48 hours (±2 h), and 72 hours (±2 h).
- **Physical examination:** 72 hours (±2 h; height and weight not required).
- **Discharge readiness assessment per the MPADSS criteria:** 2 hours (±15 min); 4 hours (±30 min), 6 hours (±30 min), 8 hours (±30 min), 12 hours (±30 min), 24 hours (±1 h), 36 hours (±2 h), 48 hours (±2 h), 60 hours (±2 h), and 72 hours (±2 h).
- **OBAS assessment:** 24 hours (±1 h), 48 hours (±2 h), and 72 hours (±2 h).
- **TSQM-9 questionnaire:** 72 hours (±2 h).
- **Wound healing assessment:** 72 hours (±2 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.)

All subjects will be encouraged to ambulate as early as possible during the 72-hour postoperative period and will be evaluated for the time to first ambulation postsurgery. Subjects will also participate in rehabilitation on the evening of Day 1, and in the morning and evening of Days 2 and 3.

7.2.3. Discharge

After the 72-hour assessments have been completed, subjects may be discharged if medically ready. If a subject is not ready to be discharged due to an AE, it should be recorded as an SAE. 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.

When a subject is discharged, the site will record the following:

- The time of discharge.
- If the subject is discharged home or to a skilled nursing facility.
- If the subject is discharged with an opioid prescription and information about the opioid prescription. See Section 3.1.2.2 for guidance on providing an opioid prescription at discharge.

Sites will also provide subjects with the following at the time of discharge:

- Instructions on managing pain after discharge (see Section 3.1.2.3).
- A diary that subjects will complete daily to record if they take any opioid medication from 72 hours through the Day 11 Visit. Note: All subjects, whether or not they were discharged with an opioid prescription, will receive an opioid diary.

7.3. Follow-Up Period

7.3.1. Day 5 Until Day 11 Visit

Subjects will continue their scheduled MMA regimen (PO ibuprofen alternating with PO acetaminophen) for 4 days after discharge (Days 5 through 8) and then as needed thereafter (see Section 3.1.2.3). Subjects will complete their opioid diary each day through the Day 11 Visit.

Sites will record all site- or subject-initiated contact between discharge and the Day 11 Visit and if any resulted in issuing an opioid prescription.

7.3.2. Day 11 Visit (±2 Days)

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

- VAS pain intensity assessment.
- NRS-R assessment.
- PGA of pain control assessment.
- Blood sample collection for the hematology and serum chemistry.
- OBAS assessment.

- TSQM-9 questionnaire.
- Wound healing assessment.
- Review subject opioid daily diary results.
- AE recording.
- Concomitant medication recording.

7.3.3. Day 29 Visit (±4 Days)

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

- VAS pain intensity assessment.
- NRS-R assessment.
- Wound healing assessment.
- AE recording.
- Concomitant medication recording.

7.4. Early Termination Visit

Subjects who withdraw early from the study will be asked to complete the following Early Termination procedures and assessments:

- Vital sign measurements (only if subject withdrew prior to 72 hours).
- Physical examination (only if subject withdrew prior to 72 hours [height and weight not required]).
- Blood sample collection for hematology and serum chemistry (only if subject withdrew prior to the Day 11 Visit).
- Review subject diary results (only if subject withdrew prior to the Day 11 Visit).
- VAS pain intensity assessment.
- NRS-R assessment.
- Wound healing assessment.
- AE recording.
- Concomitant medication recording.

7.5. Unscheduled Visits and Assessments

If signs and symptoms of suspected LAST are observed, unscheduled vital sign measurements, 12-lead ECGs, and blood sample collection for PK (all cohorts) and alpha-1-acid glycoprotein (Cohort 4 only) must be promptly performed.

Unscheduled visits and assessments should also 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 results of any unscheduled assessments should be recorded.

8. SAFETY MONITORING AND REPORTING

Investigators are responsible for the detection and documentation of AEs, SAEs, unanticipated problems, and pregnancies, as detailed in this protocol.

Investigators must review the HTX-011 Investigator's Brochure so as to be aware of the safety-related events that may be anticipated with its use. Investigators will also be versed in the latest standard of care guidelines.

8.1. Definition of Safety Parameters

8.1.1. Definition of an Adverse Event

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

An AE may be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not considered causally associated with the use of the study drug. Any abnormal physical examination finding, laboratory value, vital sign result, ECG finding, or wound healing assessment finding deemed clinically significant by the Investigator must be reported as an AE. A clinical diagnosis, rather than a change in a 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 laboratory abnormality.
  - Any laboratory abnormality that required additional diagnostic intervention, and/or follow-up visits (excluding repeat testing to confirm the abnormality).

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, an AE that 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, hospitalization 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 and does not meet the criteria of an important medical or a life-threatening event.

According to 21 Code of Federal Regulations (CFR) 812.3(s), an unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or

death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

8.1.3. Definition of 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 (HTX-011) 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. 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 Day 29 Visit. Note: the start time of all AEs during the 72-hour postoperative period must also be recorded.

For subjects who received study drug, if an Investigator becomes aware of an SAE that occurs after the subject's last study visit 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:

- **Recovered/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.
- **Recovered/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.
- **Recovering/Resolving**: The event is improving.
- **Not recovered/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.
- **Fatal**

SAEs will be followed until the event resolves (ie, when the event no longer meets any of the seriousness criteria), the condition stabilizes, or 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 that occurs during the course of this study meets the protocol definition of an SAE due to any cause, 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 any 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 any 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

Pregnancy is not considered to be an AE; however, 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

An internal Product Safety and Risk Management Committee will monitor safety data on a periodic basis throughout the study, including regular review of AEs (including SAEs), laboratory results, and other safety assessments.

The criteria for suspending the study are provided in in Section 13.5.

9. OTHER STUDY RESTRICTIONS

9.1. Contraception

Female subjects of childbearing potential must use an acceptable form of contraception in the event of sexual activity from the Screening Visit until 30 days after study drug administration. Acceptable forms of contraception include double-barrier contraception or an insertable, injectable, transdermal, or combination PO contraceptive approved by the US FDA. Subjects practicing abstinence must agree to use double-barrier contraception in the event of sexual activity.

Note: This does not apply to women in only a same-sex relationship or women in a monogamous relationship with a surgically sterile partner.

9.2. Continuous Passive Motion Machines

Continuous passive motion machines are not required in this study; however, if they are to be used, they are not allowed within the first 12 hours after study drug administration.

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. 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.

10.2. Determination of Sample Size

The sample size of 115 subjects was selected empirically without formal statistical assumptions.

10.3. Analysis Populations

Safety Population: All subjects who receive study drug will be included in the Safety Population. This population will be used for all summaries of efficacy and safety data.

PK Population: All subjects who receive at least 1 dose of study drug and have sufficient data to calculate PK parameters will be included in the PK Population. Any subject with a study drug predose concentration exceeding 5% of the C_{max} for that individual will be excluded from the PK Population for that analyte.

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, dosed, completing the 72-hour postoperative observation period, completing the study, and not completing the study by reason for withdrawal will be summarized for the Safety Population. Subject demographics and baseline characteristics will be summarized for the Safety Population and will include age, age category, sex, race, ethnicity, height, weight, and BMI.

10.4.2. Efficacy Analysis

All efficacy data will be listed and summarized by cohort and treatment group. All opiate dosages and formulations will have the MME calculated (Opioid Morphine Equivalent Conversion Factors, Centers for Disease Control and Prevention, Atlanta, GA, May 2014). During the 72-hour postoperative period, subjects who do not use a specific opioid rescue medication during a period of interest will have the specific opioid dose set to 0 for that period and will be characterized as “opioid-free” for that time interval.

10.4.2.1. 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, VAS and NRS-R scores will be imputed via last observation carried forward (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 will be used. Predose values will not be carried forward to postdose timepoints. In subjects who withdraw from the study prior to the end of 72-hour observation period, missing pain intensity scores through 72 hours that were to be collected following withdrawal will be imputed via worst observation carried forward (WOCF), in which the worst (highest) pain intensity score observed prior to withdrawal will be used for postwithdrawal values through 72 hours. Analyses that adjust for the effect of opioid rescue medication will perform windowed worst observation carried forward (wWOCF) following LOCF/WOCF (ie, perform LOCF/WOCF first, then apply wWOCF). The number and percentage of missing pain intensity scores will be summarized.

10.4.3. Safety Analysis

All safety data will be listed and summarized by cohort and 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. The incidence of TEAEs, SAEs, and ORAEs will be summarized. TEAEs 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 vital sign variables will be summarized. Abnormal vital sign values will be flagged and listed.

Wound healing assessment results will be summarized at each timepoint.

10.4.4. Pharmacokinetic Analysis

Plasma bupivacaine and meloxicam concentrations will be determined using validated liquid chromatography tandem-mass spectrometry assays. Concentrations will be calculated by interpolation from a calibration curve. PK parameters for bupivacaine and meloxicam will be calculated using noncompartmental analysis, as appropriate. Additional exploratory analyses may be performed, as appropriate, to facilitate cross-study comparisons and to fully characterize the concentration-time profiles of each analyte or other study drug components.

In Cohort 4, concentrations of alpha-1-acid glycoprotein will be summarized using descriptive statistics. As an exploratory analysis, ex vivo protein binding of bupivacaine will be determined using equilibrium dialysis. PK parameters for free bupivacaine will be calculated using noncompartmental analysis, as appropriate.

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 by the Sponsor and its designee(s), as appropriate, following Standard Operating Procedures (SOPs) to ensure that the clinical study is conducted and the data are generated, documented (recorded), and reported in compliance with the protocol, International Council for Harmonisation (ICH) E6 GCP guidelines, and applicable regulatory requirements. The accuracy, completeness, and reliability of the study data presented to the Sponsor, however, are the responsibility of the Investigator. The Investigator or designee must record all required data using the prespecified data collection method defined by the Sponsor or its designee.

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

12. REGULATORY AND ETHICAL CONSIDERATIONS

12.1. Regulatory Authority Approval

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

12.2. Ethical Conduct of the Study

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

12.3. Ethics Committee Approval

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

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

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 an 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 reconsented, informed consent will be obtained in the same manner as for the original ICF.

12.5. Confidentiality

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

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

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

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

13. STUDY ADMINISTRATION

13.1. Clinical Monitoring

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

13.2. Source Documents and Record Retention

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

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

13.3. Management of Protocol Amendments and Deviations

13.3.1. Protocol Modification

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

13.3.2. Protocol Deviations

A protocol deviation is a change, divergence, or departure from the study design or procedures defined in this protocol. The Investigator will notify the EC of any protocol deviations as required by EC guidelines and site requirements. Protocol deviations will be documented at the site and in the Sponsor files. The Sponsor is responsible for notifying the regulatory authorities of any protocol deviations, if required.

13.4. Financial Disclosure

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

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

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

13.5. Criteria For Suspending the Study

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 suspending the study to assess whether terminating the study early, modifying the study, or closing a site is warranted include, but are not limited to, the following:

- A single death or 3 non-fatal SAEs that are determined by the Sponsor to be possibly related to study drug or any scheduled study medication for which a clear alternative cause is not readily apparent.
- 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.
- Insufficiently complete and/or evaluable data.
- 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 Consolidated Standards of Reporting Trials (CONSORT) group, and Good Publication Practice (GPP). A copy of this policy will be made available to the Investigator upon request.

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

14. REFERENCE LIST

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APPENDIX A. AMERICAN SOCIETY OF ANESTHESIOLOGISTS PHYSICAL STATUS CLASSIFICATION SYSTEM

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

Abbreviations: ARD, acute renal disease; ASA, American Society of Anesthesiologists; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DIC, disseminated intravascular coagulation; DM, diabetes mellitus; ESRD, end stage renal disease; HTN, hypertension; MI, myocardial infarction; PCA, postconceptional age; PS, physical status; TIA, transient ischemic attack.

Note: The addition of "E" denotes Emergency surgery. (An emergency is defined as existing when delay in treatment of the patient would lead to a significant increase in the threat to life or body part.)

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

APPENDIX B. BODY MASS INDEX (BMI) CALCULATION

BMI = Weight in kilograms/(height in meters)^2

Meters = inches × 0.0254

Kilograms = pounds × 0.453592

Example:

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

165 lbs. × 0.453592 = 74.8 kg

71 in. × 0.0254 = 1.803 m

74.8/(1.803 × 1.803) = 23.01 kg/m^2

APPENDIX C. PAIN INTENSITY ASSESSMENTS USING THE VISUAL ANALOGUE SCALE (VAS)

For all VAS pain intensity assessments, subjects will be asked to mark their current pain level on a 10-cm line that represents pain ranging from "no pain" to "pain as bad as it could be." The site will measure to the nearest millimeter the distance between "no pain at all" and the subject's mark, which defines the subject's pain that will be recorded in the case report form.

The example VAS provided in this appendix is not to scale and must not be used for the assessment. Use the Visual Analogue Scale provided by the Sponsor.

Reference: Adapted from Haefeli M, Elfering A. Pain assessment. *Eur Spine J*. 2006;15(1):S17-S24.

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

"On a scale of 0 to 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: Adapted from Breivik H, Borchgrevink PC, Allen SM, et al. Assessment of pain. *Br J Anaesth*. 2008;101(1):17-24.

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. Discharge criteria--a new trend. *Can J Anaesth*. 1995;42(11):1056-1058.

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

"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: Adapted from Rothman M, Vallow S, Damaraju CV, and Hewitt DJ. Using the patient global assessment of the method of pain control to assess new analgesic modalities in clinical trials. *Current Medical Research and Opinion*. 2009;25,1433-1443.

APPENDIX G. OVERALL BENEFIT OF ANALGESIA SCORE (OBAS)

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

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

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

Note that a low score indicates high benefit.

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

APPENDIX H. TREATMENT SATISFACTION QUESTIONNAIRE FOR MEDICATION (TSQM-9)

The TSQM-9 will be used to assess the subject's satisfaction with their scheduled non-opioid multimodal analgesic (MMA) regimen for the treatment of their TKA-related pain. Subjects will answer 9 questions related to effectiveness, convenience, and global satisfaction.

TSQM-9 Questions	Response Options
Effectiveness	
How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?	Extremely dissatisfied Very dissatisfied Dissatisfied Somewhat satisfied Satisfied Very satisfied Extremely satisfied
How satisfied or dissatisfied are you with the way the medication relieves your symptoms?	Extremely dissatisfied Very dissatisfied Dissatisfied Somewhat satisfied Satisfied Very satisfied Extremely satisfied
How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?	Extremely dissatisfied Very dissatisfied Dissatisfied Somewhat satisfied Satisfied Very satisfied Extremely satisfied
Convenience	
How easy or difficult is it to use the medication in its current form?	Extremely difficult Very difficult Difficult Somewhat easy Easy Very easy Extremely easy

TSQM-9 Questions	Response Options
How easy or difficult is it to plan when you will use the medication each time?	Extremely difficult Very difficult Difficult Somewhat easy Easy Very easy Extremely easy
How convenient or inconvenient is it to take the medication as instructed?	Extremely inconvenient Very inconvenient Inconvenient Somewhat convenient Convenient Very convenient Extremely convenient
Global Satisfaction	
Overall, how confident are you that taking this medication is a good thing for you?	Not at all confidant A little confidant Somewhat confidant Very confidant Extremely confidant
How certain are you that the good things about your medication outweigh the bad things?	Not at all certain A little certain Somewhat certain Very certain Extremely certain
Taking all things into account, how satisfied or dissatisfied are you with this medication?	Extremely dissatisfied Very dissatisfied Dissatisfied Somewhat satisfied Satisfied Very satisfied Extremely satisfied

Reference: Bharmal M, Payne K, Atkinson M, Desrosiers M-P, Morisky DE, Gemmen E. Validation of an abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) among patients on antihypertensive medications. *Health Qual Life Outcomes*. 2009;7:36.

APPENDIX I. WOUND HEALING ASSESSMENT - SOUTHAMPTON WOUND SCORING SYSTEM

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

References:
Alam SI, Khan MY, Gul A, Jan QA. Surgical site infection. *Professional Med J*. 2014;21(2):377-381.
Bailey I. Community surveillance of complications after hernia surgery. *BMJ*. 1992;304:469-471.

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