Document Type:	Study Protocol
Official Title:	A Phase 2, Open-Label Study of the Pharmacokinetics and Safety of HTX-011 Administered Postpartum to Women Undergoing a Planned Caesarean Section
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CLINICAL STUDY PROTOCOL: HTX-011-220

Protocol Title:	A Phase 2, Open-Label Study of the Pharmacokinetics and Safety of HTX-011 Administered Postpartum to Women Undergoing a Planned Caesarean Section
Brief Title:	Phase 2 PK and Safety After C-Section
Investigational Product:	HTX-011 (bupivacaine and meloxicam) extended-release solution
Phase of Development:	2
Sponsor:	Heron Therapeutics, Inc. 4242 Campus Point Court, Suite 200 San Diego, CA 92121 USA 1-858-251-4400
Medical Monitor(s):	[redacted]
Medical Project Leader:	[redacted]

Protocol Version:	Version 6	10 September 2020
	Version 5	10 February 2020
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	Version 3	08 July 2019
	Version 2	15 May 2019
	Version 1	07 March 2019

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SPONSOR SIGNATURE

Protocol Title:	A Phase 2, Open-Label Study of the Pharmacokinetics and Safety of HTX-011 Administered Postpartum to Women Undergoing a Planned Caesarean Section
Protocol Number:	HTX-011-220

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

The electronic signature is appended.

[redacted]
Heron Therapeutics, Inc.

INVESTIGATOR AGREEMENT

CLINICAL STUDY PROTOCOL: HTX-011-220

TITLE: A Phase 2, Open-Label Study of the Pharmacokinetics and Safety of HTX-011 Administered Postpartum to Women Undergoing a Planned Caesarean Section

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 (IB), and all other information on the investigational product that were furnished to me by the Sponsor to all physicians and other study personnel responsible to me who participate in this study, and will discuss this material with them to ensure that they are fully informed regarding the investigational product and the conduct of the study.

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

Principal Investigator: _____

Address: _____

Signature: _____

Date: _____

PROTOCOL SYNOPSIS

NAME OF SPONSOR:	**Heron Therapeutics, Inc**.
NAME OF FINISHED PRODUCT:	HTX-011 (bupivacaine and meloxicam) extended-release solution
NAME OF ACTIVE INGREDIENTS:	bupivacaine and meloxicam
PROTOCOL NUMBER:	HTX-011-220
PHASE OF DEVELOPMENT:	2

PROTOCOL TITLE: A Phase 2, Open-Label Study of the Pharmacokinetics and Safety of HTX-011 Administered Postpartum to Women Undergoing a Planned Caesarean Section

STUDY SITES: Up to 10 study sites in the United States (US).

STUDY OBJECTIVES:

Primary:

- To characterize the pharmacokinetics (PK) of bupivacaine, meloxicam, dimethyl sulfoxide (DMSO), and HTX-011 tri(ethylene glycol) poly(orthoester) polymer (TEG-POE) water-soluble end products in expressed breast milk and plasma following postpartum administration of HTX-011 in women undergoing a planned Caesarean section (C-section).

Secondary:

- To assess the safety and tolerability of HTX-011 administered alone or as part of a scheduled, non-opioid multimodal analgesic (MMA) regimen in this study population.

Exploratory:

- To characterize the efficacy and duration of analgesia during the first 72 hours following administration of HTX-011 alone or as part of a scheduled, non-opioid MMA regimen in this study population.

METHODOLOGY:

This is a Phase 2, open-label, multi-cohort study of HTX-011 administered postpartum either alone or as part of a scheduled, non-opioid MMA regimen in women undergoing a planned C-section who must have chosen prospectively not to breast-feed their newborn. The study will include up to 3 cohorts. Cohorts will be conducted sequentially.

Study Overview

In Cohort 1, subjects will receive HTX-011 300 mg/9 mg. In Cohort 2, subjects will receive HTX-011 400 mg/12 mg and a scheduled, non-opioid MMA regimen. PK (in expressed breast milk and plasma), safety, and efficacy will be assessed in Cohorts 1 and 2. An optional dose-expansion cohort (Optional Cohort 3) may be conducted after Cohort 2 to further evaluate the safety and efficacy of HTX-011 400 mg/12 mg and a scheduled, non-opioid MMA regimen. No PK assessments will be conducted in Optional Cohort 3.

Cohort 1

Approximately 15 subjects will be treated in Cohort 1. Subjects will be screened within 28 days prior to the planned surgery date. Eligible subjects will be enrolled and undergo a C-section under ropivacaine spinal anesthesia on Day 1. In addition to ropivacaine spinal anesthesia, management of intraoperative anesthesia will be in accordance with the prevailing institutional practice/anesthesiologist's preference as long as it does not include bupivacaine or meloxicam. After delivery of the newborn baby, all subjects

will receive a single dose of HTX-011 300 mg/9 mg (bupivacaine/meloxicam doses) administered via instillation into the surgical site.

Cohort 2

Up to approximately 12 subjects will be treated in Cohort 2 to ensure adequate breast milk collection in at least 6 subjects. Subjects will be screened within 28 days prior to the planned surgery date. On the day of surgery (Day 1), eligible subjects will be administered oral (PO) acetaminophen 975 mg to 1 g approximately 2 hours prior to the start of anesthesia. Subjects will undergo a C-section under spinal anesthesia with ropivacaine up to 20 mg, intrathecal morphine sulfate injection (DURAMORPH®) 50 µg, and intrathecal fentanyl 20 µg. After delivery of the newborn baby, all subjects will receive a single dose of HTX-011 400 mg/12 mg administered via instillation into the surgical site. Following surgery, subjects will receive a scheduled, non-opioid MMA regimen while awake during the first 5 days after surgery (ie, Days 1 through 6) consisting of PO acetaminophen 975 mg to 1 g every 6 hours alternating with PO ibuprofen 400 mg every 6 hours.

Postoperative Follow Up for Cohorts 1 and 2

Subjects will remain in the hospital/research facility for a minimum of 72 hours after the start of HTX-011 administration to undergo postoperative assessments. Assessments will include the collection of breast milk and blood samples for PK analyses, and safety and efficacy assessments. After the 72-hour postoperative procedures and assessments have been completed, subjects may be discharged in accordance with institutional practice/Investigator preference. Sites will record if subjects are discharged with an opioid prescription and information about the opioid prescription.

At discharge, each subject will be provided a breast milk log to record breast milk expression during the follow-up period. A visiting healthcare professional will visit each subject once a day on Days 5, 6, 8, 9, and 10 to collect breast milk and blood samples for PK analyses. On Day 7 and Day 11, a visiting healthcare professional will visit the subject to collect only the breast milk samples, and the subject will return to the study site to undergo additional assessments. In Cohort 1 only, a visiting healthcare professional will visit the subject on the Day 16 Visit and collect a final blood sample and a final expressed breast milk sample for PK analyses. All subjects will return to the study site for a Day 28 Visit to undergo final study assessments.

Optional Cohort 3

After a review of data from Cohort 2, up to approximately 24 subjects may be treated in Optional Cohort 3. Subjects in Optional Cohort 3 will undergo a C-section under spinal anesthesia with ropivacaine up to 20 mg, intrathecal Duramorph 50 to 200 µg, and intrathecal fentanyl 20 µg. Subjects will receive the same HTX-011 dose and scheduled, non-opioid MMA regimen as Cohort 2 (pre- and postoperatively), and will follow the same schedule of events as Cohort 2 with the exception of PK assessments. Breast milk and blood samples for PK analysis will not be collected in Optional Cohort 3.

Postoperative Rescue Medications

Subjects should receive rescue analgesic medication only upon request for pain control, as needed, during the 72-hour postoperative observation period. Rescue medication should not be given for pain prophylaxis, but only for treating postoperative pain. Prior to the administration of the first dose of rescue medication, if the subject has not already had at least 1 postoperative pain score assessed, then a numeric rating scale of pain intensity (NRS) score must be obtained. Subjects who are not medically ready for discharge at 72 hours may receive the same analgesic rescue medication as described below to treat postoperative pain until discharge.

Cohort 1 Rescue Medication

Postoperative rescue medication during the 72-hour postoperative period will comprise any 1 or more of the following medications as needed: PO ibuprofen ≤600 mg within a 6-hour period, PO/intravenous (IV) acetaminophen ≤1 gram (1,000 mg) within a 6-hour period, PO immediate-release oxycodone ≤5 mg within a 4-hour period, and IV morphine ≤10 mg within a 2-hour period. For subjects administered any

acetaminophen-containing product, the total combined daily dose of acetaminophen must not exceed 4 grams (4,000 mg) in a 24-hour period. Combination products containing an opioid and non-opioid are not allowed. The recommended analgesic medication after discharge will be in accordance with the prevailing institutional practice/Investigator preference; however, any drug formulation containing bupivacaine or meloxicam is prohibited through the Day 16 Visit.

Cohort 2 and Optional Cohort 3 Rescue Medication

Postoperative rescue medication during the 72-hour postoperative period will initially consist of ibuprofen 400 mg PO (in addition to the scheduled MMA regimen), which may be administered at most only once every 12 hours. If pain persists approximately 30 minutes following ibuprofen rescue medication, the following rescue medications are permitted upon subject request for additional pain control: PO immediate-release oxycodone ≤5 mg within a 4-hour period and/or IV morphine ≤10 mg within a 2-hour period.

Note: Other than HTX-011, any drug formulation containing bupivacaine or meloxicam is prohibited before surgery (within 5 days for bupivacaine and within 10 days for meloxicam), during surgery, and following surgery through Day 16.

NUMBER OF PLANNED SUBJECTS: Up to approximately 51 female subjects will be enrolled and dosed: approximately 15 subjects in Cohort 1, up to approximately 12 subjects in Cohort 2, and up to approximately 24 subjects in Optional Cohort 3.

STUDY POPULATION:

Inclusion Criteria:

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

1. Is able to provide written informed consent, adhere to the study visit schedule, and complete all study assessments.
2. Is 18 years of age or older at the time of Screening visit.
3. Is expected, at the time of Screening visit, to deliver a single neonate.
4. Is scheduled to undergo a planned C-section surgery with a low transverse skin incision (eg, Pfannenstiel).
5. Has American Society of Anesthesiologists (ASA) Physical Status of I, II, or III.
6. Agrees to practice abstinence or use double-barrier contraception in the event of sexual activity and commits to the use of an acceptable form of birth control for 30 days after HTX-011 administration.
7. Agrees to refrain from the use of breast milk from this pregnancy in any manner (including, but not limited to, breastfeeding, donation, sale, or storage for later use) for 28 days after HTX-011 administration.

Exclusion criteria:

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

1. Has planned to breastfeed her neonate at any time during the 28-day period after HTX-011 administration.
2. Planned C-section under general anesthesia.
3. Has had a prior full-term pregnancy with unsuccessful breast milk expression. (This criterion is not applicable to Optional Cohort 3).
4. Has a planned concurrent surgical procedure (with the exception of a tubal ligation), unless previously approved by the Sponsor.
5. Has a contraindication or a known or suspected history of hypersensitivity or clinically significant

idiosyncratic reaction (including methemoglobinemia) to bupivacaine or ropivacaine (or other local anesthetics), meloxicam (or other nonsteroidal anti-inflammatory drugs [NSAIDs]), or to acetaminophen, morphine, or fentanyl (Cohort 2 and Optional Cohort 3 only).

6. Has been administered bupivacaine within 5 days prior to the scheduled surgery.
7. Has been administered any local anesthetic within 72 hours prior to the scheduled surgery, other than for pretreatment prior to a needle placement, to treat an adverse event (AE) that occurs after signing the informed consent form (ICF), or to decrease venous irritation (eg, caused by propofol, in which case, no more than a single dose of IV lidocaine 20 mg may be administered).
8. Has been administered systemic steroids within 5 half-lives or 10 days prior to administration of study drug (whichever is longer). Note that for purposes of this exclusion criterion, inhaled steroids are not considered systemic.
9. Has initiated treatment with any of the following medications within 1 month prior to study drug administration or is taking any of these medications to control pain: selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin, or cyclooxygenase-2 (COX-2) inhibitors. (Note: If a subject is taking one of these medications for a reason other than pain control, the subject must be on a stable scheduled dose [ie, not "as needed"] for at least 1 month prior to study drug administration.) Anxiolytics prior to surgery are permitted, if necessary.
10. Has taken NSAIDs (including meloxicam) within at least 10 days prior to surgery with the exception of subjects on low dose (≤100 mg) daily acetylsalicylic acid for cardioprotection.
11. Has current significant placental abnormality/complications including, but not limited to, placenta previa or placenta accreta.
12. Has a medical condition such that, in the opinion of the Investigator, participating in the study would pose a health risk to the subject or confound the postoperative assessments. Conditions may include, but are not limited to, any of the following:
    a. History of clinically significant cardiac abnormality such as myocardial infarction within 6 months prior to signing the ICF, New York Heart Association class III or IV, or clinically significant abnormalities of electrocardiogram (ECG) or cardiac function.
    b. History of coronary artery bypass graft surgery within 12 months prior to signing the ICF.
    c. Severe liver function impairment as defined by Child-Pugh Class C, having an aspartate aminotransferase >3 × the upper limit of normal (ULN), or having an alanine aminotransferase >3 × ULN.
    d. Severe kidney function impairment as defined by creatinine clearance (Cockcroft Gault) <30 mL/min and/or being on dialysis.
    e. History of known or suspected coagulopathy or uncontrolled anticoagulation.
    f. Platelets <100,000/μL, hemoglobin <9.5 g/dL, or hematocrit <28%.
    g. Known history of glucose-6-phosphate dehydrogenase deficiency.
13. Has uncontrolled anxiety, psychiatric, or neurological disorder that might interfere with study assessments.
14. Has had a malignancy in the preceding last year before day of surgery, with the exception of nonmetastatic basal cell or squamous cell carcinoma of the skin or localized carcinoma in situ of the cervix.
15. Has a known or suspected history of drug abuse, or a positive urine drug test at the screening visit or on the day of surgery prior to the surgery, or a recent history of alcohol abuse (ie, within 10 years). Note: Subjects with a positive urine drug test who are taking an allowed, prescribed

medication that is known to result in a positive urine drug test (eg, amphetamine and/or dextroamphetamine for attention-deficit/hyperactivity disorder, benzodiazepine for anxiety disorder) may be eligible for participation in the study if approved by the Medical Monitor. Subjects taking any marijuana are not allowed to participate in the study.

16. Has previously participated in an HTX-011 study or received an investigational product or device in a clinical trial within 30 days or within 5 elimination half-lives (whichever is longer) before surgery, or is planning to take part in another clinical trial while participating in this study.
17. Weight is <50 kg at the time of Screening visit.
18. In the Investigator's judgment, subject is likely to have been morbidly obese prior to her pregnancy.

INVESTIGATIONAL PRODUCT, DOSE, AND MODE OF ADMINISTRATION:

HTX-011 is a clear, pale yellow to yellow, viscous liquid supplied in single-dose glass vials. The vials serve only as a closed container for the drug product. For administration of study drug, the contents in the vials will be aseptically transferred to sterile syringes without needles.

A single dose of HTX-011 will be administered into the surgical site using a Luer lock applicator after delivery of the newborn baby: 300 mg/9 mg (10.5 mL withdrawn volume) in Cohort 1 and 400 mg/12 mg (14 mL withdrawn volume) in Cohort 2 and Optional Cohort 3. Prior to application of HTX-011, the uterine incision and parietal peritoneum must be sutured closed. Then following irrigation and suction and prior to closure of each subsequent layer, HTX-011 will be applied to the pain generating tissues. HTX-011 must not be instilled directly in or on the uterus or the uterine incision.

REFERENCE THERAPY, DOSE, AND MODE OF ADMINISTRATION:

Not applicable.

PROTOCOL-SPECIFIED MEDICATIONS: Additional protocol-specified medications include spinal anesthesia, postoperative rescue medication, and a scheduled, non-opioid MMA regimen (Cohort 2 and Optional Cohort 3 only).

Spinal anesthesia: In Cohort 1, C-sections will be performed under ropivacaine spinal anesthesia. In Cohort 2 and Optional Cohort 3, C-sections will be performed under spinal anesthesia with ropivacaine up to 20 mg, intrathecal Duramorph (50 μg in Cohort 2 and 50 to 200 μg in Optional Cohort 3), and intrathecal fentanyl 20 μg.

Postoperative rescue medication: In Cohort 1, rescue medication permitted to treat pain during the 72-hour postoperative period will consist of 1 or more of the following 3 medications: PO ibuprofen, PO/IV acetaminophen, PO immediate-release oxycodone, and/or IV morphine. In Cohort 2 and Optional Cohort 3, rescue medication permitted to treat pain during the 72-hour postoperative period will initially consist of ibuprofen PO. If pain persists, PO immediate-release oxycodone and/or IV morphine are permitted upon subject request for additional pain control.

MMA Regimen: In Cohort 2 and Optional Cohort 3, subjects will receive a scheduled, non-opioid MMA regimen consisting of PO acetaminophen 975 mg to 1 g approximately 2 hours prior to the start of anesthesia and PO acetaminophen 975 mg to 1 g every 6 hours alternating with ibuprofen 400 mg every 6 hours following surgery through Day 6.

DURATION OF TREATMENT: Subjects will receive a single dose of HTX-011. The total duration of study participation for each subject (from Screening through the Day 28 Visit) will be up to 60 days.

The overall duration of the study is anticipated to be approximately 15 months.

STUDY ASSESSMENTS: Safety and efficacy assessments will be performed in all cohorts. PK will be performed in Cohorts 1 and 2 only. The start of study drug (HTX-011) administration will be considered as Time 0 for all assessments.

Pharmacokinetic assessments: Expressed breast milk and blood samples will be collected through the Day 11 Visit (Cohorts 1 and 2) and through the Day 16 Visit (Cohort 1 only) to assess the PK profiles of bupivacaine, meloxicam, DMSO, and HTX-011 TEG-POE polymer water-soluble end products (pentaerythritol [PE], triethylene glycol [TEG], and TEG acid). PK blood samples may also be used to evaluate other study drug components.

Safety Assessments:

- AEs from the time the subject signs the ICF through Day 28 Visit.
- Potential local anesthetic systemic toxicity (LAST) symptoms questionnaire. Note: If neurologic and/or cardiac signs and symptoms of LAST are observed, then the following assessments must be performed if not already scheduled: vital signs, 12-lead ECG, and blood sample collection for PK.
- 12-lead ECGs (in triplicate).
- Physical examinations.
- Vital signs, including systolic and diastolic blood pressure, resting heart rate, respiratory rate, and temperature.
- Wound healing assessment using the Southampton Scale.
- Clinical laboratory tests (hematology and serum chemistry).

Efficacy Assessments:

- Numeric rating scale of pain intensity at rest (NRS-R) assessments. Subjects should be recumbent or lying supine and measurements should be obtained after the subject has been in the resting position for at least 5 minutes.
- Numeric rating scale of pain intensity with activity (NRS-A) assessments (Cohort 2 and Optional Cohort 3 only). Subjects should be in a resting position (recumbent or lying supine) and then instructed to sit up. Measurements should be obtained as soon as the subject sits up.
- Date, time of administration, amount and type of all opioid rescue medication taken during 72-hour postoperative period.
- Opioid prescription at discharge (Yes/No and if Yes, name of medication and number of units [eg, tablets, capsules] prescribed, dose, frequency, and route).

STUDY ENDPOINTS:

Primary Endpoint (Cohorts 1 and 2 only):

- Bupivacaine, meloxicam, DMSO, and TEG-POE water-soluble end product plasma and breast milk PK parameters.

Secondary Endpoints:

- Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), opioid-related adverse events (ORAEs), and potential LAST-related TEAEs.
- Change from baseline in clinical laboratory results.
- Change from baseline in vital signs.
- Wound healing assessment results at 24 hours, 72 hours, Day 7, Day 11, and Day 28.

Exploratory Endpoints:

- Mean area under the curve (AUC) of the NRS-R scores through 72 hours (AUC_{0-72}).
- Mean AUC_{0-72} of the NRS-A scores (Cohort 2 and Optional Cohort 3 only).
- Total postoperative opioid consumption (in IV morphine milligram equivalents [MME]) through 72 hours.
- Proportion of subjects who are opioid-free through 72 hours.
- Proportion of subjects who receive an opioid prescription at discharge.

STATISTICAL METHODS:

Determination of Sample Size: The sample size for each cohort was selected empirically without formal statistical assumptions.

Pharmacokinetic Analyses: Plasma and breast milk bupivacaine, meloxicam, DMSO, and TEG-POE water-soluble end products (PE, TEG, and TEG acid) concentrations will be determined in Cohorts 1 and 2 using validated liquid chromatography tandem-mass spectrometry assays. The PK parameter estimates will be calculated using non-compartmental analysis, as appropriate, and summarized. PK parameters will include, but are not limited to, C_{max}, T_{max}, AUC_{last}, AUC_{inf}, $t_{½}$, $Ae_{x\text{-}y,milk}$, and $fe_{x\text{-}y,milk}$, as appropriate. PK blood samples may also be analyzed to evaluate other study drug components.

Safety Analyses: All safety data will be listed and summarized by timepoint; no statistical hypothesis testing will be performed. All TEAEs will be summarized by System Organ Class and Preferred Term. Incidence of TEAEs, SAEs, ORAEs, and potential LAST-related TEAEs will be summarized and presented in descending order of frequency. AEs leading to study withdrawal, if any, will be listed separately. Associated laboratory parameters such as hepatic profile, renal function, and hematology values will be grouped and presented together in summary tables. For each laboratory test, individual subject values will be listed and values outside of the standard reference range will be flagged. Changes from baseline in laboratory data and shifts in laboratory data, will be summarized. Abnormal vital sign values will be flagged and listed. Potential LAST assessment questionnaire and wound healing assessment results will be summarized.

Efficacy Analyses: The mean $AUC_{0\text{-}72}$ of the NRS-R scores (all cohorts) and NRS-A scores (Cohort 2 and Optional Cohort 3 only) will be summarized. The windowed worst observation carried forward (wWOCF) method will be implemented to account for the duration effect of opioid rescue medication. Total opioid consumption through 72 hours will be calculated in IV MME and summarized using descriptive statistics. Subjects who have a total MME postoperative opioid dose = 0 through 72 hours will be characterized as "opioid-free" through 72 hours. The proportion of subjects discharged with an opioid prescription will be summarized.

Interim Analysis: No formal interim analyses are planned; however, the data will be reviewed on an ongoing basis. After at least 6 subjects have been administered HTX-011 in Cohort 1 and completed the Day 16 Visit breast milk collection, the Sponsor will conduct an analysis of PK data. If there are sufficient breast milk and plasma data to fulfill the primary objective, the study may be stopped and no more subjects will be enrolled.

SCHEDULE OF EVENTS FOR COHORTS 1 AND 2

Assessments	Time Window	Screening	Day 1		Time After HTX-011 Administration*																						
					30 min	60 min	90 min	2h	4h	6h	8h	10h	12h	18h	24h	36h	48h	60h	72h	D5[a]	D6[a]	D7[b]	D8 to D10[a]	D11[b]	D16[c]	D28	ET[d]
		≤28 days	Pre op	OR	±5 min	±5 min	±10 min	±15 min	±15 min	±15 min	±30 min	±30 min	±30 min	±30 min	±1h	±2h	±2h	±2h	±2h						±1d	±4d	
Obtain informed consent		X																									
Urine drug screen[e]		X	X																								
Assess/confirm eligibility		X	X																								
Medical history		X																									
Demographics		X																									
Physical examination[f]		X																	X								X[g]
Subject training for pain assessments		X	X																								
Vital signs		X	X		X	X	X	X	X		X		X	X	X	X	X	X	X							X	X
12-lead ECG (triplicate)		X																	X								X[g]
Hematology and serum chemistry		X													X[h]				X					X			X[i]
Scheduled MMA regimen (Cohort 2 only)[j]			X		- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	▶							
Surgery[k]				X																							
Newborn status[l]				X																							
Administer HTX-011[m]				X																							
Record opioid medication use[n]					- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	▶								
Discharge subject[o]																			X								
Record if opioid prescription at discharge																			X								
LAST questionnaire[p]					X	X		X	X					X	X				X								X[g]
Pain assessment (NRS-R)[q]						X		X	X		X		X		X	X	X	X	X								X[g]
Pain assessment (NRS-A) (Cohort 2 only)[r]						X		X	X		X		X		X	X	X	X	X								X[g]
Blood sample for PK analysis (Cohort 1)			X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[s]

Assessments	Time Window	Screening	Day 1		Time After HTX-011 Administration*																					
					30 min	60 min	90 min	2h	4h	6h	8h	10h	12h	18h	24h	36h	48h	60h	72h	D5[a]	D6[a]	D7[b]	D8 to D10[a]	D11[b]	D16[c]	D28
		≤28 days	Preop	OR	±5 min	±5 min	±10 min	±15 min	±15 min	±15 min	±30 min	±30 min	±30 min	±30 min	±1h	±2h	±2h	±2h	±2h						±1d	±4d	ET[d]
Blood sample for PK analysis (Cohort 2)			X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X[i]
Breast milk expression and collection (Cohort 1)[t]				- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - - ▶	X		X[s]
Breast milk expression and collection (Cohort 2)[t]				- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - - ▶			X[i]
Wound healing assessment[u]															X				X			X		X		X	X
Concomitant medications[v]		- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - - ▶	X
Adverse events[w]		- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - - ▶	X

Abbreviations: AE, adverse event; d, day; D, day; ECG, electrocardiogram; ET, Early Termination; h, hour(s); ICF, informed consent form; LAST, local anesthetic systemic toxicity; min, minute(s); MMA, multimodal analgesic; NRS-A, numeric rating scale of pain intensity with activity; NRS-R, numeric rating scale of pain intensity at rest; OR, operating room; PK, pharmacokinetic; PO, oral; Preop, preoperative period; TEAE, treatment-emergent adverse event.

*The start of HTX-011 administration will be considered as Time 0 for all PK, safety, and efficacy assessments. For assessments at timepoints when the subject is asleep, an attempt will be made to wake the subject. If there is no response, the assessments at these timepoints may be recorded as "Not Done." Assessments that can be done without waking the subject (eg, blood collection for PK analysis) will be completed. When blood sample collection and NRS-R assessments coincide, the NRS-R assessment should be conducted before the blood draw. See Section 6 for more information on study procedures and assessments.

[a] After discharge from the study site, a visiting healthcare professional will visit the subject once a day on Days 5, 6, 8, 9, and 10 to collect breast milk samples and blood samples for PK analyses.

[b] On Day 7 and Day 11, the visiting healthcare professional will visit the subject to collect only the breast milk samples. The subject will return to the study site that day for additional assessments.

[c] In Cohort 1 only, the visiting healthcare professional will visit the subject on the Day 16 Visit to collect a final blood sample and final expressed breast milk sample for PK analyses.

[d] Subjects who receive HTX-011 but withdraw from the study will be asked to complete Early Termination procedures based on the timing of withdrawal.

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

[f] Includes height and weight.

[g] Conducted only if subject withdraws prior to 72 hours after HTX-011 administration.

[h] Hematology only.

[i] Conducted only if subject withdraws prior to Day 11.

[j] A scheduled, non-opioid MMA regimen will administered in Cohort 2 while subjects are awake. The regimen will be initiated prior to surgery and will continue through Day 6 after surgery. Approximately 2 hours prior to the start of anesthesia, PO acetaminophen 975 mg to 1 g will be administered. After surgery, the MMA regimen will consist of PO acetaminophen 975 mg to 1 g every 6 hours alternating with PO ibuprofen 400 mg every 6 hours, so that an analgesic is taken approximately every 3 hours. The first dose will be administered once the subject is able to tolerate PO intake. After Day 6, subjects may continue one or both of the MMA medications as needed, but should not exceed ibuprofen 600 mg every 6 hours or acetaminophen 1 g every 6 hours (maximum ibuprofen dose of 2.4 g/day and maximum acetaminophen dose of 4 g/day).

[k] In Cohort 1, surgery will be performed under ropivacaine spinal anesthesia. In Cohort 2, surgery will be performed under spinal anesthesia with ropivacaine up to 20 mg, intrathecal Duramorph 50 µg, and intrathecal fentanyl 20 µg. In all cohorts, the start and stop times of surgery and the length of the surgical (ie, skin) incision will be recorded. The time of clamping of the umbilical cord will also be recorded.

[l] Information relating to the outcome of this pregnancy and health status of the newborn will be collected.

[m] A single dose of HTX-011 300 mg/9 mg (Cohort 1) or 400 mg/12 mg (Cohort 2) will be administered using a Luer lock applicator after delivery of the newborn baby. Prior to application of HTX-011, the uterine incision and parietal peritoneum must be sutured closed. Then following irrigation and suction and prior to closure of each subsequent layer, HTX-011 will be applied to the pain generating tissues. HTX-011 must not be instilled directly in or on the uterus or the uterine incision. Note: Subjects who experience a clinically significant event during surgery (eg, excessive bleeding, hemodynamic instability) that would render the subject medically unstable or complicate their postoperative course must not receive study drug and will be withdrawn from the study.

[n] If a subject requires rescue medication before the 60-minute pain intensity assessments, then an unscheduled NRS-R score (Cohorts 1 and 2) followed by an NRS-A score (Cohort 2 only) must be obtained before administering the first dose of rescue medication. These do not replace the 60-minute pain assessment(s).

[o] Subjects may be discharged if medically ready. At discharge, sites will provide subjects in Cohort 2 with instructions for following their MMA regimen through Day 6.

[p] Subjects will be monitored for any signs and symptoms of potential LAST using the LAST questionnaire (Appendix B). If potential signs and symptoms of LAST are observed, then vital sign measurements, 12-lead ECG, and blood sample collection for PK analysis must promptly be performed. If symptoms are present at a timepoint when 1 of these assessments is not scheduled, an unscheduled assessment must be performed. All potential signs and symptoms of LAST must be assessed by the Investigator and recorded as TEAEs if deemed clinically significant. If a TEAE potentially attributable to LAST is severe, regardless of relationship to study drug, then the Investigator must notify the Sponsor within 24 hours of becoming aware.

[q] NRS-R should be assessed while the subject is recumbent or lying supine (Appendix D). Measurements should be obtained after the subject has been in the resting position for at least 5 minutes.

[r] In Cohort 2, NRS-A will be assessed after NRS-R assessments have been completed. For NRS-A assessments, subjects should be in a resting position and instructed to sit up. Measurements should be obtained as soon as the subject sits up (Appendix D).

[s] Conducted only if subject withdraws prior to the Day 16 Visit sample collection.

[t] Subjects should express breast milk as often as needed to establish and maintain a milk supply. Subjects will be provided with instructions on expressing and storing (after discharged from the study site) breast milk samples. Subjects will record the start time and total number of breast milk samples collected in a breast milk log. The Laboratory Manual includes instructions on handling breast milk samples.

[u] Wound healing will be assessed using the Southampton Wound Scoring System (Appendix C). The 24-hour wound healing assessment will be performed unless clinically contraindicated.

[v] All medications taken by subjects between signing the ICF and the Day 28 Visit will be recorded.

[w] All AEs, regardless of causality or seriousness, will be recorded from the time the subject signs the ICF through the Day 28 Visit.

SCHEDULE OF EVENTS FOR OPTIONAL COHORT 3

Assessments	Time Window	Screening	Day 1		Time After HTX-011 Administration*																		
					30 min	60 min	90 min	2h	4h	6h	8h	10h	12h	18h	24h	36h	48h	60h	72h	D6[a]	D7	D11	D28	ET[b]
		≤28 days	Pre op	OR	±5 min	±5 min	±10 min	±15 min	±15 min	±15 min	±30 min	±30 min	±30 min	±30 min	±1h	±2h	±2h	±2h	±2h				±4d	
Obtain informed consent		X																						
Urine drug screen[c]		X	X																					
Assess/confirm eligibility		X	X																					
Medical history		X																						
Demographics		X																						
Physical examination[d]		X																	X					X[e]
Subject training for pain assessments		X	X																					
Vital signs		X	X		X	X	X	X	X		X		X	X	X	X	X	X	X				X	X
12-lead ECG (triplicate)		X																	X					X[e]
Hematology and serum chemistry		X													X[f]				X			X		X[g]
Scheduled MMA regimen[h]			X		- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	→				
Surgery[i]				X																				
Newborn status[j]				X																				
Administer HTX-011[k]				X																				
Record opioid medication use[l]					- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	→				
Discharge subject[m]																			X					
Record if opioid prescription at discharge																			X					
LAST questionnaire[n]					X	X		X	X					X	X				X					X[e]
Pain assessment (NRS-R)[o]						X		X	X		X		X		X	X	X	X	X					X[e]
Pain assessment (NRS-A)[p]						X		X	X		X		X		X	X	X	X	X					X[e]
Wound healing assessment[q]															X				X		X	X	X	X
Concomitant medications[r]		- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	→	X
Adverse events[s]		- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	→	X

Abbreviations: AE, adverse event; d, day; D, day; ECG, electrocardiogram; ET, Early Termination; h, hour(s); ICF, informed consent form; LAST, local anesthetic systemic toxicity; min, minute(s); MMA, multimodal analgesic; NRS-A, numeric rating scale of pain intensity with activity; NRS-R, numeric rating scale of pain intensity at rest; OR, operating room; PO, oral; postop, postoperative; Preop, preoperative period; TEAE, treatment-emergent adverse event.

*The start of HTX-011 administration will be considered as Time 0 for all safety and efficacy assessments. For assessments at timepoints when the subject is asleep, an attempt will be made to wake the subject. If there is no response, the assessments at these timepoints may be recorded as "Not Done." Assessments that can be done without waking the subject (eg, blood collection for hematology) will be completed. When blood sample collection and NRS assessments coincide, the NRS assessments should be conducted before the blood draw. See Section 6 for more information on study procedures and assessments.

[a] Day 6 is not a site visit.

[b] Subjects who receive HTX-011 but withdraw from the study will be asked to complete Early Termination procedures based on the timing of withdrawal.

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

[d] Includes height and weight.

[e] Conducted only if subject withdraws prior to 72 hours after HTX-011 administration.

[f] Hematology only.

[g] Conducted only if subject withdraws prior to Day 11.

[h] A scheduled, non-opioid MMA regimen will administered while subjects are awake. The regimen will be initiated prior to surgery and will continue through Day 6 after surgery. Approximately 2 hours prior to the start of anesthesia, PO acetaminophen 975 mg to 1 g will be administered. After surgery, the MMA regimen will consist of PO acetaminophen 975 mg to 1 g every 6 hours alternating with PO ibuprofen 400 mg every 6 hours, so that an analgesic is taken approximately every 3 hours. The first dose will be administered once the subject is able to tolerate PO intake. After Day 6, subjects may continue one or both of the MMA medications as needed, but should not exceed ibuprofen 600 mg every 6 hours or acetaminophen 1 g every 6 hours (maximum ibuprofen dose of 2.4 g/day and maximum acetaminophen dose of 4 g/day).

[i] Surgery will be performed under spinal anesthesia with ropivacaine up to 20 mg, intrathecal Duramorph 50 to 200 µg, and intrathecal fentanyl 20 µg. The start and stop times of surgery and the length of the surgical (ie, skin) incision will be recorded. The time of clamping of the umbilical cord will also be recorded.

[j] Information relating to the outcome of this pregnancy and health status of the newborn will be collected.

[k] A single dose of HTX-011 400 mg/12 mg will be administered using a Luer lock applicator after delivery of the newborn baby. Prior to application of HTX-011, the uterine incision and parietal peritoneum must be sutured closed. Then following irrigation and suction and prior to closure of each subsequent layer, HTX-011 will be applied to the pain generating tissues. HTX-011 must not be instilled directly in or on the uterus or the uterine incision. Note: Subjects who experience a clinically significant event during surgery (eg, excessive bleeding, hemodynamic instability) that would render the subject medically unstable or complicate their postoperative course must not receive study drug and will be withdrawn from the study.

[l] If a subject requires rescue medication before the 60-minute pain intensity assessments, then an unscheduled NRS-R score followed by an NRS-A score must be obtained before administering the first dose of rescue medication. These do not replace the 60-minute pain assessment(s).

[m] Subjects may be discharged if medically ready. At discharge, sites will provide subjects with instructions for following their MMA regimen through Day 6.

[n] Subjects will be monitored for any signs and symptoms of potential LAST using the LAST questionnaire (Appendix B). If potential signs and symptoms of LAST are observed, then vital sign measurements, 12-lead ECG, and blood sample collection for PK analysis must promptly be performed. If symptoms are present at a timepoint when 1 of these assessments is not scheduled, an unscheduled assessment must be performed. All potential signs and symptoms of LAST must be assessed by the Investigator and recorded as TEAEs if deemed clinically significant. If a TEAE potentially attributable to LAST is severe, regardless of relationship to study drug, then the Investigator must notify the Sponsor within 24 hours of becoming aware.

[o] NRS-R should be assessed while the subject is recumbent or lying supine (Appendix D). Measurements should be obtained after the subject has been in the resting position for at least 5 minutes.

[p] NRS-A should be assessed after NRS-R assessments have been completed. For NRS-A assessments, subjects should be in a resting position and then instructed to sit up. Measurements should be obtained as soon as the subject sits up (Appendix D).

[q] Wound healing will be assessed using the Southampton Wound Scoring System (Appendix C). The 24-hour assessment will be performed unless clinically contraindicated.

[r] All medications taken by subjects between signing the ICF and the Day 28 Visit will be recorded.

[s] All AEs, regardless of causality or seriousness, will be recorded from the time the subject signs the ICF through the Day 28 Visit.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
$A_{ex\text{-}y,milk}$	Amount of analyte excreted (Ae) in breast milk from time x to y hours
ALT	Alanine aminotransferase
ASA	American Society of Anesthesiologists
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}72}$	AUC of the NRS score through 72 hours
AUC_{last}	Area under the concentration-time curve from Time 0 to time of last quantifiable concentration
AUC_{inf}	Area under the concentration-time curve from Time 0 extrapolated to infinity
CFR	Code of Federal Regulations
C_{max}	Maximum plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
COX-2	Cyclooxygenase-2
C-section	Caesarean section
CV	Cardiovascular
DMSO	Dimethyl sulfoxide
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration
$fe_{x\text{-}y,milk}$	Fraction of dose excreted in breast milk from time x to y hours
GCP	Good Clinical Practice
GI	Gastrointestinal
GPP	Good Publication Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors

Abbreviation	Definition
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
LAST	Local anesthetic systemic toxicity
MMA	Multimodal analgesia(ic)
MME	Morphine milligram equivalent
NRS	Numeric rating scale of pain intensity
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
ORAE	Opioid-related adverse event
PE	Pentaerythritol
PK	Pharmacokinetic
PO	Oral
REB	Research Ethics Board
SAE	Serious adverse event
SAR	Serious adverse reaction
SJS	Stevens-Johnson Syndrome
SOP	Standard operating procedure
SNRI	Selective norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
$t_{½}$	Apparent terminal half-life
TEAE	Treatment-emergent adverse event
TEG	Triethylene glycol
TEG-POE	Tri(ethylene glycol) poly(orthoester) polymer
TEN	Toxic epidermal necrolysis
TKA	Total knee arthroplasty
T_{max}	Time to maximum plasma concentration
ULN	Upper limit of normal
US	United States
wWOCF	Windowed worst observation carried forward

Note: Abbreviations used only in tables, figures, or an appendix are defined in the table or figure footnotes or the appendix.

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 or ropivacaine) is a relatively simple and safe means of providing postoperative pain relief. A major limitation of most current local anesthetics is their short duration of effect (6 to 12 hours following surgery) (Kehlet 2011). Consequently, many patients are given opioids to manage pain. The requirement for opioids postoperatively is a manifestation of ineffective pain control. Reduced exposure to opioids and better pain management is associated with improved patient outcomes and reduced risk for the development of persistent pain and chronic opioid use and abuse (Barnett 2017). Therefore, there is a medical need for clinical alternatives to prescription opioids to manage postoperative acute pain. Neuraxial pain relief after Caesarean section (C-section) is relatively common (Jacques 2013; Jolly 2015; Lavoie 2013; Orbach-Zinger 2014); however, this is not a universally utilized approach (McDonnell 2009; Verstraete 2012). One in 300 opioid-naive patients exposed to opioids after cesarean birth will become persistent users of opioids (Bateman 2016). Numerous studies have sought to identify effective postpartum analgesic pharmacotherapies that avoid or require less opioid consumption (Carvalho 2017; Lavoie 2013; McDonnell 2009; Nauta 2009; Sutton 2017; Verstraete 2012; Zeng 2016). The development of an extended-release local anesthetic applicable for a broad range of surgeries that could significantly reduce both pain and opioid use after surgery and can be easily administered with a favorable safety profile would address an important public health need.

Heron Therapeutics, Inc. (Heron) has developed HTX-011 for application into the surgical site to reduce postoperative pain through 72 hours and the need for opioid analgesics. HTX-011 is a novel, extended-release, fixed-dose combination product that contains bupivacaine and low-dose meloxicam. Bupivacaine is the disease-active ingredient and meloxicam enhances the effectiveness of bupivacaine.

HTX-011 is a solution that is formulated in a proprietary tri(ethylene glycol) poly(orthoester) polymer (TEG-POE), termed Biochronomer®. It is administered as a single dose that is applied into the surgical site to coat the affected tissues. After administration, the polymer enables extended release of bupivacaine and meloxicam simultaneously for approximately 3 days, and the TEG-POE breaks down into water-soluble end products that are excreted. The extended release is achieved using a proprietary vehicle formulation consisting of TEG-POE in combination with different excipients approved for human use (dimethyl sulfoxide [DMSO], glycerol triacetate [triacetin], and maleic acid).

Bupivacaine HCl is a long acting, immediate-release, local anesthetic and meloxicam is a nonsteroidal anti-inflammatory drug (NSAID). Both have been approved by the United States (US) Food and Drug Administration (FDA) and in many countries outside the US, and have a long history of clinical use. Bupivacaine is available as a solution for injection and is approved for surgical anesthesia and for acute pain management (nerve block) in adults and children (MARCAINE USPI 2018). Meloxicam is available as a tablet for oral (PO) use and approved for

short-term symptomatic treatment of exacerbations of osteoarthrosis and long-term symptomatic treatment of rheumatoid arthritis or ankylosing spondylitis in adults (MOBIC USPI 2018).

This is a Phase 2, open-label, multi-cohort study of HTX-011 administered postpartum either alone or as part of a scheduled, non-opioid multimodal analgesic (MMA) regimen in women undergoing a planned C-section. HTX-011 will be administered after delivery of the newborn baby and closure of the uterine incision and just before wound closure, after final irrigation and suction of each layer. Bupivacaine is known to be excreted in human milk (MARCAINE USPI 2018), and although no data are available on the presence of meloxicam in human milk (MOBIC USPI 2018), some data exist for several other NSAIDs (Spigset 2000). Therefore, the primary objective of this study is to measure concentrations of bupivacaine, meloxicam, DMSO, and TEG-POE water-soluble end products in expressed breast milk and plasma from women undergoing a planned C-section who have received a single dose of HTX-011 postpartum. In addition, the concentration profiles of DMSO and the TEG-POE water-soluble end products, if any, in breast milk, will help determine if further investigations are warranted. Moreover, if DMSO and/or TEG-POE water-soluble end products are found in breast milk, the concentration data will help determine the ideal timing of breast-feeding relative to maternal dosing and dosage, including the duration recommended for discarding breast milk, and, when breast-feeding can be initiated relative to maternal HTX-011 dose or exposure. The study will also assess safety and analgesic efficacy.

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

C-section parturients need to achieve rapid optimum postoperative pain relief because of the need for expeditious recovery to enable them to care for their newborns within a few hours following surgery. It is of paramount importance that these mothers are provided with safe and effective postoperative analgesia that does not interfere with their ability to care for the infant (Fahey 2017), and the postoperative analgesia regimen should not have adverse effects on neonates who will be breast-fed.

Because of the route and timing of HTX-011 administration, neonatal exposure to bupivacaine, meloxicam, and the TEG-POE water-soluble end products is only possible through breast milk. The purpose of this study is to determine the extent to which the potential transfer of bupivacaine, meloxicam, DMSO, and TEG-POE water-soluble end products to breast milk occurs after a single dose of HTX-011, administered near the end of a C-section procedure. Safety and analgesic efficacy will also be evaluated.

This will be an open-label study, as all subjects will be administered HTX-011. HTX-011 has been studied at doses up to 600 mg/18 mg. Randomized controlled studies have evaluated HTX-011 up to 400 mg/12 mg and demonstrated a safety profile similar to bupivacaine HCl and saline placebo. This study will include up to 3 cohorts. Subjects in Cohort 1 will receive HTX-011 300 mg/9 mg. Subjects in Cohort 2 will receive HTX-011 400 mg/12 mg, the proposed maximum dose of HTX-011. Subjects in Cohort 2 will also be administered a scheduled, non-opioid background MMA regimen consisting of acetaminophen and an NSAID (ibuprofen) consistent with recommendations by the American College of Obstetricians and Gynecologists (ACOG 2018). Based on the results of Cohort 2, an optional dose-expansion cohort (Optional Cohort 3) may be conducted to further evaluate the safety and efficacy of HTX-011 400 mg/12 mg and a scheduled, non-opioid MMA regimen.

Plasma and breast milk samples will be collected from subjects in Cohorts 1 and 2 to determine the concentration of bupivacaine and meloxicam. Based on known plasma pharmacokinetic (PK) profiles of the TEG-POE water-soluble end products from a healthy volunteer study (Study 102), collection of breast milk and plasma samples in this study was planned up to an estimated 336 hours after HTX-011 administration in Cohort 1 to confirm that very little or none of the end products are present in the breast milk at this time. An interim analysis of PK data from Cohort 1 demonstrated that bupivacaine, meloxicam, DMSO, and the TEG-POE water-soluble end products were not detectable in breast milk beyond 156 hours. Based on this, PK samples will be collected in Cohort 2 through Day 11 and will not be collected on Day 16.

Safety assessments in this study are considered standard for clinical studies. Evaluations will include adverse event (AE) recording, electrocardiograms (ECGs), physical examinations, vital signs, hematology and serum chemistry, and wound healing assessments. Because local anesthetic systemic toxicity (LAST) has been associated with high bupivacaine blood concentrations, a LAST assessment questionnaire will be used to monitor for signs and symptoms potentially attributable to LAST.

Pain intensity will be assessed using the numeric rating scale of pain intensity (NRS), a validated tool for assessing pain (Breivik 2008; Safikhani 2018). Pain will be assessed at rest in all cohorts and with activity in Cohort 2 and Optional Cohort 3. The prescribed activity (sitting up from a resting position) reflects a simple daily activity for patients and has been used in C-section studies reported in the literature (Prabhu 2018). The efficacy endpoints are consistent with recommendations in the FDA Clinical Outcome Assessment Compendium (FDA 2019). Given the concern with postoperative opioid use on patient outcomes as well as the risk of long-term use and abuse, the study also includes endpoints to evaluate opioid use.

1.3. Potential Risks and Benefits

1.3.1. HTX-011

As of 27 September 2019, a total of 1,362 adult subjects (1,352 undergoing surgery and 10 healthy volunteers) have received HTX-011 as a single dose ranging from 30 mg/0.9 mg to 600 mg/18 mg via instillation and/or injection into the surgical site or via nerve block (including Mayo block) across 12 clinical studies.

There are no available human data on the presence of meloxicam or water-soluble end products of the HTX-011 polymer in human milk or on their effects on milk production or the breastfed infant. Limited published literature reports that bupivacaine and its primary metabolite, pipecoloxylidine, are present in human milk at low levels. There is no available information on effects of the bupivacaine in the breastfed infant or effects of the drug on milk production.

1.3.1.1. Safety

Safety data from 504 subjects who received HTX-011 via instillation into the surgical site in two Phase 3 studies (Study 301 in bunionectomy and Study 302 in herniorrhaphy) and two Phase 2b studies (Study 209 in total knee arthroplasty [TKA] and Study 211 in augmentation mammoplasty) were pooled for analysis. Results from these studies revealed that the safety profile of a single dose of HTX-011 was similar to the well-established safety profile of bupivacaine HCl. The types of treatment-emergent adverse events (TEAEs) reported for

HTX-011 were generally similar across studies; the most common TEAEs were nausea, constipation, dizziness, vomiting, and headache. These TEAEs were also the most common TEAEs in the saline placebo and bupivacaine HCl groups. Of these 5 most common TEAEs, those with an incidence higher in the HTX-011 group than in the saline placebo group were constipation (17.3% vs 14.6%), vomiting (16.9% vs 15.0%), and headache (11.7% vs 8.9%). The majority of TEAEs were mild or moderate in severity. The incidence of severe TEAEs was low and similar across all treatment groups.

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

Serious Adverse Events

As of 23 October 2019, no deaths were reported for subjects who received HTX-011. The incidence of serious adverse events (SAEs) in subjects who received HTX-011 was low (1.5%) and was similar to saline placebo (1.2%) and bupivacaine HCl. (2.2%). A total of 3 serious adverse reactions (SARs; SAEs considered related to study drug by the Investigator and/or the Sponsor) have been reported in 3 subjects who received HTX-011. One SAR of severe impaired healing was reported in a subject who received HTX-011 200 mg/6 mg via injection using a Mayo block in the bunionectomy study (Study 208), 1 SAR of mild wound dehiscence was reported in a subject who received HTX-011 300 mg/9 mg via combination (injection and instillation) administration technique in the abdominoplasty study (Study 203), and 1 SAR of moderate post procedural cellulitis was reported in a subject who received HTX-011 400 mg/12 mg instillation + 50 mg ropivacaine in the TKA study (Study 209). All 3 SARs resolved; the 1 SAR of impaired healing resolved with sequelae (nonserious).

1.3.1.2. Efficacy

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

1.3.1.3. Potential Risks Associated With HTX-011

An identified risk for HTX-011 is incision site erythema, which was observed primarily in bunionectomy. Most events were self-limiting, mild or moderate in severity, and resolved without intervention or sequelae. Use of HTX-011 in subjects with allergies to or hypersensitivity to bupivacaine, meloxicam, or any of the components of HTX-011 is contraindicated.

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

1.3.1.4. Potential Risks Associated With Bupivacaine

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

1.3.1.5. Potential Risks Associated With Meloxicam

Potential risks for meloxicam include the common AEs (≥5% and greater than placebo) of diarrhea, upper respiratory tract infections, dyspepsia, and influenza-like symptoms (MOBIC USPI 2018). Other potential risks for meloxicam include CV adverse reactions, gastrointestinal (GI) bleeding, and abnormal liver tests . NSAIDs may cause an increased risk of serious CV thrombotic events, myocardial infarction, and stroke, which can be fatal. Patients with known CV disease or risk factors for CV disease may be at greater risk. NSAIDs may also cause an increased risk of serious GI AEs including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach or intestines, which can be fatal. Patients with a prior history of peptic ulcer disease and/or GI bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Elderly patients are at greater risk for serious GI events. Elevations of 1 or more liver tests may occur in patients taking NSAIDs, including meloxicam. Exacerbation of asthma related to aspirin sensitivity, reduction in renal blood flow, and renal toxicity are reported risks after exposure to NSAIDs. Serious skin AEs such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal, can occur without warning. It is unclear how applicable these potential risks are for meloxicam when given as single dose via instillation into the surgical site (a novel administration method for meloxicam) for postoperative pain as part of a fixed-dose combination (eg, HTX-011).

1.3.2. Potential Risks With Other Protocol-Specified Medications

Common, as well as uncommon but severe, adverse drug reactions that are associated with 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. Opioid Medications

Opioids have the risk of addiction, abuse, and misuse, which can lead to overdose and death (DURAMORPH USPI 2019; Fentanyl Citrate USPI 2012; Morphine Sulfate Preservative-Free Injection USPI 2016; OXAYDO USPI 2018). Taking an opioid with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, respiratory depression (including serious, life-threatening and fatal respiratory depression), coma, and death. Opioids can cause sleep-related breathing disorders including central sleep apnea and sleep-related hypoxemia. Additional possible side effects include nausea, vomiting, tiredness, sleepiness, headache, dizziness, constipation including severe constipation, and abdominal pain. Other risks include skeletal muscle rigidity, skeletal muscle movement, CV depression, CV instability, severe hypotension, and adrenal insufficiency and, in subjects with seizure disorder, an increase in seizure activity. Use of opioids may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Fentanyl citrate injection and Duramorph could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Single-dose neuraxial administration of Duramorph/morphine sulfate may result in acute or delayed respiratory depression up to 24 hours. Use of an opioid in a subject already on a cytochrome P450 3A4 inhibitor or inducer may impact plasma concentrations and opioid adverse reactions. Use is contraindicated in subjects with significant respiratory depression, with acute or severe bronchial asthma, or with known or suspected GI obstruction.

1.3.2.2. Acetaminophen

Uncommon but severe adverse drug reactions with acetaminophen may include severe skin rash and liver failure (Acetaminophen Drug Facts 2015). Severe liver damage may occur if more than 4 g of acetaminophen is taken in 24 hours, if taken with other drugs containing acetaminophen, or if taken with 3 or more alcoholic drinks each day.

1.3.2.3. Ibuprofen

Ibuprofen may cause an increased risk of serious CV thrombotic events, myocardial infarction, and stroke, which can be fatal (Ibuprofen tablet USPI 2018). This risk may increase with duration of use. Patients with CV disease or risk factors for CV disease may be at greater risk. Ibuprofen may also cause an increased risk of serious GI AEs including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious GI events. Long-term administration has resulted in renal papillary necrosis and other renal injury. Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, such as ibuprofen. Notable elevations of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (approximately 3 or more times the upper limit of normal [ULN]) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice, fulminant hepatitis, liver necrosis, and hepatic failure, some of them with fatal outcomes have been reported. NSAIDs such as ibuprofen can cause serious skin adverse events such as exfoliative dermatitis, SJS, and TEN, which can be fatal. These serious events may occur without warning. Other drug reactions include hypertension, other CV events, fluid retention, edema, anemia, prolonged bleeding time, blurred

or diminished vision, scotomata, changes in color vision, and aseptic meningitis. Anaphylactoid reactions may occur in patients without known prior exposure to ibuprofen; as such, ibuprofen should not be administered to patients with aspirin sensitivity, and should be used with caution in patients with pre-existing asthma.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to characterize the PK of bupivacaine, meloxicam, DMSO, and HTX-011 TEG-POE water-soluble end products in expressed breast milk and plasma following postpartum administration of HTX-011 in women undergoing a planned C-section.

2.2. Secondary Objective

The secondary objective is to assess the safety and tolerability of HTX-011 administered alone or as part of a scheduled, non-opioid MMA regimen in this study population.

2.3. Exploratory Objective

The exploratory objective is to characterize the efficacy and duration of analgesia during the first 72 hours following administration of HTX-011 alone or as part of a scheduled, non-opioid MMA regimen in this study population.

3. INVESTIGATIONAL PLAN AND ENDPOINTS

3.1. Description of the Study Design

3.1.1. Overall Study Design

This is a Phase 2, open-label, multi-cohort study of HTX-011 administered postpartum either alone or as part of a scheduled, non-opioid MMA regimen in women undergoing a planned C-section procedure who must have chosen prospectively to not breast-feed their newborn. The study will include up to 3 cohorts. Cohorts will be conducted sequentially. In Cohort 1, subjects will receive HTX-011 300 mg/9 mg. In Cohort 2, subjects will receive HTX-011 400 mg/12 mg and a scheduled, non-opioid MMA regimen. PK (in expressed breast milk and plasma), safety, and efficacy will be assessed in Cohorts 1 and 2. An optional dose-expansion cohort (Optional Cohort 3) may be conducted after Cohort 2 to further evaluate the safety and efficacy of HTX-011 400 mg/12 mg and a scheduled, non-opioid MMA regimen. No PK assessments will be conducted in Optional Cohort 3.

3.1.1.1. Cohort 1

Approximately 15 subjects will be treated in Cohort 1. Subjects will be screened within 28 days prior to the planned surgery date. Subjects who meet all eligibility criteria will be enrolled and undergo a C-section under ropivacaine spinal anesthesia on Day 1. In addition to ropivacaine spinal anesthesia, management of intraoperative anesthesia will be in accordance with the prevailing institutional practice/anesthesiologist's preference as long as it does not include bupivacaine or meloxicam. After delivery of the newborn baby, all subjects will receive a single dose of HTX-011 300 mg/9 mg administered via instillation into the surgical site (Section 5.5).

3.1.1.2. Cohort 2

Up to approximately 12 subjects will be treated in Cohort 2 to ensure adequate breast milk collection in at least 6 subjects. Subjects will be screened within 28 days prior to the planned surgery date. On the day of surgery (Day 1), eligible subjects will be administered PO acetaminophen 975 mg to 1 g approximately 2 hours prior to the start of anesthesia. Subjects will undergo a C-section under spinal anesthesia with ropivacaine up to 20 mg, intrathecal morphine sulfate injection (DURAMORPH®) 50 µg, and intrathecal fentanyl 20 µg. After delivery of the newborn baby, all subjects will receive a single dose of HTX-011 400 mg/12 mg administered via instillation into the surgical site (Section 5.5).

Following surgery, subjects will receive a scheduled, non-opioid MMA regimen while awake during the first 5 days after surgery (ie, Days 1 through 6) consisting of PO acetaminophen 975 mg to 1 g every 6 hours alternating with PO ibuprofen 400 mg every 6 hours. The first postoperative MMA dose will be PO acetaminophen 975 mg to 1 g and will be administered once the subject is able to tolerate PO intake. Three hours after the acetaminophen MMA dose, the first dose of PO ibuprofen 400 mg will be administered. Thereafter, these 2 medications will be alternated so that an analgesic is taken approximately every 3 hours through Day 6 while the subject is awake. Upon waking from sleep, if they have missed an analgesic dose(s) (ie, if more than 3 hours has passed since taking their last pain medicine), they should immediately take the

first missed dose and restart the regimen "clock." After Day 6, subjects may continue one or both of the MMA medications as needed, but should not exceed ibuprofen 600 mg every 6 hours or acetaminophen 1 g every 6 hours (maximum ibuprofen dose of 2.4 g/day and maximum acetaminophen dose of 4 g/day).

3.1.1.3. Postoperative Follow Up for Cohorts 1 and 2

Subjects will remain in the hospital/research facility for a minimum of 72 hours after the start of HTX-011 administration to undergo postoperative assessments. Assessments include the collection of breast milk and blood samples for PK analyses and safety and efficacy assessments.

After the 72-hour postoperative procedures and assessments have been completed, subjects may be discharged in accordance with institutional practice/Investigator preference. Sites will record if subjects are discharged with an opioid prescription and information about the opioid prescription.

At discharge, each subject will be provided a breast milk log to record breast milk expression during the follow-up period. A visiting healthcare professional will visit each subject once a day on Days 5, 6, 8, 9, and 10 to collect breast milk and blood samples for PK analyses. On Day 7 and Day 11, a visiting healthcare professional will visit the subject to collect only the breast milk samples, and the subject will return to the study site that day to undergo additional assessments. In Cohort 1 only, a visiting healthcare professional will visit the subject on the Day 16 Visit to collect a final expressed breast milk sample and blood sample for PK analyses.

All subjects will return to the study site for a Day 28 Visit to undergo final study assessments.

3.1.1.4. Optional Cohort 3

After a review of data from Cohort 2, up to approximately 24 subjects may be treated in Optional Cohort 3. Subjects will undergo a C-section under spinal anesthesia with ropivacaine up to 20 mg, intrathecal Duramorph 50 to 200 μg, and intrathecal fentanyl 20 μg. Subjects will receive the same HTX-011 dose and scheduled, non-opioid MMA regimen as Cohort 2 (pre- and postoperatively), and will follow the same schedule of events as Cohort 2 with the exception of PK assessments. Breast milk and blood samples for PK analysis will not be collected in Optional Cohort 3.

3.1.2. Treatment Groups

- Cohort 1: Subjects will receive a single dose of HTX-011 300 mg/9 mg intraoperatively via instillation into the surgical site.
- Cohort 2: Subjects will receive a single dose of HTX-011 400 mg/12 mg intraoperatively via instillation into the surgical site as part of a scheduled, non-opioid MMA regimen consisting of ibuprofen and acetaminophen.
- Optional Cohort 3: Subjects will receive a single dose of HTX-011 400 mg/12 mg intraoperatively via instillation into the surgical site as part of a scheduled, non-opioid MMA regimen consisting of ibuprofen and acetaminophen.

3.1.3. Postoperative Rescue Medications

Subjects should receive analgesic medication only upon request for pain control, as needed, during the 72-hour postoperative observation period. Rescue medication should not be given for pain prophylaxis, but only for treating postoperative pain. Prior to the administration of the first dose of rescue medication, if the subject has not already had at least 1 postoperative pain score assessed, then an NRS score must be obtained. Subjects who are not medically ready for discharge at 72 hours may receive the same analgesic rescue medication as described below to treat postoperative pain until discharge.

3.1.3.1. Cohort 1 Rescue Medication

Postoperative rescue medication during the 72-hour postoperative period will comprise any 1 or more of the following medications as needed: PO ibuprofen ≤600 mg within a 6-hour period, PO/IV acetaminophen ≤1 gram (1,000 mg) within a 6-hour period, PO immediate-release oxycodone ≤5 mg within a 4-hour period, and IV morphine ≤10 mg within a 2-hour period. For subjects administered any acetaminophen-containing product, the total combined daily dose of acetaminophen must not exceed 4 grams (4,000 mg) in a 24-hour period. Combination products containing an opioid and non-opioid are not allowed. For subjects who are medically ready for discharge at 72 hours, their recommended analgesic medication after discharge will be in accordance with the prevailing institutional practice/Investigator preference; however, any drug formulation containing bupivacaine or meloxicam is prohibited through the Day 16 Visit.

3.1.3.2. Cohort 2 and Optional Cohort 3 Rescue Medication

Postoperative rescue medication during the 72-hour postoperative period will initially consist of ibuprofen 400 mg PO (in addition to the scheduled MMA regimen), which may be administered at most only once every 12 hours. If pain persists after approximately 30 minutes following ibuprofen rescue medication, the following rescue medications are permitted upon subject request for additional pain control: PO immediate-release oxycodone ≤5 mg within a 4-hour period and/or IV morphine ≤10 mg within a 2-hour period.

3.1.4. Postoperative Assessments

Safety and efficacy assessments will be performed in all cohorts. PK assessments will be performed in Cohorts 1 and 2 only.

PK assessments will include the collection of breast milk and blood samples for PK analysis of bupivacaine, meloxicam, DMSO, and HTX-011 TEG-POE polymer water-soluble end products (ie, pentaerythritol [PE], triethylene glycol [TEG], and TEG acid). PK blood samples may also be used to evaluate other study drug components.

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

Efficacy assessments will include evaluations of pain using the numeric rating scale of pain intensity at rest (NRS-R [all cohorts]) and with activity (NRS-A [Cohort 2 and Optional Cohort 3]), use of opioid medication, and opioid prescription at discharge.

More information on study procedures and assessments are provided in Section 6. The timing of procedures and assessments are provided in the SCHEDULE OF EVENTS FOR COHORTS 1 AND 2 table, SCHEDULE OF EVENTS FOR OPTIONAL COHORT 3 table, and Section 7.

3.2. Study Endpoints

3.2.1. Primary Endpoint (Cohorts 1 and 2 Only)

Bupivacaine, meloxicam, DMSO, and TEG-POE water-soluble end product plasma and breast milk PK parameters.

3.2.2. Secondary Endpoints

The secondary endpoints are as follows:

- Incidence of TEAEs, SAEs, opioid-related adverse events (ORAEs), and potential LAST-related TEAEs.
- Change from baseline in clinical laboratory results.
- Change from baseline in vital signs.
- Wound healing assessment results at 24 hours, 72 hours, Day 7, Day 11, and Day 28.

3.2.3. Exploratory Endpoints

- Mean area under the curve (AUC) of the NRS-R scores through 72 hours (AUC_{0-72}).
- Mean AUC_{0-72} of the NRS-A scores (Cohort 2 and Optional Cohort 3 only).
- Total postoperative opioid consumption (in IV morphine milligram equivalents [MME]) through 72 hours.
- Proportion of subjects who are opioid-free through 72 hours.
- Proportion of subjects who receive an opioid prescription at discharge.

3.3. Study Duration

The total duration of study participation for each subject (from Screening through the Day 28 Visit) will be up to 60 days. The overall duration of the study is anticipated to be approximately 15 months.

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

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1. Study Population

Up to approximately 51 female subjects will be enrolled and dosed at up to approximately 10 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, adhere to the study visit schedule, and complete all study assessments.
2. Is 18 years of age or older at the time of Screening visit.
3. Is expected, at the time of Screening visit, to deliver a single neonate.
4. Is scheduled to undergo a planned C-section surgery with a low transverse skin incision (eg, Pfannenstiel).
5. Has American Society of Anesthesiologists (ASA) Physical Status of I, II, or III.
6. Agrees to practice abstinence or use double-barrier contraception in the event of sexual activity and commits to the use of an acceptable form of birth control for 30 days after HTX-011 administration.
7. Agrees to refrain from the use of breast milk from this pregnancy in any manner (including, but not limited to, breastfeeding, donation, sale, or storage for later use) for 28 days after HTX-011 administration.

4.1.2. Exclusion Criteria

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

1. Has planned to breastfeed her neonate at any time during the 28-day period after HTX-011 administration.
2. Planned C-section under general anesthesia.
3. Has had a prior full-term pregnancy with unsuccessful breast milk expression. (This criterion is not applicable to Optional Cohort 3).
4. Has a planned concurrent surgical procedure (with the exception of a tubal ligation), unless previously approved by the Sponsor.
5. Has a contraindication or a known or suspected history of hypersensitivity or clinically significant idiosyncratic reaction (including methemoglobinemia) to bupivacaine or ropivacaine (or other local anesthetics), meloxicam (or other NSAIDs), or to acetaminophen, morphine, or fentanyl (Cohort 2 and Optional Cohort 3 only).
6. Has been administered bupivacaine within 5 days prior to the scheduled surgery.

7. Has been administered any local anesthetic within 72 hours prior to the scheduled surgery, other than for pretreatment prior to a needle placement, to treat an AE that occurs after signing the informed consent form (ICF), or to decrease venous irritation (eg, caused by propofol, in which case, no more than a single dose of IV lidocaine 20 mg may be administered).
8. Has been administered systemic steroids within 5 half-lives or 10 days prior to administration of study drug (whichever is longer). Note that for purposes of this exclusion criterion, inhaled steroids are not considered systemic.
9. Has initiated treatment with any of the following medications within 1 month prior to study drug administration or is taking any of these medications to control pain: selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin, or cyclooxygenase-2 (COX-2) inhibitors. (Note: If a subject is taking one of these medications for a reason other than pain control, the subject must be on a stable scheduled dose [ie, not "as needed"] for at least 1 month prior to study drug administration.) Anxiolytics prior to surgery are permitted, if necessary.
10. Has taken NSAIDs (including meloxicam) within at least 10 days prior to surgery with the exception of subjects on low dose (≤100 mg) daily acetylsalicylic acid for cardioprotection.
11. Has current significant placental abnormality/complications including, but not limited to, placenta previa or placenta accreta.
12. Has a medical condition such that, in the opinion of the Investigator, participating in the study would pose a health risk to the subject or confound the postoperative assessments. Conditions may include, but are not limited to, any of the following:
    a. History of clinically significant cardiac abnormality such as myocardial infarction within 6 months prior to signing the ICF, New York Heart Association class III or IV, or clinically significant abnormalities of ECG or cardiac function.
    b. History of coronary artery bypass graft surgery within 12 months prior to signing the ICF.
    c. Severe liver function impairment as defined by Child-Pugh Class C, having an AST >3 × the ULN, or having an ALT >3 × ULN.
    d. Severe kidney function impairment as defined by creatinine clearance (Cockcroft Gault) <30 mL/min and/or being on dialysis.
    e. History of known or suspected coagulopathy or uncontrolled anticoagulation.
    f. Platelets <100,000/µL, hemoglobin <9.5 g/dL, or hematocrit <28%.
    g. Known history of glucose-6-phosphate dehydrogenase deficiency.
13. Has uncontrolled anxiety, psychiatric, or neurological disorder that might interfere with study assessments.
14. Has had a malignancy in the preceding last year before day of surgery, with the exception of nonmetastatic basal cell or squamous cell carcinoma of the skin or localized carcinoma in situ of the cervix.
15. Has a known or suspected history of drug abuse, or a positive urine drug test at the screening visit or on the day of surgery prior to the surgery, or a recent history of alcohol

abuse (ie, within 10 years). Note: Subjects with a positive urine drug test who are taking an allowed, prescribed medication that is known to result in a positive urine drug test (eg, amphetamine and/or dextroamphetamine for attention-deficit/hyperactivity disorder, benzodiazepine for anxiety disorder) may be eligible for participation in the study if approved by the Medical Monitor. Subjects taking any marijuana are not allowed to participate in the study.

16. Has previously participated in an HTX-011 study or received an investigational product or device in a clinical trial within 30 days or within 5 elimination half-lives (whichever is longer) before surgery, or is planning to take part in another clinical trial while participating in this study.
17. Weight is <50 kg at the time of Screening visit.
18. In the Investigator's judgment, subject is likely to have been morbidly obese prior to her pregnancy.

4.2. Method of Assigning Subjects to Treatment Groups

Subjects who meet the eligibility criteria (Section 4.1) will be enrolled and scheduled for surgery and study drug administration.

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

Subjects who fail to meet the eligibility criteria should not, under any circumstances, receive HTX-011.

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

4.3. Blinding

Not applicable because this is an open-label study.

4.4. Subject Withdrawal and Replacement

4.4.1. Subject Withdrawal

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

Possible reasons for early withdrawal include the following:

- AE.
- Withdrawal by subject.
- Death.

- Lost to follow-up.
- Investigator's decision.
- Sponsor's decision.
- Failure to meet 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 (Section 7.4).

If a subject withdraws early, the subject should be reminded not to breastfeed for 28 days after HTX-011 administration. If a subject withdraws early and gives their infant breast milk (breastfeeds or uses a bottle) before 28 days, the subject will be asked to consent to allow the Sponsor to follow the growth and development of the infant for 2 months following HTX-011 administration.

4.4.2. Subject Replacement

Subjects who are eligible but withdraw before dosing will be replaced until enrollment is complete.

5. STUDY TREATMENT

All subjects will receive a single dose of study drug intraoperatively while undergoing a C-section. Study drug is defined as HTX-011 (investigational product).

HTX-011 will be supplied by the Sponsor.

5.1. Description of Investigational Product

HTX-011 is a clear, pale yellow to yellow, viscous liquid supplied in single-dose glass vials. The vials serve only as a closed container for the drug product. For administration of study drug, the contents in the vials will be aseptically transferred to sterile syringes without needles as described in the Pharmacy Manual.

5.2. Manufacturing, Packaging, and Labeling

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

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

5.3. Storage

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

5.4. Preparation

HTX-011 will be prepared at the study site. HTX-011 will be prepared in syringes without a needle. Refer to the Pharmacy Manual for details on the study drug preparation.

5.5. Study Drug Administration

A single dose of HTX-011 will be administered into the surgical site using a Luer lock applicator after delivery of the newborn baby. A dose of 300 mg/9 mg (10.5 mL withdrawn volume) will be administered in Cohort 1 and 400 mg/12 mg (14 mL withdrawn volume) will be administered in Cohort 2 and Optional Cohort 3. Prior to application of HTX-011, the uterine incision and parietal peritoneum must be sutured closed. Then following irrigation and suction and prior to closure of each subsequent layer, HTX-011 will be applied to the pain generating tissues. HTX-011 must not be instilled directly in or on the uterus or the uterine incision. A complete description of study drug administration is provided in the Pharmacy Manual.

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

5.6. Study Drug Compliance

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

5.7. Study Drug Accountability

HTX-011 provided for this study will be used only as directed in the study protocol. In accordance with Good Clinical Practice (GCP), Investigators are required to maintain accurate and up-to-date records of all study drug to permit reconciliation. The Investigator or designee must maintain adequate records of distribution, including the date received, number and units received, and 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 clinical monitor and/or auditor. The 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.

6. STUDY PROCEDURES AND ASSESSMENTS

The following sections describe the study procedures and assessments that will be performed during the study. The timing of procedures and assessments is provided in Section 7, the SCHEDULE OF EVENTS FOR COHORTS 1 AND 2 table, and the SCHEDULE OF EVENTS FOR OPTIONAL COHORT 3 table.

6.1. Medical History and Demographics

6.1.1. Medical History

A complete medical history will be obtained before enrollment to ensure subjects qualify for the study. Medical history will be obtained through subject interview. A review of the subject's medical records from their primary care physician is recommended. Data collected will include medical and surgical history. Information on any previous pregnancy(ies), including number and outcomes, will be collected on the pregnancy eCRF.

6.1.2. Newborn Status

The following information relating to the outcome of this pregnancy and health status of the newborn will be collected:

- Defects detected in prenatal testing.
- Neonatal status at birth (normal/abnormal).
- Gestational weeks at birth.
- Length, weight, head circumference.
- Apgar score at 1 minute and 5 minutes.
- Resuscitation required (yes/no).
- Intensive care admission (yes/no).

6.1.3. Demographics

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

6.2. Prior and Concomitant Therapy

All medications taken by subjects between signing the ICF and the Day 28 Visit will be recorded. The dosing regimen of "prn" should not be recorded on the eCRF.

During the 72-hour postoperative period, the name, dose, and route, as well as the start date and time, of concomitant medications must be recorded. Medications include prescription or over-the-counter medications (including herbal products and vitamins). For subjects entering on a stable dose of permitted medication, any change in dose should also be recorded.

Notes: All medications received during this 72-hour period must have a start time recorded. IV fluids and oxygen used during surgery do not need to be recorded unless being used to treat an AE.

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.

In Cohort 1, subjects will undergo a C-section under ropivacaine spinal anesthesia on Day 1. In addition to ropivacaine spinal anesthesia, management of intraoperative anesthesia will be in accordance with the prevailing institutional practice/anesthesiologist's preference as long as it does not include bupivacaine or meloxicam. In Cohort 2 and Optional Cohort 3, C-sections will be performed under spinal anesthesia with ropivacaine (up to 20 mg), intrathecal Duramorph (50 µg in Cohort 2 and 50 to 200 µg in Optional Cohort 3), and intrathecal fentanyl 20 µg.

Information on analgesic medications permitted during the 72-hour postoperative period and after discharge is provided in Section 3.1.3.

6.2.2. Prohibited Medications

6.2.2.1. Medications Prohibited Prior to Surgery

Refer to exclusion criteria 6 through 10 and 15 for medications that are prohibited prior to the scheduled surgery (Section 4.1.2).

Note: Other than HTX-011, any drug formulation containing bupivacaine or meloxicam is prohibited before surgery (within 5 days for bupivacaine and within 10 days for meloxicam).

6.2.2.2. Medications Prohibited During Surgery and From Time 0 Through Day 16 Visit

General anesthesia is not permitted as a preplanned component of surgery. If unexpected intraoperative findings require conversion to general anesthesia, then the subject must not receive HTX-011 and must be withdrawn immediately from participation in the study. Bupivacaine and meloxicam are also not permitted as part of intraoperative anesthesia management.

With the exception of rescue medications specified in Section 3.1.3 and the MMA regimen for Cohort 2 (and Optional Cohort 3) outlined in Section 3.1.1.2, no other analgesic agents are permitted during the 72-hour postoperative observation period, and any drug formulation containing bupivacaine or meloxicam is prohibited through the Day 16 Visit.

6.3. Pharmacokinetic Assessments (Cohorts 1 and 2 Only)

Expressed breast milk and blood samples will be collected from all subjects in Cohorts 1 and 2 to assess the PK profiles of bupivacaine, meloxicam, DMSO, and HTX-011 TEG-POE polymer water-soluble end products (PE, TEG, and TEG acid). PK blood samples may also be used to evaluate other study drug components.

6.3.1. Expressed Breast Milk Samples

Subjects will be provided with an electric breast pump for expression of breast milk. A specialized lactation consultant or nurse should be made available to assist and train the subjects on how to use the breast pump. In addition, the lactation consultant or nurse should counsel the subjects on the process of stopping lactation at the completion of study participation.

Subjects should express breast milk as often as needed during the study to establish and maintain a milk supply. Every time the subject expresses milk, both breasts should be emptied completely. Subjects will record the start time and total number of breast milk samples collected in a breast milk log.

Subjects will collect expressed breast milk samples postpartum through Day 11 (Cohorts 1 and 2), and on the Day 16 Visit (Cohort 1 only). (Note: some subjects may not be able to express milk during the first 72 hours). A visiting healthcare professional will visit the subject once a day after discharge through Day 11 to collect the expressed breast milk samples. A visiting healthcare professional will also visit the subject at the Day 16 Visit to collect a final expressed breast milk sample for PK analyses.

Subjects will be provided with instructions on expressing and storing (after discharged from the study site) breast milk samples. The Laboratory Manual includes instructions on the breast pump and handling breast milk samples.

6.3.2. Blood Samples

Blood samples for PK analysis will be collected at specified timepoints pre- and postoperatively (see the SCHEDULE OF EVENTS FOR COHORTS 1 AND 2 table for timepoints). After discharge, a visiting healthcare professional will visit each subject once a day on Days 5, 6, 8, 9, and 10 (Cohorts 1 and 2), and again on the Day 16 Visit (Cohort 1 only), to collect blood samples for PK analysis. On Day 7 and Day 11, blood sample collection for PK analysis will be at the study site.

Blood samples may be drawn using a properly maintained indwelling cannula.

Detailed instructions on sample collection, processing, storage, and shipping procedures are provided in the Laboratory Manual.

6.4. Safety Assessments

6.4.1. Adverse Events

All AEs regardless of causality or seriousness will be recorded from the time the subject signs the ICF through the Day 28 Visit. Additional safety information is provided in Section 8.

Any abnormal laboratory value, vital sign result, signs or symptoms of potential LAST, or wound healing assessment finding deemed clinically significant by the Investigator must be recorded as AE.

6.4.2. Local Anesthetic Systemic Toxicity Assessment

A LAST assessment questionnaire is provided (Appendix B) to monitor for neurologic and/or cardiac signs and symptoms potentially attributable to LAST, which include prodromal symptoms such as dizziness, tinnitus, metallic taste, and perioral numbness (Vasques 2015).

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

Signs and symptoms of potential LAST deemed clinically significant by the Investigator must be recorded as TEAEs. If a TEAE potentially attributable to LAST is severe, regardless of relationship to study drug, then the Investigator must notify the Sponsor **within 24 hours of becoming aware.**

6.4.3. Physical Examinations

Physical examination will include an evaluation of the following: head, eyes, ears, nose, and throat as well as CV, respiratory, GI, neurological, dermatological, and musculoskeletal systems. Height and weight will be recorded at the Screening Visit.

Abnormal physical examination findings will be evaluated for clinical significance. Any physical examination AEs that are considered serious, including those that may reflect endometritis in the postpartum period, must be reported to the Sponsor within 24 hours of first awareness and followed proactively.

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

6.4.4. Vital Signs

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

Vital signs should be promptly recorded for subjects who have signs or symptoms that may be attributed to LAST (see Section 6.4.2).

6.4.5. 12-Lead Electrocardiograms

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

A 12-lead ECG recorded in triplicate must promptly be performed for subjects who have signs or symptoms that may be attributed to LAST (see Section 6.4.2).

6.4.6. Wound Healing Evaluation

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. Abnormal wound healing findings will be evaluated for clinical significance and followed to resolution.

6.4.7. Clinical Laboratory Tests

Blood and urine samples will be collected for diagnostic screening tests and for safety laboratory tests (hematology and serum chemistry). A list of clinical laboratory tests and parameters is provided in Table 1. Scheduled hematology and serum chemistry tests will be performed by a central laboratory. Urine samples collected for drug screening will be tested at the study site using kits provided by the central laboratory.

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

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

Table 1: Clinical Laboratory Tests

Diagnostic Screening Tests (Study Site):			
Urine Drug screen: Amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates/opioids, and phencyclidine.			
Safety Laboratory Tests (Central Laboratory):			
Hematology	Serum Chemistry		
Red blood cell count Hematocrit Hemoglobin Mean corpuscular volume Platelet count White blood cell count (with automated differential)	ALT Albumin Alkaline phosphatase AST Bicarbonate Blood urea nitrogen Calcium	Chloride Creatinine Direct bilirubin Gamma-glutamyltransferase Glucose Lactate dehydrogenase Magnesium	Phosphorus Potassium Sodium Total bilirubin Total protein Uric acid

6.5. Efficacy Assessments

6.5.1. Pain Intensity Assessments

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

Pain intensity scores will be assessed using an 11-point numeric rating scale (NRS, 0–10; see Appendix D) where 0 represents “no pain” and 10 represents “worst pain imaginable” (Breivik

2008). In Cohort 1, pain will be assessed at rest (NRS-R). In Cohort 2 and Optional Cohort 3, pain will be assessed first at rest (NRS-R) and then with activity (NRS-A).

- *NRS-R assessments*: Subjects should be recumbent or lying supine and measurements should be obtained after the subject has been in the resting position for at least 5 minutes.
- *NRS-A assessments*: Subjects should be in a resting position (recumbent or lying supine) and then instructed to sit up. Measurements should be obtained as soon as the subject sits up.

6.5.2. Opioid Rescue Medication Through 72 Hours

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

6.5.3. Opioid Prescription at Discharge

Sites will record if a subject is discharged with a prescription for opioids (yes/no). If a subject is discharged with an opioid prescription, the site will collect information on the name of the medication and number of units (eg, tablets, capsules) prescribed as well as the recommended dose, frequency, and route.

7. TIMING OF PROCEDURES AND ASSESSMENTS

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

Unless there is a safety concern, every effort should be made to avoid protocol deviations. For pain assessments at timepoints when the subject is asleep, an attempt should be made to wake the subject. If there is no response, the assessments at these timepoints may be recorded as "Not Done." Assessments that can be done without waking the subject (eg, blood collection for PK) should be completed. Additional visits and/or assessments are permitted (see Section 7.5) if clinically indicated in the opinion of the Investigator.

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

- NRS-R assessment.
- NRS-A assessment (Cohort 2 and Optional Cohort 3 only).
- Vital signs.
- 12-lead ECG.
- LAST assessment.
- Blood sample collection.
- Physical examination.
- Wound healing assessment.

7.1. Screening Period (Day -28 to Day -1)

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

Screening procedures and assessments will include the following:

- Urine drug screen.
- Medical history.
- Demographic recording.
- Physical examination (including weight and height).
- Subject training for pain intensity assessments.
- Vital signs measurements.
- 12-lead ECG (in triplicate).

- Blood sample collection for the hematology and serum chemistry.
- Prior and concomitant medication recording (from the time the subject signs the ICF).
- AE recording (from the time the subject signs the ICF).

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

Only subjects who meet the eligibility criteria will be enrolled.

7.2. Treatment and Postoperative Observation Period

7.2.1. Day of Surgery (Day 1)

7.2.1.1. Prior to Surgery

On Day 1, subjects will be reassessed for study eligibility. This includes a urine drug screen test. Results must be confirmed as negative prior to performing any additional assessments.

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

- Subject refresher training for pain (NRS) assessments.
- Vital signs measurements.
- Blood sample collection for PK analysis (Cohorts 1 and 2).
- Prior and concomitant medication recording.
- AE recording.

In Cohort 2 and Optional Cohort 3, subjects will be administered PO acetaminophen 975 mg to 1 g approximately 2 hours prior to the start of anesthesia.

7.2.1.2. Surgery and Study Drug Administration

Subjects will undergo planned C-section procedure with a low transverse skin incision (eg, Pfannenstiel) in accordance with the institutional practice/Investigator's discretion. Sites should follow intraoperative safety monitoring in accordance ASA Standards for Basic Anesthetic Monitoring (American Society of Anesthesiologists 2015). The start and stop times of surgery and the length of the surgical (ie, skin) incision 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 or staple for surgical wound closure will be considered the end of surgery. The time of clamping of the

umbilical cord will also be recorded. Data regarding the health of the newborn will be recorded (see Section 6.1.2).

Subjects will be administered HTX-011 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.

A single dose of HTX-011 will be administered after delivery of the newborn baby and closure of the uterine incision and just before wound closure, after final irrigation and suction of each layer. HTX-011 will be administered via instillation into the surgical site using a Luer lock applicator. A complete description of HTX-011 administration technique is provided in the Pharmacy Manual.

The start of study drug administration will be considered as Time 0 for all study assessments.

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

After surgery, subjects will be transferred to the postoperative care area in accordance with the institutional practice.

7.2.2. Postoperative Assessment Period (Up to 72 Hours)

Subjects will remain in the hospital/research facility for a minimum of 72 hours after the start of study drug administration to undergo postoperative assessments. During the inpatient period, subjects in Cohort 2 and Optional Cohort 3 will be administered a scheduled, non-opioid MMA regimen (Section 7.2.2.1). All subjects will undergo postoperative assessments (Section 7.2.2.2).

7.2.2.1. Protocol-Specific Medication During Inpatient Period

In Cohort 2 and Optional Cohort 3, as soon as subjects are able to tolerate oral intake, they will be started on a MMA regimen consisting of PO acetaminophen 975 mg to 1 g every 6 hours alternating with PO ibuprofen 400 mg every 6 hours.

In all cohorts, subjects may be administered rescue medication if needed to treat pain, as detailed in Section 3.1.3.

7.2.2.2. Study Procedures and Assessments During Inpatient Period

Study procedures and assessments to be performed during the postoperative assessment period are outlined below. Timepoints are referenced to the start of study drug administration (Time 0). Actual times will be recorded for all events in the subject's eCRF.

- **Physical examination:** 72 hours (±2 hours).
- **Vital signs measurements**: 30 minutes (±5 min), 60 minutes (±5 min), 90 minutes (±10 min), 2 hours (±15 min); 4 hours (±15 min), 8 hours (±30 min), 12 hours (±30 min), 18 hours (±30 min), 24 hours (±1 hour), 36 hours (±2 hours), 48 hours (±2 hours), 60 hours (±2 hours), and 72 hours (±2 hours).
- **12-lead ECG (triplicate):** 72 hours (±2 hours).

- **LAST assessment using LAST questionnaire**: 30 minutes (±5 min), 60 minutes (±5 min), 2 hours (±15 min), 4 hours (±15 min), 18 hours (±30 min), 24 hours (±1 hour), and 72 hours (±2 hours).
  - Note: If neurologic and/or cardiac signs and symptoms of LAST are observed, then vital sign measurements, 12-lead ECG (in triplicate), and blood sample collection for PK must be promptly performed. If symptoms are present at a timepoint when 1 of these assessments is not scheduled, an unscheduled assessment must be performed.
- **NRS-R assessment:** 60 minutes (±5 min), 2 hours (±15 min), 4 hours (±15 min), 8 hours (±30 min), 12 hours (±30 min); 24 hours (±1 hour), 36 hours (±2 hours), 48 hours (±2 hours), 60 hours (±2 hours), and 72 hours (±2 hours).
- **NRS-A assessment (Cohort 2 and Optional Cohort 3):** 60 minutes (±5 min), 2 hours (±15 min), 4 hours (±15 min), 8 hours (±30 min), 12 hours (±30 min); 24 hours (±1 hour), 36 hours (±2 hours), 48 hours (±2 hours), 60 hours (±2 hours), and 72 hours (±2 hours).
- **Breast milk samples for PK (Cohorts 1 and 2)**: Subjects should express breast milk as often as needed to maintain a milk supply (note that subjects may not be able to express milk during the first 72 hours). Subjects must record the start time and total number of breast milk samples collected in a breast milk log.
- **Blood samples for PK (Cohorts 1 and 2):**
  - A PK sample will be collected at 30 minutes (±5 min) for Cohort 2 only.
  - PK samples will be collected for both Cohorts 1 and 2 at the following timepoints: 60 minutes (±5 min), 2 hours (±15 min), 4 hours (±15 min), 6 hours (±15 min), 8 hours (±30 min), 10 hours (±30 min), 12 hours (±30 min), 18 hours (±30 min); 24 hours (±1 hour), 36 hours (±2 hours), 48 hours (±2 hours), 60 hours (±2 hours), and 72 hours (±2 hours).
- **Blood sample collection for hematology and serum chemistry**: 24 hours (±1 hour; hematology only) and 72 hours (±2 hours).
- **Wound healing assessment:** 24 hours (±1 hour [unless clinically contraindicated]), and 72 hours (±2 hours).
- **Concomitant medication recording:** the start date and time of all concomitant medications during the timeframe between study drug administration and 72 hours must be recorded.
- **Use of rescue medication recording:** the start date and time of all rescue medications during the timeframe between study drug administration and 72 hours must be recorded.
- **AE recording:** the start date and time of all AEs during the timeframe between study drug administration and 72 hours must be recorded.

7.2.3. End of the Postoperative Assessment Period

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

7.2.3.1. Cohorts 1 and 2

For subjects in Cohorts 1 and 2 who are not discharged at 72 hours (Day 4), breast milk expression and collection, and blood sample collection for PK analyses should continue as detailed in the SCHEDULE OF EVENTS FOR COHORTS 1 AND 2 table. At discharge, subjects in Cohorts 1 and 2 will be given a breast milk log to record breast milk expression during the follow-up period.

7.2.3.2. Cohort 2 and Optional Cohort 3

At discharge, sites will provide subjects in Cohort 2 and Optional Cohort 3 with instructions for following their MMA regimen through Day 6.

7.2.3.3. All Cohorts

Sites will record if subjects are discharged with an opioid prescription and if they are, information on the opioid prescription (Section 6.5.3).

7.3. Follow-Up Period: Day 5 Through Day 28

Subjects in Cohort 2 and Optional Cohort 3 will continue their scheduled MMA regimen (PO ibuprofen alternating with PO acetaminophen) after discharge through Day 6.

Subjects in Cohorts 1 and 2 will continue to express breast milk every day from discharge through Day 11 and will record the start time and total number of breast milk samples collected in the breast milk log. Every day after discharge (ie, on Days 5, 6, 7, 8, 9, 10, and 11), a visiting healthcare professional will visit the subject, and on Days 7 and 11, the subject will also return for a site visit.

7.3.1. Day 5 and Day 6 (Home Visit [Cohorts 1 and 2 Only])

On Days 5 and 6, the visiting healthcare professional will take a blood sample for PK analyses and will collect all breast milk samples that the subject expressed.

7.3.2. Day 7 (Home Visit [Cohorts 1 and 2 Only] and Site Visit [All Cohorts])

On Day 7, the visiting healthcare professional will collect all breast milk samples that the subject expressed in Cohorts 1 and 2.

Subjects in all cohorts will also return to the study site to undergo the following procedures and assessments:

- Blood sample for PK analyses (Cohorts 1 and 2).
- Wound healing assessment.

- Concomitant medication recording.
- AE recording.

7.3.3. Days 8 Through 10 (Home Visit [Cohorts 1 and 2 Only])

On Days 8, 9, and 10, the visiting healthcare professional will take a blood sample for PK analyses and will collect all breast milk samples that the subject expressed.

7.3.4. Day 11 (Home Visit [Cohorts 1 and 2 Only] and Site Visit [All Cohorts])

On Day 11, the visiting healthcare professional will collect all breast milk samples that the subject expressed in Cohorts 1 and 2.

Subjects in all cohorts will return to the study site to undergo the following procedures and assessments:

- Blood sample collection for hematology and serum chemistry.
- Blood sample collection for PK analysis (Cohorts 1 and 2 only).
- Wound healing assessment.
- Concomitant medication recording.
- AE recording.

After the Day 11 Visit, subjects in Cohort 1 only will continue to express breast milk in order to maintain a milk supply, but will dispose of the breast milk.

7.3.5. Day 16 Visit (±1 Day) (Home Visit [Cohort 1 Only])

On the Day 16 Visit, the subject in Cohort 1 will perform a final expression of breast milk for collection, emptying both breasts. The visiting healthcare professional will visit the subject on Day 16 to collect the final samples of breast milk and collect a final blood sample for PK analysis.

7.3.6. Day 28 Visit (±4 Days) (Site Visit [All Cohorts])

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

- Vital signs measurement.
- Wound healing assessment.
- Concomitant medication recording.
- AE recording.

7.4. Early Termination Visit

Subjects who receive HTX-011 but withdraw from the study before their Day 28 Visit will be asked to complete Early Termination procedures, which will include the following:

- Vital signs.
- Wound healing assessment.

- Concomitant medication recording.
- AE recording.
- Physical examination (if withdrew prior to 72 hours).
- 12-lead ECG (triplicate) (if withdrew prior to 72 hours).
- LAST assessment using LAST questionnaire (if withdrew prior to 72 hours).
- NRS-R assessment (if withdrew prior to 72 hours).
- NRS-A assessment (if withdrew prior to 72 hours [Cohort 2 and Optional Cohort 3]).
- Blood sample collection for hematology and serum chemistry (if withdrew prior to Day 11).
- Breast milk sample collection (if withdrew prior to Day 16 Visit [Cohort 1 only] or if withdrew prior to Day 11 Visit [Cohort 2 only]).
- Blood sample collection for PK analysis (if withdrew prior to Day 16 Visit [Cohort 1 only] or if withdrew prior to Day 11 Visit [Cohort 2 only]).

7.5. Unscheduled Visits and Assessments

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

- Vital signs.
- Physical examination.
- 12-lead ECG (in triplicate).
- Wound healing assessment.
- Concomitant medication recording.
- AE recording.
- Blood sample collection to determine plasma bupivacaine concentration (if the unscheduled visit is potentially related to a cardiac or neurological TEAE).
- Blood sample collection for hematology and chemistry.

8. SAFETY MONITORING AND REPORTING

Investigators are responsible for the detection and documentation of AEs, SAEs, SARs, serious suspected adverse reactions, unanticipated problems, or pregnancies, as detailed in this protocol.

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

8.1. Definition of Safety Parameters

8.1.1. Definition of an Adverse Event

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

An AE may be any unfavorable and unintended sign (including an abnormal laboratory finding) or disease temporally associated with the use of a study drug, whether or not considered causally associated with the use of the study drug. Any abnormal laboratory value, vital sign result, signs or symptoms of potential LAST, or wound healing assessment finding deemed clinically significant by the Investigator must be reported as AE. A clinical diagnosis, rather than changes in laboratory analytes or other assessments, should be recorded (eg, anemia rather than low hemoglobin value).

Examples of AEs include the following:

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

- Any laboratory abnormality that required further diagnostic investigation.

The following examples are not considered AEs:

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

8.1.2. Definition of a Serious Adverse Event

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

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

The following events do not meet the definition of an SAE: hospitalization for elective treatment of a pre-existing condition that does not worsen from baseline, hospitalizations for a standard procedure for study drug administration and routine monitoring of the studied indication not associated with any deterioration in condition, social or convenience admission to a hospital, prolongation of a hospitalization for social or convenience reasons not associated with the occurrence of an AE, or hospitalization or an emergency room visit that lasts less than 24 hours that does not meet the criteria of an important medical or a life-threatening event.

According to 21 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 a Suspected Adverse Reaction

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

8.1.4. Definition of a Serious Suspected Adverse Reaction

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

8.1.5. Definition of Unanticipated Problems

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

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

An unanticipated adverse device effect is defined in Section 8.1.2.

8.2. Classification of Adverse Events

8.2.1. Severity of Adverse Events

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

- **Mild:** Event is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.
- **Moderate:** Event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

- **Severe:** Event interrupts a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2. Relationship to Study Drug

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

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

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

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

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

8.3.1. Adverse Event and Serious Adverse Event Monitoring

All AEs regardless of causality or seriousness will be recorded from the time the subject signs the ICF through the Day 28 Visit. Note: the start time of all AEs during the 72-hour postoperative period must also be recorded.

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

8.3.2. Follow-Up of Events

After the occurrence of an AE or SAE, the Investigator is required to follow each subject proactively and provide further information on the subject's condition. All AEs and SAEs

documented at a previous visit or contact and designated as ongoing will be reviewed at subsequent visits or contacts.

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

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

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

8.4. Reporting Procedures

8.4.1. Reporting Serious Adverse Events to the Sponsor

If the Investigator determines that an event meets the protocol definition of an SAE due to any cause that occurs during the course of this study, regardless of relationship to study drug, he/she must notify the Sponsor by entering the SAE information into the eCRF **within 24 hours of the Investigator becoming aware of the SAE**.

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

Email Address: Heron_PV@ubc.com

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

- AE record.
- Medical history.
- Prior and concomitant medications.

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

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

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

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

8.4.2. Reporting Unanticipated Problems to the Sponsor

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

Email Address: Heron_PV@ubc.com

The following information will be included with unanticipated problem reporting:

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

It is the Investigator's responsibility to report an 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.

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

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

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

8.4.4. Pregnancy Reporting

Pregnancy is not considered to be an AE. In the event a female subject becomes pregnant within 28 days after receiving study drug, she should notify the Investigator immediately. The Investigator must attempt to follow the pregnancy to term or termination in order to report on outcome and health status of mother and child.

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

Email Address: Heron_PV@ubc.com

8.5. Safety Oversight

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

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

9. OTHER STUDY RESTRICTIONS

9.1. Contraception

Subjects must use an acceptable form of contraception in the event of sexual activity during the 30 days after HTX-011 administration. Acceptable forms of contraception include double-barrier contraception or an insertable, injectable, transdermal, or combination oral contraceptive approved by applicable regulatory authorities. Note: This does not apply to women who have had a sterilization procedure at the time of C-section, who are in only a same-sex relationship, or who are in a monogamous relationship with a surgically sterile partner.

10. STATISTICAL CONSIDERATIONS

10.1. General Considerations

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

10.2. Determination of Sample Size

The sample size for each cohort was selected empirically without formal statistical assumptions.

10.3. Analysis Populations

10.3.1. Pharmacokinetic Population (Cohorts 1 and 2 Only)

The PK Population will include all subjects who receive study drug and who have sufficient PK data and do not have protocol deviations or AEs that may significantly affect the PK of analytes. Subjects in this population will be included in all PK summaries.

10.3.2. Safety Population

The Safety Population will include all subjects who receive HTX-011. Subjects in this population will be included in all disposition, demographic, safety, and efficacy analyses.

10.4. Statistical Analysis Methods

10.4.1. Disposition and Demographics

All disposition and demographics data will be listed for the Safety Population.

10.4.2. Pharmacokinetic Analysis (Cohorts 1 and 2 Only)

All PK analyses will be carried out using the PK Population. Plasma and breast milk bupivacaine, meloxicam, DMSO, TEG-POE water-soluble end products (PE, TEG, and TEG acid) concentrations will be determined using validated liquid chromatography tandem-mass spectrometry assays. The PK parameter estimates will be calculated using non-compartmental analysis, as appropriate, and summarized. PK parameters will include, but are not limited to, C_{max}, T_{max}, AUC_{last}, AUC_{inf}, $t_{½}$, $Ae_{x\text{-}y,milk}$, and $fe_{x\text{-}y,milk}$, as appropriate. PK blood samples may also be analyzed to evaluate other study drug components.

10.4.3. Safety Analysis

All safety analyses will be carried out using the Safety Population. All safety data will be listed and summarized by timepoint; no statistical hypothesis testing will be performed. AEs that occur from the time the subject signs the ICF and prior to 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 summarized by System Organ Class and Preferred Term. Incidence of TEAEs, SAEs, ORAEs, and potential LAST-related TEAEs will be summarized and presented in descending order of frequency. AEs leading to study withdrawal, if any, will be listed separately.

Associated laboratory parameters such as hepatic profile, renal function, and hematology values will be grouped and presented together in summary tables. For each laboratory test, individual subject values will be listed and values outside of the standard reference range will be flagged. Changes from baseline in laboratory data, and shifts in laboratory data, will be summarized.

Abnormal vital sign values will be flagged and listed. Potential LAST assessment questionnaire and wound healing assessment results will be summarized.

10.4.4. Efficacy Analysis

The efficacy analysis will be carried out using the Safety Population. All efficacy data will be summarized. No statistical hypothesis testing will be performed. The mean $AUC_{0\text{-}72}$ of NRS-R scores (all cohorts) and NRS-A scores (Cohort 2 and Optional Cohort 3) will be summarized. The windowed worst observation carried forward (wWOCF) method will be implemented to account for the duration effect of opioid rescue medication. 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). Total opioid consumption through 72 hours will be calculated in IV MME and summarized using descriptive statistics. Subjects who have a total MME postoperative opioid dose = 0 through 72 hours will be characterized as "opioid-free" through 72 hours. The proportion of subjects discharged with an opioid prescription will be summarized.

10.5. Interim Analysis

No formal interim analyses are planned; however, the data will be reviewed on an ongoing basis. After at least 6 subjects in Cohort 1 have been administered HTX-011 and completed the Day 16 Visit breast milk collection, the Sponsor will conduct an analysis of PK data. A minimum of 6 to 8 subjects is considered sufficient for the PK objective (Draft FDA *Guidance for Industry, Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling*, February 2005). If there are sufficient breast milk and plasma data to fulfill the primary objective, the study may be stopped and no more subjects will be enrolled.

11. QUALITY ASSURANCE AND QUALITY CONTROL

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

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

12. REGULATORY AND ETHICAL CONSIDERATIONS

12.1. Regulatory Authority Approval

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

12.2. Ethical Conduct of the Study

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

12.3. Ethics Committee Approval

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

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

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

12.4. Informed Consent Process

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

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

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

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

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

12.5. Confidentiality

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

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

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

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

13. STUDY ADMINISTRATION

13.1. Clinical Monitoring

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

13.2. Source Documents and Record Retention

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

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

13.3. Management of Protocol Amendments and Deviations

13.3.1. Protocol Modification

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

13.3.2. Protocol Deviations

Protocol deviations are a change, divergence, or departure from the study design or procedures defined in this protocol. The Investigator will notify the EC of any protocol deviations as required by EC guidelines and site requirements. Protocol deviations will be documented at the

site and in the Sponsor files. The Sponsor is responsible for notifying the regulatory authorities of any protocol deviations, if required.

13.4. Financial Disclosure

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

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

Any Investigator(s) added as investigational staff to the FDA 1572 form must complete the Financial Disclosure for Clinical Investigators Form at the start of his/her participation in the study.

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

13.5.1. Suspension of Study

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

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

Following a review of the safety data by the Sponsor, a decision will be made to either resume, modify, or terminate the study.

13.5.2. Termination of Study or Investigational Site

After at least 6 subjects have been enrolled and administered HTX-011 in Cohort 1, the Sponsor will conduct an analysis of all available data; if there are sufficient breast milk and plasma data to fulfill the primary objective, the study may be stopped and no more subjects will be enrolled.

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

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

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

13.6. Publication and Information Disclosure Policy

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

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

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

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

14. REFERENCE LIST

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APPENDIX A. AMERICAN SOCIETY OF ANESTHESIOLOGISTS PHYSICAL STATUS CLASSIFICATION SYSTEM

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

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

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

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

APPENDIX B. LOCAL ANESTHETIC SYSTEMIC TOXICITY ASSESSMENT

This Local Anesthetic Systemic Toxicity (LAST) questionnaire is provided to monitor for early neurologic and cardiac signs and symptoms of LAST at the timepoints listed in Section 7, the SCHEDULE OF EVENTS FOR COHORTS 1 AND 2 table, and the SCHEDULE OF EVENTS FOR OPTIONAL COHORT 3 table.

If a subject has signs or symptoms that may be attributed to LAST, vital sign measurements, 12-lead ECG, and blood sample collection for PK must be performed. In cases where those assessments are already scheduled within that time window, they do not need to be repeated. If symptoms are present at a timepoint when 1 of these assessments is not scheduled, an unscheduled assessment must be performed.

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

Local Anesthetic Systemic Toxicity (LAST) Questionnaire

Record "Present" or "Absent" for each of the following symptoms. Signs and symptoms that are present and are deemed clinically significant by the Investigator should be entered on the electronic case report form (eCRF) as adverse events (AEs).

Notes:

- If a TEAE potentially attributable to LAST is severe (Section 8.2.1), regardless of relationship to study drug, the Investigator must notify the Sponsor within 24 hours of of when the Investigator is first aware of the event.
- If a TEAE potentially attributable to LAST qualifies as an SAE (Section 8.1.2), the Investigator must notify the Sponsor within 24 hours of when the Investigator is first aware of the event.

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

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

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 (≤2cm)
B	Along wound (>2 cm)
C	Large volume
D	Prolonged (>3 days)
Major complication	
IV. Pus:	
A	At 1 point only (≤2cm)
B	Along wound (>2 cm)
V. Deep or severe wound infection with or without tissue breakdown; haematoma requiring aspiration	

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

The following question will be answered by the subject for NRS at rest (NRS-R; all cohorts) and NRS with activity (NRS-A; Cohort 2 and Optional Cohort 3) pain intensity assessments:

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

The response must be one of the following:

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

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

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