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Official Title:	A Phase 4, Randomized, Blinded, Active-Controlled Study of HTX-011 in Subjects Undergoing Different Surgical Procedures
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CLINICAL STUDY PROTOCOL: HTX-011-401

Protocol Title:	A Phase 4, Randomized, Blinded, Active-Controlled Study of HTX-011 in Subjects Undergoing Different Surgical Procedures
Brief Title:	A Multi-surgery Assessment of ZYNRELEF (HTX-011), AMAZE
Test Product:	HTX-011 (bupivacaine and meloxicam) extended-release solution
Phase of Development:	4
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 3 16 November 2021 Version 2 22 September 2021 Version 1 24 August 2021

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SPONSOR SIGNATURE

Protocol Title:	A Phase 4, Randomized, Blinded, Active-Controlled Study of HTX-011 in Subjects Undergoing Different Surgical Procedures
Protocol Number:	HTX-011-401

This protocol Version 3 has been reviewed and approved by the Sponsor.

The electronic signature is appended.

[redacted]
Heron Therapeutics, Inc.

INVESTIGATOR AGREEMENT

CLINICAL STUDY PROTOCOL: HTX-011-401

TITLE: A Phase 4, Randomized, Blinded, Active-Controlled Study of HTX-011 in Subjects Undergoing Different Surgical Procedures

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 study drugs and study devices that are 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 test product and the conduct of the study.

I agree to keep records on all subject information (ie, medical records, source documents, 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 regulations and national Good Clinical Practice (GCP) regulations and guidelines.

Principal Investigator: _____

Address: _____

Signature: _____

Date (DD Month YYYY): _____

PROTOCOL SYNOPSIS

NAME OF SPONSOR:	Heron Therapeutics, Inc.
NAME OF TEST PRODUCT:	HTX-011 (bupivacaine and meloxicam) extended-release solution
NAME OF ACTIVE INGREDIENTS:	bupivacaine and meloxicam
PROTOCOL NUMBER:	HTX-011-401
PHASE OF DEVELOPMENT:	4
PROTOCOL TITLE: A Phase 4, Randomized, Blinded, Active-Controlled Study of HTX-011 in Subjects Undergoing Different Surgical Procedures	
STUDY SITES: Up to 6 sites in the United States (US).	

STUDY OBJECTIVES:

Primary

- To assess the safety and tolerability of HTX-011 in subjects undergoing different surgical procedures.

Secondary

- To characterize the bupivacaine and meloxicam pharmacokinetic (PK) parameters following administration of HTX-011 in these study populations.

Exploratory

- To assess the pharmacodynamic (PD) activity of HTX-011 in these study populations based on postoperative pain and opioid use.

BACKGROUND AND RATIONALE FOR THE STUDY:

HTX-011 is a novel, non-opioid, fixed-dose, extended-release local anesthetic containing bupivacaine and low-dose meloxicam formulated in a proprietary polymer that is administered as a single dose applied into the surgical site prior to wound closure. HTX-011 is approved as ZYNRELEF™ in the US and Europe for postoperative analgesia in specified procedures. The purpose of this study is to obtain safety, PK, and PD data in additional surgical procedures to support the expanded use of ZYNRELEF.

METHODOLOGY:

This is a Phase 4, randomized, blinded, active-controlled, multicohort study to evaluate HTX-011 compared with bupivacaine HCl in subjects undergoing different surgical procedures. The study will include 2 cohorts, which will be conducted in parallel. Each cohort will enroll subjects undergoing a unique surgical procedure: total shoulder arthroplasty (TSA) in Cohort 1 and abdominoplasty in Cohort 2.

In each cohort, approximately 30 subjects will be randomized in a 2:1 ratio to HTX-011 or bupivacaine HCl, respectively. In both cohorts, all subjects will receive a scheduled postoperative non-opioid multimodal analgesic (MMA) regimen. Subjects and site personnel performing postoperative safety and PD assessments will be blinded to treatment assignments; however, unblinded site staff may collect samples for PK analysis. The Sponsor will be unblinded, but will maintain the blind when interacting with blinded site staff.

Cohort 1 (TSA)

- HTX-011 400 mg/12 mg + MMA (N=20).
- Bupivacaine HCl 0.25% 100 mg + MMA (N=10).

Cohort 2 (abdominoplasty)

- HTX-011 400 mg/12 mg + MMA (N=20).
- Bupivacaine HCl 0.25% 125 mg + MMA (N=10).

Study Overview

Subjects will be screened within 28 days prior to the planned surgery date. Subjects who meet the eligibility criteria will be randomized within 1 business day prior to surgery. On the day of surgery (Day 1), subjects who continue to meet the eligibility criteria will undergo surgery. Before surgery, subjects will be shown an instructional video that will describe what to expect after surgery.

During surgery, all subjects will receive a single dose of study drug (HTX-011 or bupivacaine HCl). In addition, at the discretion of the anesthesiologist/surgeon, subjects may receive intravenous (IV) fentanyl (up to 3 µg/kg body weight, not exceeding 200 µg, in Cohort 1; up to 1.5 µg/kg, not exceeding 100 µg, in Cohort 2). All subjects will receive a single dose of either IV morphine 5 to 10 mg or IV hydromorphone 1 to 2 mg just prior to the application of dermal sutures.

Subjects will remain in the facility through 72 hours postdose for PK, safety, and PD assessments. Subjects will receive a scheduled non-opioid MMA regimen over the 72-hour postoperative period consisting of oral (PO) acetaminophen 1 g every 8 hours (q8h) alternating with PO ibuprofen 400 mg q8h, so that an analgesic is taken approximately every 4 hours. The first dose of the postoperative MMA regimen will be administered once the subject is able to tolerate PO intake.

Prior to discharge (Day 4), subjects will be shown an instructional video on what to expect after discharge. Subjects will be instructed at discharge to continue their scheduled MMA regimen through Day 7 and will receive instructions on how to complete the daily diary to record opioid use through the Day 15 Visit.

PK sampling will occur through Day 7. On Day 5 (96-hour timepoint), Day 6 (120-hour timepoint), and Day 7 (144-hour timepoint), PK sample collection will be performed at the study site or via a home visit. For subjects with drains, all drainage fluid will be collected and pooled over 12-hour intervals through 72 hours and may be used to measure the bupivacaine concentration.

All subjects will return to the study site on Day 15 to complete End-of-Study assessments.

Postoperative Analgesia

Postoperative Rescue Medication

During the 72-hour postoperative period, subjects should receive rescue medication only upon request for pain control. Permitted postoperative rescue medication includes the following:

- PO ibuprofen 400 mg and PO acetaminophen 500 mg (in addition to and independent from the scheduled MMA regimen), which may be administered at most only once every 12 hours as rescue. Ibuprofen and acetaminophen must be the first rescue medication given every time rescue medication is requested by the subject, provided that ≥12 hours have elapsed since the last administration of ibuprofen/acetaminophen as rescue medication and the total acetaminophen is ≤4 g within a 24-hour period.

  Subjects may be administered opioid rescue medication between 30 minutes and 12 hours after receiving ibuprofen/acetaminophen as rescue medication, if additional rescue medication is requested:
  - PO immediate-release oxycodone (≤10 mg within a 4-hour period) OR
  - IV morphine (≤5 mg within a 4-hour period).

Opioid rescue medication should not be given for pain prophylaxis, but only for treating postoperative pain. Combination products containing an opioid and non-opioid are not allowed. Nonsteroidal anti-inflammatory drugs (NSAIDs) or other analgesic agents are not permitted during the 72-hour

postoperative period, except for ibuprofen and acetaminophen per protocol and low-dose (≤100 mg) daily acetylsalicylic acid for cardioprotection.

Prior to the administration of the first dose of rescue medication, if the subject has not already had at least 1 postoperative pain score assessed, then a numeric rating scale (NRS) of pain intensity at rest (NRS-R) score followed by an NRS of pain intensity with activity (NRS-A) score must be obtained.

Opioid Prescriptions at and After Discharge

If a subject did not receive any opioids or received <5 IV morphine milligram equivalents (MME; eg, <10 mg of oxycodone) within 12 hours prior to discharge, the subject should not receive an opioid prescription at discharge. If a subject received ≥5 IV MME within 12 hours prior to discharge, the Investigator may provide the subject with a prescription for PO immediate-release oxycodone tablets: no more than twenty 5 mg immediate-release oxycodone, take 1 to 2 pills (5 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 in the electronic data capture (EDC) whether subjects are discharged with an opioid prescription and information about the opioid prescription, if provided.

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 15 Visit. Sites will record in the EDC all site- or subject-initiated contact between discharge and the Day 15 Visit and whether any contact resulted in issuing an opioid prescription.

NUMBER OF PLANNED SUBJECTS: Approximately 60 subjects will be enrolled and dosed. Each cohort/surgical procedure will enroll approximately 30 subjects.

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 ≥18 years of age at the time of the Screening Visit.
4. Has an American Society of Anesthesiologists Physical Status of I, II, or III.
5. Subjects of childbearing potential (defined as premenopausal and capable of becoming pregnant) must meet all of the following criteria:
   - Is not pregnant and not planning on becoming pregnant during the study. Subjects must have a negative pregnancy test at Screening and on Day 1 before surgery.
   - Is not lactating.
   - Is practicing abstinence; or is in a monogamous relationship with a partner who cannot impregnate the subject (eg, is surgically sterile); or agrees to use double-barrier contraception or an insertable, injectable, transdermal, or combination oral contraceptive approved by applicable regulatory authorities in the event of sexual activity from the Screening Visit through 30 days after study drug administration.
6. Is scheduled to undergo a unilateral reverse or traditional TSA under deep sedation or under general anesthesia (Cohort 1 only).
7. Is scheduled to undergo abdominoplasty without liposuction under deep sedation or under general anesthesia (Cohort 2 only).

Exclusion Criteria

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

1. Has a planned concurrent surgical procedure during the study.
2. Is undergoing a revision surgery.
3. Is currently receiving worker's compensation or has pending litigation regarding an injury.
4. 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 surgical procedure and which may confound the postoperative assessments.
5. Has 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), acetaminophen, oxycodone, morphine, or hydromorphone.
6. History of severe allergic reaction (eg, asthma or urticaria requiring medical intervention) due to aspirin or other NSAIDs, or known history of severe gastrointestinal adverse reactions associated with NSAID use (eg, peptic ulcer disease and/or gastrointestinal bleed).
7. Has taken meloxicam within 10 days prior to the scheduled surgery, or any NSAID within 24 hours prior to the scheduled surgery, with the exception of subjects on low-dose (≤100 mg) daily acetylsalicylic acid for cardioprotection.
8. Opioid use for most days within the last 3 months prior to Screening in the opinion of the Investigator.
9. Has taken long-acting opioids within 3 days prior to the scheduled surgery.
10. Has taken any opioids within 48 hours prior to the scheduled surgery.
11. Has been administered immediate-release bupivacaine HCl within 5 days prior to the scheduled surgery, or a modified-release bupivacaine product (ie, Exparel®, Posimir®, or Xaracoll®) within 14 days prior to the scheduled surgery.
12. Has been administered any local anesthetic within 72 hours prior to the scheduled surgery. Exceptions include use of lidocaine 1% up to 2 mL subcutaneously prior to a needle placement, and up to 20 mg IV to decrease venous irritation caused by propofol.
13. Has initiated treatment with any of the following medications within 1 month prior to study drug administration: selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin, duloxetine, or cyclooxygenase-2 (COX-2) inhibitors. (Note: If a subject is taking one of these medications, 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.
14. Has been administered systemic steroids within 5 half-lives or 10 days prior to the scheduled surgery (whichever is longer). Exception includes use of inhaled, ophthalmic, and topical steroids.
15. Previously participated in a Heron-sponsored HTX-011 clinical study, or received ZYNRELEF at any time.
16. 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.
17. Has a known or suspected history of drug abuse, a positive drug screen (except for cannabinoids) on the day of surgery, or a history of alcohol abuse (within the past 5 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 must agree to refrain from cannabinoids for 7 days prior to until 7 days after surgery.

18. Suspected or confirmed active coronavirus disease 2019 (COVID-19) infection.
19. Has a medical condition such that, in the opinion of the Investigator, participating in the study would pose a health risk to the subject or confound the postoperative assessments. Conditions may include, but are not limited to, any of the following:
    a. History of clinically significant cardiac abnormality such as myocardial infarction within 6 months prior to signing the informed consent form (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. History of liver cirrhosis, an aspartate aminotransferase >3 × the upper limit of normal (ULN), or 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.
20. Is currently undergoing treatment for hepatitis B, hepatitis C, or HIV.
21. Has uncontrolled anxiety or a psychiatric or neurological disorder that, in the opinion of the Investigator, might interfere with study assessments.
22. 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.
23. Has undergone 3 or more surgeries within 12 months prior to signing the ICF, other than for diagnostic procedures (eg, colonoscopy).
24. Has a body mass index (BMI) >40 kg/m^2.
25. Had undergone prior abdominoplasty (mini or complete) or major abdominal wall surgery (eg, ventral hernia repair, exploratory laparotomy). Prior cesarean section is permitted (Cohort 2 only).

STUDY DRUG: Study drug is defined as HTX-011 (test product) and bupivacaine HCl (control product).

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION:

HTX-011 will be supplied by the Sponsor in a commercially available ZYNRELEF kit. Each kit contains HTX-011 as a clear, pale-yellow to yellow, viscous liquid in a 20 mL glass vial that provides 14 mL of HTX-011, along with sterile, individually packaged components for administration, including a vented vial spike, 2 Luer lock syringes, 2 Luer lock applicators, and 2 syringe tip caps.

Subjects randomized to HTX-011 will receive a single dose of HTX-011 400 mg/12 mg (14 mL) after final irrigation and suctioning of the respective application areas. HTX-011 will be administered intraoperatively by periarticular and/or soft tissue application into the surgical site with the provided Luer lock applicators (without a needle).

Cohort 1 (TSA): Approximately 7 mL will be applied in the intracapsular region prior to joint capsule closure, then approximately 3.5 mL below and 3.5 mL above the deltoid-pectoral muscle suture.

Cohort 2 (abdominoplasty): Approximately 8 to 10 mL will be applied with the Luer lock applicator into the “canal” below the plication of the rectus abdominus muscles; approximately equal amounts

will be applied cranial to and caudal to the umbilicus. The remaining volume will be used to coat the muscles and subcutaneous tissues prior to skin closure.

CONTROL PRODUCT, DOSE, AND MODE OF ADMINISTRATION:

Subjects randomized to bupivacaine HCl will receive a single dose of bupivacaine HCl (without epinephrine) that will be supplied by the Sponsor.

Cohort 1 (TSA): Bupivacaine HCl 0.25% 100 mg (40 mL) by injection into the surgical wound per Investigator standard of care.

Cohort 2 (abdominoplasty): Bupivacaine HCl 0.25% 125 mg (50 mL) by injection into the surgical wound per Investigator standard of care.

OTHER PROTOCOL-SPECIFIED MEDICATIONS:

Intraoperative Medication: During surgery, at the discretion of the anesthesiologist/surgeon, subjects may receive IV fentanyl as follows: Cohort 1 subjects may receive up to 3 µg/kg body weight, not exceeding 200 µg; and Cohort 2 subjects may receive up to 1.5 µg/kg body weight, not exceeding 100 µg. All subjects will receive a single dose of either IV morphine 5 to 10 mg or IV hydromorphone 1 to 2 mg at the end of surgery, just prior to the application of dermal sutures. Fentanyl, morphine, and hydromorphone will be provided by the site.

MMA Regimen: Subjects will receive a scheduled non-opioid MMA regimen throughout the 72-hour postoperative period. Sites will supply the MMA regimen during the inpatient period. The first dose of the MMA regimen will be administered once the subject is able to tolerate PO intake. PO acetaminophen 1 g will be taken q8h. Four hours after the first dose of acetaminophen, PO ibuprofen 400 mg will be taken q8h, alternating the 2 medications so that an analgesic is taken approximately every 4 hours. The total combined daily dose of acetaminophen from any acetaminophen-containing product taken must not exceed 4 g (4,000 mg) as severe liver damage may occur.

Prior to discharge (Day 4), subjects will be instructed to continue their scheduled MMA regimen through Day 7, while awake. To ensure there is not a gap in MMA once discharged, sites will provide subjects with a prescription for acetaminophen and ibuprofen for their postdischarge MMA regimen during the Screening Visit. Subjects should fill the prescription before their surgery.

Rescue Medication: Rescue medications permitted to treat pain during the 72-hour postoperative period include the following:

- PO ibuprofen 400 mg and PO acetaminophen 500 mg, which may be administered only once every 12 hours as rescue medication. Ibuprofen and acetaminophen must be the first rescue medication given every time rescue medication is requested, provided that:
  - At least 12 hours have elapsed since the last administration of ibuprofen/acetaminophen **as rescue medication** (ie, **not** the last scheduled MMA regimen dose) AND
  - The total acetaminophen dose is ≤4 g within a 24-hour period, including both the 1g q8h administered as part of the scheduled MMA regimen and any 500 mg doses administered as rescue medication.

  Between 30 minutes and 12 hours after receiving ibuprofen and acetaminophen as rescue medication, subjects may be administered opioid rescue medication, if additional rescue medication is requested:
  - PO immediate-release oxycodone (≤10 mg within a 4-hour period) OR
  - IV morphine (≤5 mg within a 4-hour period).

Rescue medications will be provided by the site.

DURATION OF TREATMENT: Subjects will receive a single dose of study drug (HTX-011 or bupivacaine HCl) during surgery and a scheduled non-opioid MMA regimen for up to 7 days after

surgery. The total duration of study participation for each subject (from Screening through the Day 15 Visit ±2 days) will be up to 45 days. The overall duration of the study is anticipated to be approximately 12 months.

STUDY ASSESSMENTS:

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

Safety Assessments

- Adverse events (AEs) from the time the subject signs the ICF through the Day 15 Visit.
- Physical examinations.
- Vital signs, including blood pressure, heart rate, respiratory rate, and temperature.
- Wound healing assessments using the Southampton Wound Scoring System.
- Clinical laboratory tests (hematology and serum chemistry).
- Local anesthetic systemic toxicity (LAST) questionnaire.

PK Assessments

Blood samples will be collected to measure the plasma concentrations of bupivacaine and meloxicam. Alpha-1-acid glycoprotein and other study drug components may be evaluated. Bupivacaine concentrations may also be measured in drainage fluid in subjects with drains.

PD Assessments

- Use of rescue medication: Date, time of administration, amount, and type of all rescue medication taken from study drug administration through 72 hours. Opioid use will be recorded through Day 15.
- Pain intensity assessments using NRS-R and NRS-A will be performed from the time of study drug administration through 72 hours and on Day 15. The NRS-R score will be obtained first after the subject has been in a resting position for at least 5 minutes. After the NRS-R score has been obtained, the NRS-A score will be obtained.
    - *Cohort 1 (TSA):*
        - NRS-R: Subjects should be seated comfortably or reclining.
        - NRS-A: Subjects will be asked to adduct the operated arm into the side of their body for 3 seconds.
    - *Cohort 2 (abdominoplasty):*
        - NRS-R: Subjects should be resting in a comfortable reclined position.
        - NRS-A: Subjects will be asked to cough.
- 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.
- Opioid prescription at discharge.
- Site- or subject-initiated postdischarge contact through the Day 15 Visit.
- Opioid prescription after discharge through the Day 15 Visit.
- Subject daily diary to record whether opioids were taken from discharge through the Day 15 Visit.

STUDY ENDPOINTS:

Primary Endpoint

- Incidence of treatment-emergent adverse events (TEAEs).

Secondary Endpoints

- Maximum concentration (C_{max}) of bupivacaine.
- Time of occurrence of maximum concentration (T_{max}) of bupivacaine.
- Area under the concentration-time curve from Time 0 to the time of the last quantifiable concentration (AUC_{last}) of bupivacaine.
- Area under the concentration-time curve from Time 0 extrapolated to infinity (AUC_{inf}) of bupivacaine.
- Apparent terminal half-life ($t_{½}$) of bupivacaine.

Other Secondary Endpoints

- PK profile of meloxicam.
- TEAEs leading to study withdrawal and serious adverse events (SAEs).
- Change from baseline in clinical laboratory results.
- Change from baseline in vital signs.

Exploratory Endpoints

- Mean total postoperative opioid consumption (in IV MME) through 72 hours.
- Proportion of subjects who are opioid-free through 72 hours and through Day 15.
- 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 15 Visit.
- Mean area under the curve (AUC) of the NRS scores through 72 hours.
- Proportion of subjects achieving a score of "good" or better (>1) pain control based on PGA at each timepoint.
- Proportion of subjects who first achieve an MPADSS score ≥9 at each timepoint.

STATISTICAL METHODS:

Each cohort will be analyzed separately following completion of that cohort.

Determination of Sample Size

The sample size of 30 subjects per cohort was selected empirically without formal statistical assumptions.

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 potential opioid-related adverse events (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 a validated liquid chromatography tandem-mass spectrometry assay. 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. Bupivacaine concentrations may also be determined in drainage fluid for subjects with drains.

PD Analyses

All PD data will be summarized and listed by cohort and by treatment group.

Interim Analysis

No formal interim analysis is planned.

SCHEDULE OF EVENTS

Screening Period

	Screening	
	≤28 days	**≤1 day**
Obtain informed consent	X	
Drug screen[a]	X	
Pregnancy test (subjects of childbearing potential only)[a]	X	
Assess/confirm eligibility	X	
Medical history[b]	X	
Demographics	X	
Physical examination[c]	X	
Vital signs[d]	X	
12-lead ECG (single)	X	
COVID-19 diagnostic test (rapid antigen test or nucleic acid amplification test per institutional practice)	X	
Hematology and serum chemistry tests	X	
Subject randomization[e]		X
Concomitant medications [f]	----------▶	----------▶
Adverse events[f]	----------▶	----------▶
Provide subjects with prescription for postdischarge MMA regimen[g]	X	

Abbreviations: COVID-19, coronavirus disease 2019; ECG, electrocardiogram; MMA, multimodal analgesic.
Note: Study days are in relation to the planned surgery date (Day 1).

[a] The drug screen (urine) and pregnancy test (urine or serum) should be performed first. Results should be confirmed negative prior to performing any additional assessments. 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.

[b] To include history of chronic opioid use.

[c] Height and weight will also be recorded.

[d] Vital sign measurements include blood pressure, resting heart rate, respiration rate, and body temperature.

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

[f] Record all medications and adverse events from the time the subject signs the informed consent form.

[g] Sites will provide subjects with a prescription for acetaminophen and ibuprofen for their postdischarge MMA regimen. Subjects should fill the prescription before their surgery.

Inpatient and Follow-Up Periods

		Inpatient Period (Days 1 to 4)																Follow-Up Period				
																		D5[a]	D6[a]	D7[a]	D15	
				30 min	1h	2h	4h	6h	8h	12h	20h	24h	36h	40h	48h	54h	60h	72h	96h	120h	144h		
	Time Window	Preop	OR	±5 min	±10 min	±15 min	±30 min	±30 min	±30 min	±30 min	±1h	±1h	±2h	±2h	±2h	±2h	±2h	±2h	±6h	±6h	±6h	±2d	ET[b]
Drug screen[c]		X																					
Pregnancy test (subjects of childbearing potential only)[c]		X																					
Assess/confirm eligibility		X																					
Physical examination																		X					X[d]
Vital signs[e,f]		X										X			X			X					X[d]
12-lead ECG (triplicate)[f]																							
Confirm negative COVID-19 diagnostic test result (rapid antigen test or nucleic acid amplification test per institutional practice)		X																					
Hematology and serum chemistry tests																		X				X	X
Instructional video for subjects (before surgery)[g]		X																					
Subject training for pain assessments		X																					
Surgery			X																				
Administer study drug, fentanyl (optional), and either morphine or hydromorphone			X																				
Administer MMA regimen[h]				- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - - ►		

		Inpatient Period (Days 1 to 4)																Follow-Up Period				
																		D5[a]	D6[a]	D7[a]	D15	
				30 min	1h	2h	4h	6h	8h	12h	20h	24h	36h	40h	48h	54h	60h	72h	96h	120h	144h		
	Time Window	**Preop**	**OR**	**±5 min**	**±10 min**	**±15 min**	**±30 min**	**±30 min**	**±30 min**	**±30 min**	**±1h**	**±1h**	**±2h**	**±2h**	**±2h**	**±2h**	**±2h**	**±2h**	**±6h**	**±6h**	**±6h**	**±2d**	**ET[b]**
Pain intensity assessments (NRS-R and NRS-A)[i]					X[j]	X	X	X	X	X		X	X		X		X	X				X	X
Discharge readiness per MPADSS[k]						X	X	X	X	X		X	X		X		X	X					
PGA of pain control												X			X			X				X	
Wound healing assessment																		X				X	X
PK blood sample[f]	X[l]		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
LAST questionnaire	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X					
AAG blood sample	X[l]										X			X			X						
Drainage fluid collection[m]			-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	----→					
Instructional video for subjects (before discharge)[n]																		X					
Discharge subject																		X					
Record if opioid prescription given at discharge																		X					
Provide opioid daily diary to all subjects[o]																		X					
Record site or subject contact and if opioid prescription given																			-----	-----	-----	----→	
Subjects record opioid use in daily diary[p]																			-----	-----	-----	----→	
Review subject diary at site[q]																						X	X[r]
Concomitant medications[s]	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	----→	X
Adverse events[s]	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	----→	X

Abbreviations: AAG, alpha-1-acid glycoprotein; COVID-19, coronavirus disease 2019; D or d, day(s); ECG, electrocardiogram; ET, Early Termination; h, hour(s); min, minutes; LAST, local anesthetic systemic toxicity; MMA, multimodal analgesic; MPADSS, Modified Postanaesthetic Discharge Scoring System; NRS-A, numeric rating scale of pain intensity with activity; NRS-R, numeric rating scale of pain intensity at rest; OR, operating room; PGA, Patient Global Assessment; PK, pharmacokinetic(s); Preop, preoperative.

Notes: The start of study drug administration will be considered Time 0 for all safety, PK, and pharmacodynamic assessments. 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 procedures and assessments.

[a] On Day 5 (96-hour timepoint), Day 6 (120-hour timepoint), and Day 7 (144-hour timepoint), PK sample collection will be performed at the study site or via a home visit.

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

[c] The drug screen (urine) and pregnancy test (urine or serum) 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.

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

[e] Vital sign measurements include blood pressure, resting heart rate, respiration rate, and body temperature.

[f] If an AE of suspected LAST occurs, an ECG (triplicate), vital signs, and blood sample for PK analysis should be obtained promptly. If a scheduled blood sample for PK analysis has been obtained within 30 minutes prior to the AE occurring, the sample collection does not need to be repeated.

[g] Before surgery, subjects will be shown an instructional video that will describe what to expect after surgery.

[h] The scheduled postoperative MMA regimen will consist of oral (PO) acetaminophen 1 g every 8 hours (q8h) alternating with PO ibuprofen 400 mg q8h, so that an analgesic is taken approximately every 4 hours. The first dose of the postoperative MMA regimen (acetaminophen) will be administered once the subject is able to tolerate PO intake. Subjects will receive a scheduled non-opioid MMA regimen throughout the 72-hour postoperative period. At discharge (Day 4), subjects will be instructed to continue their scheduled MMA regimen through Day 7, during waking hours.

[i] NRS-R scores will be obtained first. After the NRS-R score has been obtained, the NRS-A score will be obtained.

[j] 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, NRS-R and NRS-A scores must be obtained.

[k] 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.

[l] Preoperative blood samples must be collected before administering anesthesia.

[m] For subjects with drains, all drainage fluid will be collected and pooled over 12-hour intervals through 72 hours (ie, 0-12 hours, 12-24 hours, 24-36 hours, etc) and may be used to measure bupivacaine concentrations.

[n] Prior to discharge, subjects will be shown an instructional video on what to expect after discharge including instructions on their MMA regimen and how to complete the daily diary.

[o] 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 15 Visit.

[p] Subjects will complete a daily diary to record if they take any opioid medication from discharge through Day 15 Visit.

[q] Subject diary results will be reviewed at each visit and at the Day 15 Visit. If a subject recorded "yes" for taking an opioid, sites must record the medication on the concomitant medication electronic case report form (eCRF).

[r] Only if subject withdraws between discharge and Day 15 Visit.

[s] Record all medications and adverse events from the time the subject signs the informed consent form (ICF) through the Day 15 Visit.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
BMI	Body mass index
CFR	Code of Federal Regulations
C_{max}	Maximum concentration
CNS	Central nervous system
CYP3A4	Cytochrome P450 isoenzyme 3A4
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council for Harmonisation
IV	Intravenous(ly)
LAST	Local anesthetic systemic toxicity
MMA	Multimodal analgesia/analgesic
MME	Morphine milligram equivalents
MPADSS	Modified Postanaesthetic Discharge Scoring System
NRS	Numeric rating scale
NRS-A	Numeric rating scale of pain intensity with activity
NRS-R	Numeric rating scale of pain intensity at rest
NSAID	Nonsteroidal anti-inflammatory drug
PACU	Postanesthesia care unit
PD	Pharmacodynamic(s)
PGA	Patient Global Assessment
PK	Pharmacokinetic(s)
PO	Oral(ly)
q8h	Every 8 hours
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event

Abbreviation	Definition
TKA	Total knee arthroplasty
TSA	Total shoulder arthroplasty
ULN	Upper limit of normal
US	United States
USPI	United States package insert

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). 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.

HTX-011 is a novel, non-opioid, fixed-dose, extended-release local anesthetic containing bupivacaine and low-dose meloxicam formulated in a proprietary polymer that is administered as a single dose applied into the surgical site prior to wound closure. HTX-011 has been approved as ZYNRELEF™ in the United States (US) and Europe for postoperative analgesia in specified procedures. The purpose of this study is to obtain safety, pharmacokinetic (PK), and pharmacodynamic (PD) data in additional surgical procedures to support the expanded use of ZYNRELEF.

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

This is a Phase 4, randomized, blinded, active-controlled, multicohort study to evaluate HTX-011 compared with bupivacaine HCl (without epinephrine) in subjects undergoing different surgical procedures. Each cohort will enroll subjects undergoing a unique surgical procedure: total shoulder arthroplasty (TSA) in Cohort 1 and total abdominoplasty in Cohort 2. This will be the first study of HTX-011 in TSA. A prior Phase 2a study of HTX-011 was conducted in total abdominoplasty using a combination of injection and instillation as the route of administration of HTX-011. Superiority was demonstrated for combination of injection and instillation administration compared with saline placebo and bupivacaine HCl, but not for instillation-only administration. PK data confirmed that there was a loss of HTX-011 when administered via instillation in this study which was attributed to irrigation and suction occurring after application of HTX-011. Subsequent studies required final irrigation and suction to be complete prior to administering HTX-011, which has resulted in consistent positive results.

Subjects will be randomized to receive either HTX-011 or bupivacaine HCl. The study will use a single-blinded design. Subjects and assessors will be blinded to the treatment assignments to minimize potential bias in subject selection as well as postoperative safety and PD assessments; however, unblinded site staff may collect samples for PK analysis. The Sponsor will be unblinded, but will maintain the blind when interacting with blinded site staff.

The dose of HTX-011 that will be evaluated in each cohort, 400 mg/12 mg, is the maximum recommended dose. HTX-011 will be applied into the surgical site with a Luer lock applicator, the approved method of HTX-011 administration.

Bupivacaine HCl without epinephrine was selected as the active comparator because it is the widely accepted standard for local analgesia. The dose of bupivacaine HCl, 100 mg for TSA and 125 mg for abdominoplasty, is within the range of dosing in bupivacaine labeling (Marcaine USPI 2018) and is based on feedback from experts on standard doses used in clinical practice for these procedures. The route of administration for bupivacaine HCl, injection into the surgical site, is consistent with the prescribing information and clinical practice.

All subjects will follow a scheduled non-opioid multimodal analgesic (MMA) regimen. MMA 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). Acetaminophen and ibuprofen were selected for the scheduled multimodal regimen in this study using doses consistent with the prescribing information for each medication. Both are commonly used analgesics with a long history of use and relatively few side effects. These pain medications are frequently given as part of multimodal therapy for pain management following surgery. Sites will supply the MMA regimen during the inpatient period. To ensure there is not a gap in MMA once discharged, sites will provide subjects with a prescription for acetaminophen and ibuprofen for their postdischarge MMA regimen during the Screening Visit, and subjects should fill the prescription before their surgery.

Safety is the primary objective of this study; therefore, the primary study endpoint will evaluate the incidence of treatment-emergent adverse events (TEAEs). Safety assessments in this study are considered standard for clinical studies of these surgical procedures. Evaluations will include adverse event (AE) and serious adverse event (SAE) recording, hematology and serum chemistry, vital signs, physical examinations, wound healing assessments, and local anesthetic systemic toxicity (LAST) questionnaire. If an AE of suspected LAST occurs, an electrocardiogram (ECG, triplicate), vital signs, and a blood sample for PK analysis should be obtained promptly. If a scheduled blood sample for PK analysis has been obtained within 30 minutes prior to the AE occurring, the sample collection does not need to be repeated.

Secondary study endpoints will evaluate bupivacaine and meloxicam PK parameters. The PK timepoints for this study were selected to characterize systemic exposure of bupivacaine and meloxicam and obtain PK profiles for these surgical procedures. Bupivacaine concentration in drainage fluid in subjects with drains may also be assessed.

Exploratory endpoints will evaluate postoperative opioid use and pain scores using the numeric rating scale (NRS) (Breivik 2008; Haefeli 2006) of pain intensity at rest (NRS-R) and with activity (NRS-A). Discharge readiness and patient-reported outcomes will also be assessed.

1.3. Potential Risks and Benefits

1.3.1. HTX-011

HTX-011 (ZYNRELEF) contains bupivacaine, an amide local anesthetic, and meloxicam, an NSAID, and is indicated in adults for soft tissue or periarticular instillation to produce postsurgical analgesia for up to 72 hours after bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty (TKA).

1.3.1.1. Potential Risks Associated With HTX-011

Refer to the ZYNRELEF US package insert (USPI) for potential risks including contraindications, warnings, and precautions (ZYNRELEF USPI 2021).

No studies of HTX-011 in subjects undergoing TSA have been conducted; however, the potential risks are expected to parallel the safety in the ZYNRELEF USPI. Adverse reactions were assessed in 504 subjects receiving HTX-011 via instillation for bunionectomy, open inguinal herniorrhaphy, and TKA surgeries. The most common adverse reactions with incidence higher in the HTX-011 group versus the saline placebo group were constipation (17.3% vs 14.6%), vomiting (16.9% vs 15.0%), and headache (11.7% vs 8.9%).

Mini and complete abdominoplasty were previously examined in a Phase 2a, randomized, observer-blind, placebo- and active-controlled study in adult subjects. Various administration techniques, including injection, instillation, and a combination of injection and instillation, were evaluated. Doses of HTX-011 evaluated in this study ranged from 200 mg/6 mg to 600 mg/18 mg and included this protocol's dose of 400 mg/12 mg dose. For mini abdominoplasty, 48 subjects were treated with HTX-011 and 63 subjects were treated with saline placebo and for complete abdominoplasty, 77 subjected were treated with HTX-011, 32 subjects were treated with saline placebo, and 17 subjects were treated with bupivacaine HCl as active control. There was a total of 2 SAEs (both wound dehiscence, both resolved) in 2 subjects: 1 subject who received HTX-011 300 mg/9 mg and 1 who received bupivacaine HCl. The most common AEs in the HTX-011-treated abdominoplasty subjects (all doses pooled) included nausea, headache, constipation, vomiting, and pruritus. For further information refer to the HTX-011 Investigator's Brochure.

1.3.1.2. Efficacy

Efficacy has not been established for TSA; however, approval for a similar indication of TKA is documented in the ZYNRELEF USPI (ZYNRELEF USPI 2021).

The potential benefit for HTX-011 for total abdominoplasty is discussed in Section 1.2.

1.3.2. Potential Risks Associated With Bupivacaine HCl and Other Protocol-Specified Medications

Common, as well as uncommon but severe, adverse drug reactions that are associated with bupivacaine HCl and the other protocol-specified medications are listed below. The Investigator should refer to the respective package inserts for detailed information on risks associated with these medications.

1.3.2.1. Bupivacaine HCl

Bupivacaine, an amide local anesthetic, is indicated in adults for the production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures (MARCAINE USPI 2020). Use in children under 12 years of age is not recommended.

Bupivacaine has risk of cardiac arrest when used in obstetrical anesthesia.

Bupivacaine is contraindicated for use (1) in obstetrical paracervical block anesthesia due to risk of fetal bradycardia and death, (2) in intravenous (IV) regional anesthesia or Bier Block, and (3) in those with known hypersensitivity for bupivacaine or amide type anesthetics or components.

Warnings and precautions of bupivacaine include the following:

- Dose-related toxicities requiring monitoring of cardiovascular and respiratory vital signs and state of consciousness.
- Methemoglobinemia reported with local anesthetic use.
- Chondrolysis with intra-articular infusion.
- Risk of cardiac arrest with IV regional anesthesia use (Bier block).
- Risk of systemic toxicities including central nervous system (CNS), cardiac, and respiratory with unintended intravascular or intrathecal injection.

The most commonly encountered acute adverse reactions that demand immediate countermeasures were related to the CNS and the cardiovascular system. CNS-related adverse reactions were characterized by excitation and/or depression of the CNS and included restlessness, anxiety, dizziness, tinnitus, blurred vision, tremors, convulsions, drowsiness, unconsciousness, respiratory arrest, nausea, vomiting, chills, and pupillary constriction. Cardiac system-related adverse reactions were characterized by depression of the myocardium, decreased cardiac output, heart block, hypotension, bradycardia, and ventricular arrhythmias (including ventricular tachycardia and ventricular fibrillation), and cardiac arrest.

For more information on bupivacaine, refer to the local product label.

1.3.2.2. Other Protocol-Specified Medications

1.3.2.2.1. Acetaminophen

Acetaminophen in tablets, capsules, and solution forms for oral use are over-the-counter medications indicated for the temporary relief of minor aches and pain in adults, children, and infants (Acetaminophen Solution USPI 2021; Acetaminophen Tablets USPI 2021).

Acetaminophen and acetaminophen-containing products have been associated with cases of acute liver failure and cases of liver transplant or death which are mostly associated with doses above the recommended maximum daily limit and are contraindicated in patients with severe hepatic impairment or severe active liver disease.

Contraindications also include use in patients with known hypersensitivity or allergy to acetaminophen or other product components.

Warnings and precautions include (1) risk of hepatic injury, failure, and death with doses higher than recommended, (2) caution when using in patients with hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia, and severe renal impairment (creatinine clearance ≤30 mL/min), (3) immediate discontinuation at the first appearance of skin rash or symptoms associated with allergy or hypersensitivity due to risk of rare, but serious, potentially fatal skin reactions, such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), and (4) exercise care when administering to avoid overdosing which has been associated with death.

The most common adverse reactions in adults include nausea, vomiting, headache, and insomnia. The most common adverse reactions in children include nausea, vomiting, constipation, pruritus, agitation, and atelectasis.

1.3.2.2.2. Nonsteroidal Anti-inflammatory Drugs

NSAIDs include over-the-counter and prescription drugs (for example ibuprofen) in tablet, capsule, or suspension forms and are indicated for the temporary relief of minor aches and pains due to headache, muscular aches, minor pain of arthritis, toothache, backache, the common cold, and menstrual cramps, and temporary fever reduction in adults, children, and infants (Ibuprofen Caplets USPI 2020; Ibuprofen Suspension USPI 2020).

NSAIDs increase the risk for the following:

- Serious cardiovascular thrombotic events including myocardial infarction and stroke, which can be fatal.
- Serious gastrointestinal AEs including bleeding, ulcerations, and perforations, which can be fatal.

Contraindications for the use of NSAIDs include the following:

- Known hypersensitivity to the NSAID or components of the product.
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs.
- In the setting of coronary artery bypass surgery.

Warnings and precautions include the following:

- Inform subjects of hepatotoxicity risk and discontinue for abnormal liver test or developing signs and symptoms of liver disease.
- Monitor for impaired response to antihypertensive medications via blood pressure.
- Assess risk versus benefit for use in subjects with severe heart failure or edema.
- Assess risk versus benefit for use in subjects with renal or hepatic impairment, heart failure, dehydration, or hypovolemia.
- Seek emergency help for anaphylactic reactions.
- Discontinue with appearance of skin rash or hypersensitivity.

- Avoid use in pregnant women at 30 weeks gestation or greater due to premature closure of fetal ductus arteriosus.
- Monitor hemoglobin and hematocrit for anemia.

Common adverse reactions are similar among NSAIDs and for meloxicam, as an example, include (incidence ≥2%) diarrhea, nausea, and abdominal discomfort (MOBIC Tablets USPI 2021).

1.3.2.2.3. Opioid Medications

Opioids (including oxycodone, morphine, fentanyl, and hydromorphone) are indicated for the control of pain. Generally, the efficacy and safety of opioids have not been established in children. See package inserts for additional information and any risk evaluation and mitigation strategies (Dilaudid Injection USPI 2019; Fentanyl Citrate Injection Solution USPI 2020; Morphine Sulfate USPI 2021; OXAYDO Tablets USPI 2021).

Opioids expose users to risk of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk and monitor for abuse. Serious, life-threatening, or fatal respiratory depression may occur. Accidental ingestion of opioids can result in fatal overdose. Prolonged use of opioids during pregnancy can result in neonatal opioid withdrawal syndrome which requires appropriate treatment. Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Assess alternative concomitant medications, limit dosage and duration, and monitor for respiratory function and sedation. Concomitant use of certain opioids, for example fentanyl, with cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitors or discontinuation of CYP3A4 inducers can result in fatal overdoses.

Contraindications for opioids include (1) use in patients with significant respiratory depression, (2) use in patients with acute or severe bronchial asthma without adequate monitoring and resuscitative equipment, (3) concurrent use of monoamine oxidases inhibitors within the last 14 days, (4) use in patients with known or suspected gastrointestinal obstruction, and (5) use in patients hypersensitive to opioids.

Warnings and precautions include (1) monitor for life-threatening respiratory depression in patients with chronic pulmonary disease or in elderly, cachectic, or debilitated patients, (2) monitor for adrenal insufficiency and treat with corticosteroids while weaning opioid dose, (3) monitor for severe hypotension and avoid use in patients with circulatory shock, (4) monitor for sedation and respiratory depression in patients with increased intracranial pressure, brain tumors, head injury, or impaired consciousness, (5) monitor for skeletal muscle rigidity and manage with neuromuscular blocking agents, and (6) monitor for serotonin syndrome and discontinue opioid if suspected.

Common adverse reactions observed with opioids include constipation, nausea, sedation, somnolence, respiratory depression, apnea, rigidity, bradycardia, headache, vomiting, pruritus, insomnia, dizziness, and asthenia.

1.3.3. Potential Risks Associated With Protocol-Specified Device

The custom Luer lock applicator is a marketed device used for administration of HTX-011 without a needle into the surgical site for bunionectomy, inguinal hernia repair, and TKA; its use

is investigational in this study. Although not observed in clinical studies, there is a potential risk for the Luer lock applicator to detach from the syringe during HTX-011 application if not properly attached during preparation.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary study objective is to assess the safety and tolerability of HTX-011 in subjects undergoing different surgical procedures.

2.2. Secondary Objective

The secondary study objective is to characterize the bupivacaine and meloxicam PK parameters following administration of HTX-011 in these study populations.

2.3. Exploratory Objective

The exploratory study objective is to assess the PD activity of HTX-011 in these study populations based on postoperative pain and opioid use.

3. INVESTIGATIONAL PLAN AND ENDPOINTS

3.1. Description of the Study Design

3.1.1. Overall Study Design

This is a Phase 4, randomized, blinded, active-controlled, multicohort study to evaluate HTX-011 compared with bupivacaine HCl in subjects undergoing different surgical procedures. The study will include 2 cohorts, which will be conducted in parallel. Each cohort will enroll subjects undergoing a unique surgical procedure: TSA in Cohort 1 and abdominoplasty in Cohort 2.

In each cohort, approximately 30 subjects will be randomized in a 2:1 ratio to HTX-011 or bupivacaine HCl, respectively. In both cohorts, all subjects will receive a scheduled postoperative non-opioid MMA regimen. Subjects and site personnel performing postoperative safety and PD assessments will be blinded to treatment assignments; however, unblinded site staff may collect samples for PK analysis. The Sponsor will be unblinded, but will maintain the blind when interacting with blinded site staff.

Cohort 1 (TSA)

- HTX-011 400 mg/12 mg + MMA (N=20).
- Bupivacaine HCl 0.25% 100 mg + MMA (N=10).

Cohort 2 (abdominoplasty)

- HTX-011 400 mg/12 mg + MMA (N=20).
- Bupivacaine HCl 0.25% 125 mg + MMA (N=10).

3.1.2. Study Schedule

Subjects will be screened within 28 days prior to the planned surgery date. Subjects who meet the eligibility criteria will be randomized within 1 business day prior to surgery. On the day of surgery (Day 1), subjects who continue to meet the eligibility criteria will undergo surgery. Before surgery, subjects will be shown an instructional video that will describe what to expect after surgery.

During surgery, all subjects will receive a single dose of study drug (HTX-011 [administered after final irrigation and suctioning of the respective application areas] or bupivacaine HCl [administered per Investigator standard of care]). In addition, at the discretion of the anesthesiologist/surgeon, subjects may receive IV fentanyl as follows: Cohort 1 subjects may receive up to 3 µg/kg body weight, not exceeding 200 µg; and Cohort 2 subjects may receive up to 1.5 µg/kg body weight, not exceeding 100 µg. All subjects will receive a single dose of either IV morphine 5 to 10 mg or IV hydromorphone 1 to 2 mg at the end of surgery, just prior to the application of dermal sutures.

Subjects will remain in the facility through 72 hours postdose for PK, safety, and PD assessments. Subjects will receive a scheduled non-opioid MMA regimen throughout the 72-hour postoperative period consisting of oral (PO) acetaminophen 1 g every 8 hours (q8h) alternating with PO ibuprofen 400 mg q8h, so that an analgesic is taken approximately every

4 hours. The first dose of the postoperative MMA regimen will be administered once the subject is able to tolerate PO intake. The total combined daily dose of acetaminophen from any acetaminophen-containing product taken must not exceed 4 g (4,000 mg) as severe liver damage may occur.

Prior to discharge on Day 4, subjects will be shown an instructional video on what to expect after discharge. Subjects will be instructed at discharge to continue their scheduled MMA regimen through Day 7, while awake, and will receive instructions on how to complete the daily diary to record opioid use through the Day 15 Visit.

PK sampling will occur through Day 7. On Day 5 (96-hour timepoint), Day 6 (120-hour timepoint), and Day 7 (144-hour timepoint), PK sample collection will be performed at the study site or via a home visit. For subjects with drains, all drainage fluid will be collected and pooled over 12-hour intervals through 72 hours and may be used to measure the bupivacaine concentration.

All subjects will return to the study site on Day 15 to complete End-of-Study assessments.

3.1.3. Postoperative Analgesia

3.1.3.1. Prescription for Postdischarge MMA Medications

During the Screening Visit, sites will provide subjects with a prescription for acetaminophen and ibuprofen for their postdischarge MMA regimen. Subjects should fill the prescription before their surgery.

3.1.3.2. Postoperative Rescue Medication

During the 72-hour postoperative period, subjects should receive rescue medication only upon request for treating postoperative pain; rescue medication should not be given for pain prophylaxis. Permitted postoperative rescue medication includes the following:

- PO ibuprofen 400 mg and PO acetaminophen 500 mg (in addition to and independent from the scheduled MMA regimen), which may be administered at most only once every 12 hours as rescue. Ibuprofen and acetaminophen must be the first rescue medication given every time rescue medication is requested by the subject, provided that ≥12 hours have elapsed since the last administration of ibuprofen/acetaminophen as rescue medication and the total acetaminophen dose is ≤4 g within a 24-hour period, including both the 1g q8h administered as part of the scheduled MMA regimen and any 500 mg doses administered as rescue medication.

  Between 30 minutes and 12 hours after receiving ibuprofen and acetaminophen as rescue medication, subjects may be administered opioid rescue medication as follows, if additional rescue medication is requested.

  – PO immediate-release oxycodone (≤10 mg within a 4-hour period) OR
  – IV morphine (≤5 mg within a 4-hour period).

Combination products containing an opioid and non-opioid are not allowed. NSAIDs or other analgesic agents are not permitted during the 72-hour postoperative period, except for ibuprofen

and acetaminophen per protocol and low-dose (≤100 mg) daily acetylsalicylic acid for cardioprotection.

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 an NRS-R score followed by an NRS-A score must be obtained.

3.1.3.3. Opioid Prescriptions At and After Discharge

If a subject did not receive any opioids or received <5 IV morphine milligram equivalents (MME; eg, <10 mg of oxycodone) within 12 hours prior to discharge, the subject should not receive an opioid prescription at discharge. If a subject received ≥5 IV MME within 12 hours prior to discharge, the Investigator may provide the subject with a prescription for PO immediate-release oxycodone tablets: no more than twenty 5 mg immediate release oxycodone, take 1 to 2 pills (5 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 in the electronic data capture (EDC) whether subjects are discharged with an opioid prescription and information about the opioid prescription, if provided.

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 15 Visit. Sites will record in the EDC all site- or subject-initiated contact between discharge and the Day 15 Visit and whether any contact resulted in issuing an opioid prescription.

3.1.4. Postoperative Assessments

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

Blood samples will be collected to measure the plasma concentrations of bupivacaine and meloxicam. Alpha-1-acid glycoprotein and other study drug components may be evaluated. Bupivacaine concentrations may also be measured in drainage fluid in subjects with drains.

PD assessments will include pain intensity, the use of postoperative analgesia, discharge readiness, and Patient Global Assessment (PGA) of pain control.

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 tables.

3.2. Study Endpoints

3.2.1. Primary Endpoint

- Incidence of TEAEs.

3.2.2. Secondary Endpoints

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

- Area under the concentration-time curve from Time 0 to the time of the last quantifiable concentration (AUC_{last}) of bupivacaine.
- Area under the concentration-time curve from Time 0 extrapolated to infinity (AUC_{inf}) of bupivacaine.
- Apparent terminal half-life ($t_{½}$) of bupivacaine.

3.2.3. Other Secondary Endpoints

- PK profile of meloxicam.
- TEAEs leading to study withdrawal and SAEs.
- Change from baseline in clinical laboratory results.
- Change from baseline in vital signs.

3.2.4. Exploratory Endpoints

- Mean total postoperative opioid consumption (in IV MME) through 72 hours.
- Proportion of subjects who are opioid-free through 72 hours and through Day 15.
- 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 15 Visit.
- Mean area under the curve (AUC) of the NRS scores through 72 hours.
- Proportion of subjects achieving a score of "good" or better (>1) pain control based on PGA at each timepoint.
- Proportion of subjects who first achieve a Modified Postanaesthetic Discharge Scoring System (MPADSS) score ≥9 at each timepoint.

3.3. Study Duration

The overall duration of the study is anticipated to be approximately 12 months. The total duration of study participation for each subject (from Screening through the Day 15 Visit ±2 days) will be up to 45 days.

For regulatory reporting purposes, the end of the study is defined as the date of the last subject's last visit.

3.4. Study Stopping Rules

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).

Enrollment in the study will be temporarily suspended if the Sponsor discovers the occurrence of any of the following:

- Two subjects with a non-fatal suspected unexpected serious adverse reaction (SUSAR) at any time during the study.
- A confirmed event of LAST.
- Any death for which a clear alternative cause (unrelated to study drug) is not readily apparent.

Following a review of the data by the Sponsor, a decision will be made to either resume, modify, or stop the study. 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 Ethics Committee (EC) and provide the reason(s) for study termination.

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1. Study Population

Approximately 60 subjects will be enrolled in the study at up to 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 ≥18 years of age at the time of the Screening Visit.
4. Has an American Society of Anesthesiologists Physical Status of I, II, or III.
5. Subjects of childbearing potential (defined as premenopausal and capable of becoming pregnant) must meet all of the following criteria:
   - Is not pregnant and not planning on becoming pregnant during the study. Subjects must have a negative pregnancy test at Screening and on Day 1 before surgery.
   - Is not lactating.
   - Is practicing abstinence; or is in a monogamous relationship with a partner who cannot impregnate the subject (eg, is surgically sterile); or agrees to use double-barrier contraception or an insertable, injectable, transdermal, or combination oral contraceptive approved by applicable regulatory authorities in the event of sexual activity from the Screening Visit through 30 days after study drug administration.
6. Is scheduled to undergo a unilateral reverse or traditional TSA under deep sedation or under general anesthesia (Cohort 1 only).
7. Is scheduled to undergo abdominoplasty without liposuction under deep sedation or under general anesthesia (Cohort 2 only).

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 during the study.
2. Is undergoing a revision surgery.
3. Is currently receiving worker's compensation or has pending litigation regarding an injury.
4. 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 surgical procedure and which may confound the postoperative assessments.
5. Has 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), acetaminophen, oxycodone, morphine, or hydromorphone.

6. History of severe allergic reaction (eg, asthma or urticaria requiring medical intervention) due to aspirin or other NSAIDs, or known history of severe gastrointestinal adverse reactions associated with NSAID use (eg, peptic ulcer disease and/or gastrointestinal bleed).
7. Has taken meloxicam within 10 days prior to the scheduled surgery, or any NSAID within 24 hours prior to the scheduled surgery, with the exception of subjects on low-dose (≤100 mg) daily acetylsalicylic acid for cardioprotection.
8. Opioid use for most days within the last 3 months prior to Screening in the opinion of the Investigator.
9. Has taken long-acting opioids within 3 days prior to the scheduled surgery.
10. Has taken any opioids within 48 hours prior to the scheduled surgery.
11. Has been administered immediate-release bupivacaine HCl within 5 days prior to the scheduled surgery, or a modified-release bupivacaine product (ie, Exparel®, Posimir®, or Xaracoll®) within 14 days prior to the scheduled surgery.
12. Has been administered any local anesthetic within 72 hours prior to the scheduled surgery. Exceptions include use of lidocaine 1% up to 2 ml subcutaneously prior to a needle placement, and up to 20 mg IV to decrease venous irritation caused by propofol.
13. Has initiated treatment with any of the following medications within 1 month prior to study drug administration: selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin, duloxetine, or cyclooxygenase-2 (COX-2) inhibitors. (Note: If a subject is taking one of these medications, 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.
14. Has been administered systemic steroids within 5 half-lives or 10 days prior to the scheduled surgery (whichever is longer). Exception includes use of inhaled, ophthalmic, and topical steroids.
15. Previously participated in a Heron-sponsored HTX-011 clinical study, or received ZYNRELEF at any time.
16. 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.
17. Has a known or suspected history of drug abuse, a positive drug screen (except for cannabinoids) on the day of surgery, or a history of alcohol abuse (within the past 5 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 must agree to refrain from cannabinoids for 7 days prior to until 7 days after surgery.

18. Suspected or confirmed active coronavirus disease 2019 (COVID-19) infection.
19. Has a medical condition such that, in the opinion of the Investigator, participating in the study would pose a health risk to the subject or confound the postoperative assessments. Conditions may include, but are not limited to, any of the following:
    a. History of clinically significant cardiac abnormality such as myocardial infarction within 6 months prior to signing the informed consent form (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. History of liver cirrhosis, an aspartate aminotransferase >3 × the upper limit of normal (ULN), or 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.
20. Is currently undergoing treatment for hepatitis B, hepatitis C, or HIV.
21. Has uncontrolled anxiety or a psychiatric or neurological disorder that, in the opinion of the Investigator, might interfere with study assessments.
22. 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.
23. Has undergone 3 or more surgeries within 12 months prior to signing the ICF, other than for diagnostic procedures (eg, colonoscopy).
24. Has a body mass index (BMI) >40 kg/m^2.
25. Had undergone prior abdominoplasty (mini or complete) or major abdominal wall surgery (eg, ventral hernia repair, exploratory laparotomy). Prior cesarean section is permitted (Cohort 2 only).

4.2. Method of Assigning Subjects to Treatment Groups

The Investigator must evaluate the subject's medical history and the results of all Screening assessments to determine study eligibility. Subjects who meet the Screening eligibility criteria (Section 4.1) will be randomized to either HTX-011 or bupivacaine HCl within 1 business day prior to surgery, using a computer-generated randomization scheme. Subjects do not need to be present for randomization to occur. No subject may receive study drug prior to randomization.

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

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

The site's pharmacy and surgical staff will not be blinded to the treatment assignments because HTX-011 is a colored, viscous solution whereas bupivacaine HCl is a clear aqueous solution, and the volume and method of study drug administration are different between treatment groups. However, subjects will not be aware of the study drug they receive, and, once surgery is completed and the subject is transferred to the postanesthesia care unit (PACU), Investigators and all site staff involved in postoperative safety and PD assessments will be blinded to the treatment assignment; however, unblinded site staff may collect samples for PK analysis. The Sponsor will be unblinded, but will maintain the blind when interacting with blinded site staff.

4.3.1. Breaking the Blind

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

If a study site becomes aware of an inadvertent or accidental unblinding event, the site must notify the Sponsor within 24 hours of becoming aware of the event.

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

4.4. Subject Withdrawal and Replacement

4.4.1. Subject Withdrawal

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

Possible reasons for early withdrawal include the following:

- AE.
- Withdrawal by subject.
- Death.
- Lost to follow-up.
- Pregnancy.
- Investigator's decision.

- Sponsor's decision.
- Failure to meet randomization or eligibility 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.

4.4.2. Subject Replacement

Randomized subjects who withdraw from the study will not be replaced.

5. STUDY DRUG AND PROTOCOL-SPECIFIED DEVICE

All subjects will receive a single dose of study drug intraoperatively while undergoing surgery. Study drug is defined as HTX-011 (test product) and bupivacaine HCl (control product). Study drug will be supplied by the Sponsor.

HTX-011 will be administered using a custom Luer lock applicator, which will also be supplied by the Sponsor.

5.1. Description of Study Drug

5.1.1. Test Product (HTX-011)

HTX-011 will be supplied in a commercially available ZYNRELEF™ kit, which contains a 20 mL vial that provides 14 mL of HTX-011, and all of the supplies required for preparation and administration. HTX-011 is a clear, pale-yellow to yellow, viscous liquid supplied in a clear glass vial containing 400 mg bupivacaine and 12 mg meloxicam. The vials serve only as a closed container for the drug product. The kit also contains sterile, individually packaged components for administration, including a vented vial spike, 2 Luer lock syringes, 2 Luer lock applicators, and 2 syringe tip caps.

For administration of test product, the contents in the vial will be aseptically transferred to sterile syringes as described in the Instructions for Use and Pharmacy Manual.

5.1.2. Control Product (Bupivacaine HCl)

Bupivacaine HCl 0.25% (without epinephrine) will be supplied in individually labeled cartons containing a single-dose 30 mL (75 mg) vial.

5.2. Packaging and Labeling

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

5.3. Storage

HTX-011 will be stored 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature] and protected from light and moisture. Bupivacaine HCl will be stored as per the prescribing information.

The storage location should be locked with restricted access. A temperature log must be maintained to monitor the storage location temperature.

5.4. Preparation

Study drug will be prepared at the study site. HTX-011 will be prepared in syringes without a needle and with a Luer lock applicator attached to the end of the syringe. Bupivacaine HCl will be prepared in syringes with a needle.

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

5.5. Study Drug Administration

Eligible subjects will be administered study drug unless they experience a clinically significant event during surgery (eg, excessive bleeding, hemodynamic instability) that would render the subject medically unstable or complicate their postoperative course or study completion.

HTX-011 will be applied into the surgical site prior to wound closure. Bupivacaine HCl will be injected into the surgical wound per site standard of care. 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.

5.5.1. HTX-011 Administration

Subjects randomized to HTX-011 will receive a single dose of HTX-011 400 mg/12 mg (14 mL) after final irrigation and suctioning of the respective application areas. HTX-011 will be administered intraoperatively by periarticular and/or soft tissue application into the surgical site with the provided Luer lock applicators (without a needle).

5.5.1.1. Cohort 1 (TSA)

Approximately 7 mL will be applied with the Luer lock applicator into the intracapsular region prior to joint capsule closure, then approximately 3.5 mL below and 3.5 mL above the deltoid-pectoral muscle suture.

5.5.1.2. Cohort 2 (Abdominoplasty)

Approximately 8 to 10 mL will be applied with the Luer lock applicator into the “canal” below the plication of the rectus abdominus muscles; approximately equal amounts will be applied cranial to and caudal to the umbilicus. The remaining volume will be used to coat the muscles and subcutaneous tissues prior to skin closure.

5.5.2. Bupivacaine HCl Administration

Subjects randomized to bupivacaine HCl will receive a single dose of bupivacaine HCl 0.25% by injection into the surgical wound per Investigator standard of care: 100 mg (40 mL) in Cohort 1 (TSA) and 125 mg (50 mL) in Cohort 2 (abdominoplasty).

5.6. Study Drug Compliance

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

5.7. Study Drug Accountability

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

received, lot numbers, dispensing, and return or destruction of all study drug (ie, accountability or dispensing logs).

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

5.8. Protocol-Specified Device

The custom Luer lock applicator is a marketed device used for administration of HTX-011 without a needle into the surgical site for bunionectomy, inguinal hernia repair, and TKA; its use is investigational in this study.

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 the Schedule of Events tables.

6.1. Medical History and Demographics

6.1.1. Medical History

A complete medical history, including surgical history and chronic opioid use, will be obtained to ensure subjects qualify for the study. Medical history will be obtained through subject interview. In addition, a review of the subject's medical records from their primary care physician is recommended.

6.1.2. Demographics

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

6.2. Prior and Concomitant Therapy

All medications taken by subjects between signing the ICF and the Day 15 Visit will be recorded on the eCRFs.

During the inpatient postoperative period, the name, dose, and route, as well as the start date and time, and stop date and time, if applicable, 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. The dosing regimen of "prn" should not be recorded.

After discharge until the Day 15 Visit, at least the start date, and stop date if applicable, 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 prophylactically or to treat nausea and/or vomiting.

During surgery, all subjects will receive either IV morphine or IV hydromorphone, and may also receive fentanyl, as described in Section 3.1.2.

Postoperative analgesia medications permitted to treat pain are outlined in Section 3.1.3.

6.2.2. Prohibited Medications

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 the exclusion criteria for a full list of 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 or bupivacaine HCl; fentanyl; and morphine or hydromorphone) 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 a single administration of lidocaine 1% up to 20 mg IV may be administered).

Local administration of antibiotics (eg, vancomycin) directly into the surgical site is also prohibited, unless approved by the Sponsor's medical monitor.

6.2.2.3. Medications Prohibited During the Postoperative Period

With the exception of the scheduled non-opioid MMA regimen (Section 3.1.2), rescue medications (Section 3.1.3.2), and oxycodone after discharge (Section 3.1.3.3), no other analgesic agents, including other NSAIDs, are permitted through Day 15 except for cannabinoids, which are allowed 7 days after surgery.

6.3. Instructional Videos

Before surgery, subjects will be shown an instructional video that will describe what to expect after surgery.

Prior to discharge, subjects will be shown an instructional video on what to expect after discharge including instructions on their MMA regimen and how to complete the daily diary.

6.4. Surgery

Subjects will undergo TSA (Cohort 1) or abdominoplasty (Cohort 2) under deep sedation or under general anesthesia. Spinal, epidural, and regional anesthesia (eg, transversus abdominis plane [TAP] block or interscalene block) are not permitted. Sites should follow intraoperative safety monitoring in accordance with American Society of Anesthesiologists (ASA) Standards for Basic Anesthetic Monitoring (American Society of Anesthesiologists 2015). The start and stop time of surgery and additional surgical details should be recorded in the eCRF. 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. After immediate postoperative recovery, subjects will be transferred to the PACU.

6.5. Safety Assessments

6.5.1. Adverse Events

All AEs, regardless of causality or seriousness, will be recorded from the time the subject signs the ICF through the Day 15 Visit. Additional safety monitoring and reporting information is provided in Section 8.

An abnormal finding from any safety assessment that meets the definition of an AE or requires medical intervention (eg, medication, IV fluids) should be deemed clinically significant by the Investigator and must be recorded as AE.

Any abnormal finding from a safety assessment that is not considered clinically significant should not be recorded as an AE.

6.5.2. Physical Examinations

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

Baseline height and weight measurements will be conducted at the Screening Visit 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.

6.5.3. 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 and the abnormal vital sign result must be recorded on an eCRF (scheduled or unscheduled assessment eCRF, as applicable).

6.5.4. Wound Healing Assessments

Surgical wound healing will be assessed using the Southampton Wound Scoring System (Appendix C). 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 should be recorded as an AE and should be followed to resolution.

6.5.5. 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.

Laboratory results will be reviewed by the Investigator. Laboratory values outside of the normal reference range will be evaluated for clinical significance. An abnormal laboratory result deemed clinically significant by the Investigator must be recorded as an AE. Laboratory results recorded as an AE should be followed to resolution, stabilization, or until no longer considered clinically significant. Results for any unscheduled laboratory tests that result in identification of an AE or that are performed to follow the AE 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 Site):		
Pregnancy test (urine or serum): Human chorionic gonadotropin test (subjects of childbearing potential only) Drug screen (urine): Amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates/opioids, and phencyclidine COVID-19 test: rapid antigen test or nucleic acid amplification test per institutional practice		
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

6.5.6. Local Anesthetic Systemic Toxicity (LAST) Assessments

Subjects will be assessed with a LAST questionnaire (Appendix G) to monitor for signs and symptoms potentially attributable to LAST. Signs and symptoms deemed clinically significant by the Investigator must be recorded as AEs and followed to resolution.

If an AE of suspected LAST occurs, an ECG (triplicate), vital signs, and a blood sample for PK analysis should be obtained promptly. If a scheduled blood sample for PK analysis has been obtained within 30 minutes prior to the AE occurring, the sample collection does not need to be repeated.

6.6. Pharmacokinetic Assessments

PK sampling will occur through Day 7. On Day 5 (96-hour timepoint), Day 6 (120-hour timepoint), and Day 7 (144-hour timepoint), PK sample collection will be performed at the study site or via a home visit.

Blood samples will be collected to measure plasma concentrations of bupivacaine and meloxicam. Alpha-1-acid glycoprotein and other study drug components may be evaluated. Blood samples may be collected using a properly maintained indwelling cannula.

Bupivacaine concentrations may also be measured in drainage fluid in subjects with drains.

Samples will be sent to a bioanalytical laboratory for analysis. Detailed instructions on sample collection, processing, storage, and shipping procedures are provided in the Laboratory Manual.

6.7. Pharmacodynamic Assessments

6.7.1. Rescue Medication Use and Opioid Prescriptions

6.7.1.1. Rescue Medication Use

Postoperative rescue medication will be recorded through the 72-hour postoperative period. The name, dose, and route as well as the date and time of administration must be recorded.

6.7.1.2. Opioid Prescriptions At and After Discharge

Guidance on opioid prescription at and after discharge is provided in Section 3.1.3.3. Sites will record if subjects are discharged with an opioid prescription and information about the opioid prescription. Sites will also record if any subjects are provided an opioid prescription after discharge through the Day 15 Visit and information about the 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 15 Visit (Appendix G).

6.7.2. Pain Intensity Assessments

Subjects will evaluate their current pain level using an 11-point NRS (0 to 10) where 0 represents "no pain" and 10 represents "worst pain imaginable" (Appendix D). The NRS-R score will be obtained first after the subject has been in a resting position for at least 5 minutes. After the NRS-R score has been obtained, the NRS-A score will be obtained. Subjects will receive training by the site on how to provide pain intensity assessments.

TSA (Cohort 1)

- *NRS-R assessments*: Subjects should be seated comfortably or reclining.
- *NRS-A assessments*: Subjects will be asked to adduct the operated arm into the side of their body for 3 seconds.

Abdominoplasty (Cohort 2)

- *NRS-R assessments*: Subjects should be resting in a comfortable reclined position.

- *NRS-A assessments*: Subjects will be asked to cough.

6.7.3. Modified Postanaesthesic Discharge Scoring System (MPADSS) Assessments

Discharge readiness will be assessed using the MPADSS, 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.

Note: In the ambulation parameter of the MPADSS assessment, if a subject is unable to ambulate for any reason, a score of 0 should be recorded even if the subject does not have dizziness.

See Appendix E for the MPADSS.

6.7.4. Discharge Information

Sites will record when subjects are discharged and if subjects are discharged home or to a skilled nursing facility. If a subject is not ready to be discharged due to an AE, it must be recorded as an SAE (Section 8.1.2). If a subject is ready for discharge but is not discharged for any reason other than AE, the reason must be recorded on the eCRF.

6.7.5. Patient Global Assessment (PGA) of Pain Control

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

7. GUIDANCE FOR COMPLETING PROCEDURES AND ASSESSMENTS

Study procedures and assessments are described in Section 6. The timing of procedures and assessments is provided in the Schedule of Events tables. The start of study drug administration will be considered Time 0 for all safety, PK, and PD assessments.

Unless there is a safety concern, every effort should be made to avoid protocol deviations by completing procedures and assessments according to the protocol guidance. Actual times will be recorded for all events, and events performed outside the specified ranges should be documented as deviations.

During the Screening period, urine drug screen tests (all subjects) and urine or serum pregnancy tests (subjects of childbearing potential only) should be performed and confirmed as negative prior to performing any additional assessments. The definition of a subject of childbearing potential is provided in Section 9.1.

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

- AE assessment.
- LAST questionnaire.
- PGA of pain control assessment.
- Pain intensity assessments (NRS-R followed by NRS-A).
- Vital sign measurements.
- 12-lead ECG recording.
- Blood sample collection.
- Physical examination.
- Wound healing 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 should be recorded as “Not done.” Assessments that can be done without waking the subject (eg, blood and drain fluid collection) should be completed.

Unscheduled visits and assessments should be performed if clinically indicated in the opinion of the Investigator. Except when urgent clinical evaluation is necessary, it is expected that the Investigator will have the subject return for an unscheduled visit rather than directing the subject to a hospital emergency room. The results of any unscheduled assessments should be recorded on the eCRF.

8. SAFETY MONITORING AND REPORTING

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

Investigators must review the HTX-011 Investigator's Brochure to be aware of the safety-related events that may be anticipated with its use.

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 study drug interrupted or discontinued.
  - Any laboratory abnormality that required the subject to receive specific treatment for the laboratory abnormality.
  - Any laboratory abnormality that required further diagnostic investigation 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 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 the following:
  - Elective treatment of a pre-existing condition that does not worsen from baseline.
  - 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.
- 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 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 and bupivacaine HCl) 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.

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 when entering the information into the eCRF or completing the SAE reporting form, in the event 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 will be recorded from the time the subject signs the ICF through the Day 15 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, the Investigator is required to follow each subject proactively and provide further information on the subject's condition. All AEs 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 (see Section 8.1.2) 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

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 using the same process and timelines as for the 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 (see Section 8.1.3), 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 problem 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.

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 periodic reporting requirements.

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.

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. 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 subject 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 (ie, approximately monthly unless more frequent monitoring is necessary due to high enrollment or safety concern), including regular review of AEs, laboratory results, and other safety assessment results.

Criteria for stopping the study or closing a study site for safety issues are provided in Section 3.4 and Section 13.5, respectively.

9. OTHER STUDY RESTRICTIONS

9.1. Contraception

A subject of childbearing potential is defined as a premenopausal subject capable of becoming pregnant. This includes subjects on oral, injectable, or mechanical contraception; subjects who are not in a relationship; and subjects whose partners have been vasectomized or have received or are utilizing mechanical contraceptive devices.

Subjects of childbearing potential must use an acceptable form of contraception in the event of sexual activity from the Screening Visit through 30 days after study drug administration. Acceptable forms of contraception include double-barrier contraception or an insertable, injectable, transdermal, or combination oral contraceptive approved by applicable regulatory authorities.

Note: Contraception requirements do not apply to subjects of childbearing potential who are practicing abstinence or who are in a monogamous relationship with a partner who cannot impregnate the subject (eg, is surgically sterile).

10. STATISTICAL CONSIDERATIONS

10.1. General Considerations

Each cohort will be analyzed separately following completion of that cohort. All data will be listed by subject. Unless otherwise specified, baseline is defined as the last observed measurement, whether scheduled or unscheduled, prior to Time 0. 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 in this study 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. The actual treatment received will be used for analysis in this population. This population will be used for all summaries of safety data.

PK Population: All subjects who receive at least 1 dose of study drug and have sufficient data to calculate PK parameters and do not have protocol deviations thought to significantly affect the PK of bupivacaine or meloxicam will be included in the PK Population. Any subject with a predose concentration exceeding 5% of the C_{max} for that individual will be excluded from the PK Population.

10.4. Statistical Analysis Methods

10.4.1. Disposition and Demographics

The number and percentage of subjects in each analysis population will be summarized. Subject disposition, including the number of subjects screened, randomized, dosed, and completing the study, will be summarized. Screening failures and early study withdrawal will also be summarized.

Subject demographics and baseline characteristics will be summarized for the Safety Population and will include age, age category, sex at birth, race, ethnicity, height, and weight.

10.4.2. Safety Analysis

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

AEs that occur between the time the subject signs the ICF and the start of study drug administration will be considered pretreatment AEs. AEs that start during or after study drug administration, or AEs with an onset prior to study drug administration that worsen after study drug administration will be considered TEAEs. All TEAEs will be coded and tabulated by System Organ Class and Preferred Term. Incidence of TEAEs, SAEs, and potential

opioid-related adverse events (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 parameter, 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 scheduled postbaseline assessment timepoint for vital sign variables will be summarized. Abnormal vital sign values will be flagged and listed, and predefined out-of-range values will be summarized.

Wound healing assessment results will be summarized at each timepoint.

10.4.3. Pharmacokinetic Analyses

Plasma bupivacaine and meloxicam concentrations will be determined using a validated liquid chromatography tandem-mass spectrometry assay. Concentrations will be calculated by interpolation from a calibration curve. PK parameters for bupivacaine and meloxicam will be calculated using noncompartmental analysis, as appropriate. If alpha-1-acid glycoprotein is evaluated, concentrations will be summarized using descriptive statistics. 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.

Bupivacaine concentrations may also be determined in drainage fluid for subjects with drains.

10.4.4. Pharmacodynamic Analyses

All PD data will be listed and summarized by cohort and by 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). Subjects who do not use postoperative opioids 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.

10.5. Interim Analysis

No formal interim analysis is 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 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 by the Sponsor (or designee), or inspected by a regulatory authority at any time during the study or after study completion. In the event of an audit or inspection, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, the competent authority, or other regulatory authority 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 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.

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 re-consented. 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 re-approval.

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

12.4. Informed Consent Process

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

The Sponsor (or its designee) will provide Investigators with 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, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF details the requirements of the participant and the fact that he/she is free to withdraw at any time without giving a reason and without prejudice to his/her further medical care. Before informed consent is obtained, the subject should be given ample time and opportunity to inquire about the details of the study. All questions must be answered to the satisfaction of the subject.

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

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

12.5. Confidentiality

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

The Investigator agrees to comply with all applicable national, state, and local laws and regulations relating to the privacy of a subject's 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. During the study, the Sponsor's study monitors will contact the study site via site visits or remote monitoring 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 process and documents, the site's essential 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 authorities 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 regulatory authorities and ECs, ICFs, monitoring visit logs and records, laboratory certification or quality control procedures, and laboratory reference ranges and reports. Access to study documents and records will be strictly controlled (Section 12.5).

Study documents and records must be retained for at least 2 years after the last approval of a marketing application in the US and until there are no pending or contemplated marketing applications in the US or until at least 2 years have elapsed since the formal discontinuation of clinical development of the test product. However, these documents must 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 Amendments

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.

13.4. Financial Disclosure

The Sponsor will determine whether the study is a Covered Clinical Study and is subject to 21 CFR Part 54, Financial Disclosure by Clinical Investigators.

For a Covered Clinical Study, 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 any changes after 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 Food and Drug Administration (FDA) 1572 form must complete the Financial Disclosure for Clinical Investigators Form at the start of his/her participation in the study.

13.5. Criteria for Study Site Closure

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

- Failure of the Principal 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 a study site is closed by the Sponsor, written notification documenting the reason for study site closure will be provided to the Investigator and regulatory authorities. The Investigator will promptly inform the EC and provide the reason(s) for study site closure.

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.

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, the 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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Acetaminophen Tablets USPI. ACETAMINOPHEN 325MG RS- acetaminophen 325mg tablet. Legacy Pharmaceutical Packaging, LLC; 2021.

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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 CALCULATION

Body mass index (BMI) = (Weight in kilograms [kg])/(height in meters [m])^2

Weight in pounds × 0.453592 = weight in kg

Height in inches × 0.0254 = height in m

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

165 pounds × 0.453592 = 74.8 kg

71 inches × 0.0254 = 1.803 m

BMI = 74.8 kg/(1.803 m × 1.803 m) = 23.01 kg/m^2

APPENDIX C. WOUND HEALING ASSESSMENT - SOUTHAMPTON WOUND SCORING SYSTEM

Grade	Appearance
0	Normal healing
I. Normal healing with mild bruising or erythema:	
A	Some bruising
B	Considerable bruising
C	Mild erythema
II. Erythema plus other signs of inflammation:	
A	At 1 point
B	Around sutures
C	Along wound
D	Around wound
III. Clear or haemoserous discharge:	
A	At 1 point only (≤2 cm)
B	Along wound (>2 cm)
C	Large volume
D	Prolonged (>3 days)
Major complication	
IV. Pus:	
A	At 1 point only (≤2 cm)
B	Along wound (>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.

APPENDIX D. PAIN INTENSITY ASSESSMENTS USING THE NUMERIC RATING SCALE

"On a scale of 0 to 10, please rate your pain by selecting the 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. MODIFIED POSTANAESTHESIC DISCHARGE SCORING SYSTEM CRITERIA

The Modified Postanaesthesic 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 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. LOCAL ANESTHETIC SYSTEMIC TOXICITY ASSESSMENT

This local anesthetic systemic toxicity (LAST) questionnaire is provided to monitor for signs and symptoms potentially attributable to LAST at the timepoints listed in the SCHEDULE OF EVENTS section.

If an adverse event (AE) of suspected LAST occurs, an electrocardiogram (ECG, triplicate), vital signs, and a blood sample for PK analysis should be obtained promptly. If a scheduled blood sample for PK analysis has been obtained within 30 minutes prior to the AE occurring, the sample collection does not need to be repeated.

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

LAST Questionnaire

Record "Present" or "Absent" for each of the following symptoms. If signs and symptoms are deemed clinically significant by the Investigator they must be entered on the electronic case report form (eCRF) as AEs and followed to resolution.

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

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

APPENDIX H. HTX-011-401 PATIENT DIARY

Subjects will be discharged with a diary to record any opioid use between discharge and the Day 15 Visit. Subjects must bring their diary with them to all site visits.

The diary on the following pages should be used.

HTX-011-401 PATIENT DIARY

To be completed by site staff:

Subject ID #: _____

Please complete the diary until (date):_____

If you have concerns, please call your healthcare provider at: _____

To be completed by patient:

Have you taken any opioid medication since you have been discharged from the hospital? (A list of opioid medications is provided at the end of this diary for your reference.)

☐ YES

☐ NO

If Yes, please write the name and the dose of each opioid medication you took in its own row on the diary below, along with the day and time you took it and the reason why you took it.

Please bring your diary with you each time you return for a follow-up appointment. Once you have completed the last entry on the diary, please sign and date the last page.

Date (MM/DD/YY)	Time (HH:MM) am/pm	Name of Opioid (Refer to Opioid Reference List attached)	Number of Pills Taken / Dosage of Each Pill (in mg)	Reason for Taking Opioid
	___ : ___ (HH : MM) AM / PM (circle one)		_____ pills _____ mg each pill	☐ Surgical pain ☐ Other (specify) _____
	___ : ___ (HH : MM) AM / PM (circle one)		_____ pills _____ mg each pill	☐ Surgical pain ☐ Other (specify) _____

Date (MM/DD/YY)	Time (HH:MM) am/pm	Name of Opioid (Refer to Opioid Reference List attached)	Number of Pills Taken / Dosage of Each Pill (in mg)	Reason for Taking Opioid
	___ : ___ (HH : MM) AM / PM (circle one)		_____ pills _____ mg each pill	☐ Surgical pain ☐ Other (specify) _____
	___ : ___ (HH : MM) AM / PM (circle one)		_____ pills _____ mg each pill	☐ Surgical pain ☐ Other (specify) _____
	___ : ___ (HH : MM) AM / PM (circle one)		_____ pills _____ mg each pill	☐ Surgical pain ☐ Other (specify) _____
	___ : ___ (HH : MM) AM / PM (circle one)		_____ pills _____ mg each pill	☐ Surgical pain ☐ Other (specify) _____
	___ : ___ (HH : MM) AM / PM (circle one)		_____ pills _____ mg each pill	☐ Surgical pain ☐ Other (specify) _____
	___ : ___ (HH : MM) AM / PM (circle one)		_____ pills _____ mg each pill	☐ Surgical pain ☐ Other (specify) _____

Date (MM/DD/YY)	Time (HH:MM) am/pm	Name of Opioid (Refer to Opioid Reference List attached)	Number of Pills Taken / Dosage of Each Pill (in mg)	Reason for Taking Opioid
	___ : ___ (HH : MM) AM / PM (circle one)		_____ pills _____ mg each pill	☐ Surgical pain ☐ Other (specify) _____
	___ : ___ (HH : MM) AM / PM (circle one)		_____ pills _____ mg each pill	☐ Surgical pain ☐ Other (specify) _____
	___ : ___ (HH : MM) AM / PM (circle one)		_____ pills _____ mg each pill	☐ Surgical pain ☐ Other (specify) _____
	___ : ___ (HH : MM) AM / PM (circle one)		_____ pills _____ mg each pill	☐ Surgical pain ☐ Other (specify) _____
	___ : ___ (HH : MM) AM / PM (circle one)		_____ pills _____ mg each pill	☐ Surgical pain ☐ Other (specify) _____
	___ : ___ (HH : MM) AM / PM (circle one)		_____ pills _____ mg each pill	☐ Surgical pain ☐ Other (specify) _____

Date (MM/DD/YY)	Time (HH:MM) am/pm	Name of Opioid (Refer to Opioid Reference List attached)	Number of Pills Taken / Dosage of Each Pill (in mg)	Reason for Taking Opioid
	___ : ___ (HH : MM) AM / PM (circle one)		_____ pills _____ mg each pill	☐ Surgical pain ☐ Other (specify) _____
	___ : ___ (HH : MM) AM / PM (circle one)		_____ pills _____ mg each pill	☐ Surgical pain ☐ Other (specify) _____
	___ : ___ (HH : MM) AM / PM (circle one)		_____ pills _____ mg each pill	☐ Surgical pain ☐ Other (specify) _____

Once you have completed the last entry on the diary, please sign and date.

Patient Signature _____ Date _____

Opioid Reference List

Acetaminophen and Codeine	Fiorinal with codeine	Oxycodone
Acetaminophen and Hydrocodone	Homatropine Methylbromide, and Hydrocodone	Oxycodone and Aspirin
Acetaminophen and Oxycodone	Hycodan	Oxycodone/acetaminophen
Acetaminophen, Caffeine, and Dihydrocodone	Hydrocodone	Oxycodone/APAP
Actiq	Hydrocodone and Acetaminophen	Oxycodone/aspirin
Anexsia	Hydrocodone and Ibuprofen	OxyContin
Apadaz	Hydrocodone Polistirex, and Chlorpheniramine	Oxymorphone
Apokyn	Hydromet	Percocet
Belbuca	Hydromorphone	Percodan
Buprenex	Hysingla	Promethazine and codeine
Buprenorphine	Infumorph	Reprexain
Butalbital, Acetaminophen, Caffeine, and Codeine	Kadian	Roxicodone
Butalbital, Aspirin, Caffeine, and Codeine	Kynmobi	Sublimaze
Butrans	Lazanda	Sublocade
Carisoprodol, Aspirin, and Codeine	Meperedine	Suboxone
Codeine	Methadone hydrochloride	Subsys
Codeine, Aspirin, APAP	Methadose	Trezix
Demerol	Mitigo	Triacin-C
Dilaudid	Morphine sulfate	TussiCaps
Duragesic	MS Contin	Tuzistra
Duramorph	Norco	Xtampza
Fentanyl	Nucynta	Xtampza ER
Fentora	Oxaydo	Zohydro
Fioricet with Codeine	Oxycet	Zubsolv

Note: if you cannot find the opioid medication you have taken in this list, please consult your healthcare provider at the number listed above for guidance on what to write on your diary.

Signature Page for VV-CLIN-005233 v1.0

Approval Task	[redacted] 18-Nov-2021 18:09:32 GMT+0000

Signature Page for VV-CLIN-005233 v1.0