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Official Title:	A Phase 3b, Randomized, Open-Label Study of HTX-011 as the Foundation of a Non-opioid, Multimodal Analgesic Regimen to Decrease Opioid Use Following Unilateral Open Inguinal Herniorrhaphy
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CLINICAL STUDY PROTOCOL: HTX-011-304

Protocol Title:	A Phase 3b, Randomized, Open-Label Study of HTX-011 as the Foundation of a Non-opioid, Multimodal Analgesic Regimen to Decrease Opioid Use Following Unilateral Open Inguinal Herniorrhaphy
Brief Title:	Study of Post-Herniorrhaphy Non-opioid MMA Regimens
Investigational Product:	HTX-011 (bupivacaine and meloxicam) extended-release solution
Phase of Development:	3b
Sponsor:	Heron Therapeutics, Inc. 4242 Campus Point Court, Suite 200 San Diego, CA 92121 USA 1-858-251-4400
Medical Monitor(s):	Mark Marino, MD 1-914-513-6459 mmarino@herontx.com
Medical Project Leader:	[redacted] Senior Vice President, Clinical Development [redacted] [redacted]
Protocol Version:	Version 3.0 — 12 September 2019 Version 2.0 — 14 August 2019 Version 1.0 — 22 March 2019

SPONSOR SIGNATURE

Protocol Title:	A Phase 3b, Randomized, Open-Label Study of HTX-011 as the Foundation of a Non-opioid, Multimodal Analgesic Regimen to Decrease Opioid Use Following Unilateral Open Inguinal Herniorrhaphy
Protocol Number:	HTX-011-304

This protocol Version 3.0 has been reviewed and approved by the Sponsor.

The electronic signature is appended.

[redacted]
Senior Vice President, Clinical Development
Heron Therapeutics, Inc.

INVESTIGATOR AGREEMENT

CLINICAL STUDY PROTOCOL: HTX-011-304

TITLE: A Phase 3b, Randomized, Open-Label Study of HTX-011 as the Foundation of a Non-opioid, Multimodal Analgesic Regimen to Decrease Opioid Use Following Unilateral Open Inguinal Herniorrhaphy

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 INGREDIENT(S):	bupivacaine and meloxicam
PROTOCOL NUMBER:	HTX-011-304
PHASE OF DEVELOPMENT:	3b

PROTOCOL TITLE: A Phase 3b, Randomized, Open-Label Study of HTX-011 as the Foundation of a Non-opioid, Multimodal Analgesic Regimen to Decrease Opioid Use Following Unilateral Open Inguinal Herniorrhaphy

STUDY SITES: Up to approximately 50 sites in the United States (US).

STUDY OBJECTIVES:

Primary Objective:

Part 1: To identify which of 2 postoperative non-opioid multimodal analgesic (MMA) regimens, with intraoperative administration of HTX-011 as the foundation, results in the highest proportion of subjects who do not require a prescription for postoperative opioid medication following unilateral open inguinal herniorrhaphy.

Part 2: To confirm, in a larger study population, the proportion of subjects who do not require a prescription for postoperative opioid medication following unilateral open inguinal herniorrhaphy with intraoperative administration of HTX-011 as the foundation of a non-opioid MMA regimen selected based on the results of Part 1 of the study.

Secondary Objectives:

- To assess postdischarge opioid consumption.
- To assess subject satisfaction with the postoperative MMA regimen.

METHODOLOGY: This is a Phase 3b, open-label study in subjects undergoing unilateral open inguinal herniorrhaphy, conducted in 2 sequential parts.

In both parts of the study, subjects will be screened within 28 days of surgery. In Part 2 only, a questionnaire will be administered at the Screening Visit to obtain baseline information about subjects' nicotine dependence, alcohol use, substance abuse, anxiety, depression, and catastrophizing behavior.

In Part 1, subjects will be randomized to one of 2 parallel cohorts, each with a different postoperative non-opioid MMA regimen:

- *Cohort 1 MMA regimen*: PO ibuprofen 600 mg every 6 hours, starting once the subject is able to tolerate PO intake. Three hours after the first dose of ibuprofen, start PO acetaminophen 1 g every 6 hours, alternating the 2 medications so that an analgesic is taken approximately every 3 hours.
- *Cohort 2 MMA regimen*: PO ibuprofen 600 mg and PO acetaminophen 1 g taken together every 6 hours, starting once the subject is able to tolerate PO intake.

In Part 2, each subject will be assigned to one of these 2 MMA regimens per Investigator discretion rather than randomization.

On the day of surgery (Day 1), approximately 2 hours prior to the start of induction of anesthesia, all subjects will receive both oral (PO) acetaminophen 1 g and PO ibuprofen 400 mg together. Subjects who continue to meet the eligibility criteria will undergo open inguinal herniorrhaphy with mesh. During

surgery, the use of intravenous (IV) fentanyl is permitted for intraoperative pain control.

Near the completion of surgery, a single dose of HTX-011 300 mg/9 mg will be applied into the surgical site. Following final irrigation and suction of each fascial layer, HTX-011 should be administered so that all tissues receive adequate coverage at both the level below and the level above the fascia. Following surgery, once the subject is able to tolerate PO intake, the first dose of the assigned postoperative MMA regimen will be administered. The second dose may also be administered at the site, depending upon the regimen and the time of discharge. Prior to discharge, opioid rescue medication may be administered, if required, per institutional standard of care. Subjects will be discharged per the hospital/research facility practice, with instructions to follow their assigned postoperative non-opioid MMA regimen.

Pain intensity will be assessed at discharge, using a Numeric Rating Scale at rest (NRS-R) and, in Part 1 only, with activity (NRS-A). For the NRS-R pain intensity assessment, subjects should be recumbent or lying supine, and measurements should be obtained after the subject is in the resting position for at least 5 minutes. For the NRS-A pain intensity assessment, subjects should be recumbent or lying supine and instructed to sit up; measurements should be obtained as soon as the subject has sat up from the resting position.

If the subject has an NRS-R pain intensity score of <6 and has not received a postoperative opioid prior to discharge, a prescription for an opioid medication will **not** be provided at discharge. Subjects who have an NRS-R score ≥6 or have received a postoperative opioid prior to discharge, or both, **may** be provided with a prescription for oxycodone (ten 5 mg pills; do not substitute).

After discharge, up to the Day 15 visit, if a subject contacts the site about postoperative pain related to the surgery, a prescription for oxycodone (ten 5 mg pills; do not substitute) may be provided at the Investigator's discretion. Thereafter, postoperative pain should be addressed per institutional standard of care.

Subjects will be instructed to adhere to their assigned non-opioid MMA regimen while awake during the first 5 days after surgery (ie, Days 1 through 6). Upon waking from sleep, if they have missed an analgesic dose(s) (ie, if more than 3 hours [Cohort 1] or more than 6 hours [Cohort 2] 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 their MMA medications as needed but should not exceed ibuprofen 600 mg every 6 hours and/or acetaminophen 1 g every 6 hours.

In Part 1, subjects will return to the site on Days 15 (± 2 days) and 29 (± 4 days) for follow-up visits.

In Part 2, subjects will return to the site for their final on-site visit on Day 15 (± 2 days). A safety follow-up visit will be conducted via telephone on Day 29 (± 4 days).

NUMBER OF PLANNED SUBJECTS:

Part 1: Up to approximately 90 subjects will be dosed in Cohorts 1 and 2 (approximately 45 per cohort).

Part 2: Up to approximately 380 subjects will be dosed.

STUDY POPULATION:

Inclusion Criteria

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

1. Is able to provide written informed consent.
2. Is able to adhere to the study visit schedule and complete all study assessments.
3. Is male or female and ≥18 years of age at Screening.
4. Is scheduled and medically fit to undergo an elective unilateral open inguinal herniorrhaphy with mesh under deep sedation or general anesthesia; no neuraxial technique (eg, no spinal or epidural).
5. Has an American Society of Anesthesiologists (ASA) Physical Status of I, II, or III.

6. Female subjects are eligible only if all the following apply:
    a. Not pregnant (female subjects of childbearing potential must have a negative urine pregnancy test at screening and on Day 1 before surgery).
    b. Not lactating.
    c. Not planning to become pregnant during the study.
    d. Is surgically sterile (eg, has had a bilateral tubal ligation); or is at least 2 years postmenopausal; or is in a monogamous relationship with a partner who is surgically sterile; or is practicing abstinence or agrees to use double barrier contraception in the event of sexual activity; or is using an insertable, injectable, transdermal, or combination PO contraceptive approved by applicable regulatory authorities for greater than 2 months prior to screening and commits to the use of an acceptable form of birth control for the duration of the study and for 30 days after study drug administration. Note: women in only a same-sex relationship do not need to meet this criterion.

Exclusion Criteria

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

1. Has a planned concurrent surgical procedure (eg, bilateral herniorrhaphy).
2. Has a pre-existing concurrent acute or chronic painful physical/restrictive condition, including chronic disability, expected to require analgesic treatment in the postoperative period for pain that is not strictly related to the herniorrhaphy and which may confound the postoperative assessments.
3. Has a contraindication or a known or suspected history of hypersensitivity or clinically significant idiosyncratic reaction (including methemoglobinemia) to bupivacaine (or other local anesthetics), meloxicam, ibuprofen, oxycodone, or acetaminophen.
4. **Part 1 only**: Has known or suspected daily use of opioids for 7 or more consecutive days within the previous 6 months. **Part 2 only**: Has known or suspected history of persistent opioid use, defined as daily, or almost daily, use of opioids for a period of at least 30 days within the previous 6 months.
5. Has taken any opioids within 24 hours prior to the scheduled surgery.
6. 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 asthma or urticarial/ allergic-type reactions after taking aspirin or NSAIDs.
    b. History of clinically significant cardiac abnormality such as myocardial infarction within 6 months prior to signing the Informed Consent Form (ICF), New York Heart Association class III or IV, or clinically significant abnormalities of electrocardiogram (ECG) or cardiac function.
    c. History of coronary artery bypass graft surgery within **12 months (Part 1)** or **6 months (Part 2)** prior to signing the ICF.
    d. History of severe liver function impairment as defined by Child-Pugh Class C, having an aspartate aminotransferase >3 × the upper limit of normal (ULN), or having an alanine aminotransferase >3 × ULN.
    e. History of severe kidney function impairment as defined by creatinine clearance (Cockcroft Gault) <30 mL/min, being on dialysis.
    f. Known history of glucose-6-phosphate dehydrogenase deficiency.
7. Has uncontrolled anxiety, psychiatric, or neurological disorder that, in the opinion of the

Investigator, might interfere with study assessments.

8. Has a known or suspected history of drug abuse, has a positive drug screen on the day of surgery (in Part 2, positive result for cannabinoids acceptable), consumes 3 or more alcoholic drinks every day, or has a recent history of alcohol abuse. Note: Subjects with a positive drug screen who are taking an allowed, prescribed medication that is known to result in a positive drug test (eg, amphetamine and dextroamphetamine for attention-deficit/hyperactivity disorder, benzodiazepine for anxiety disorder) may be eligible for participation in the study at the discretion of the Sponsor. **Part 1 only**: Subjects taking any marijuana (medical or recreational) are not allowed to participate in the study.

INVESTIGATIONAL PRODUCT, DOSE, AND MODE OF ADMINISTRATION: HTX-011 is an extended-release, dual-acting, fixed-dose combination product that contains bupivacaine (a long-acting, immediate-release, local anesthetic) and low-dose meloxicam (an NSAID), formulated in a proprietary tri(ethylene glycol) poly(orthoester) (TEG-POE) polymer, termed Biochronomer®. HTX-011 will be supplied by the Sponsor as a sterile, viscous liquid in 20 mL clear glass vials. HTX-011 will be prepared for administration using a device provided by the Sponsor. A single dose of HTX-011 300 mg/9 mg (bupivacaine/meloxicam doses) will be administered intraoperatively by application into the surgical site, using sterile syringes and applicators supplied by the Sponsor.

Required Concomitant Medications: Protocol-specified medications PO acetaminophen and PO ibuprofen will be provided by the Sponsor in Part 2.

REFERENCE THERAPY, DOSE, AND MODE OF ADMINISTRATION: Not applicable.

DURATION OF TREATMENT: Subjects will receive a single dose of study drug intraoperatively. The duration of study participation for each subject, from Screening through the final (Day 29) visit, will be up to 61 days.

The overall duration of the study is anticipated to be approximately 12 months.

STUDY ASSESSMENTS: The start of HTX-011 administration will be considered as Time 0 for all assessments.

Efficacy Assessments

- Postoperative opioid administration prior to discharge, including date/time, dose, and route of administration.
- Opioid prescription at discharge, including date/time and reason (NRS-R ≥6; or subject received postoperative, predischarge opioid; or both).
- Postdischarge opioid prescription details through the Day 15 visit, including date/time and dose.
- Postdischarge opioid consumption through the Day 15 visit, via patient recall.
- Subject-initiated, postdischarge, site contacts about postoperative pain related to the surgery, through the Day 15 visit, including date/time and any action taken, including whether it resulted in an opioid prescription.
- Pain intensity score at the time of discharge.
- Treatment Satisfaction Questionnaire for Medication (9-question; TSQM-9) regarding the MMA regimen.

Safety Assessments

- Adverse events (AEs) from the time the subject signs the ICF through the final on-site study visit (Day 29 in Part 1, Day 15 in Part 2); serious adverse events (SAEs) through Day 29 in both parts of the study.
- Vital signs (resting heart rate, blood pressure, respiration rate, and body temperature) at the Screening Visit, preoperatively on Day 1, at Discharge, and at the Day 15 visit.
- Part 1 only: Clinical safety laboratory tests (hematology and serum chemistry) at the Screening and

Day 15 visits.

STUDY ENDPOINTS:

Efficacy Endpoints:

- *Primary*: Proportion of subjects who do not receive a postoperative opioid prescription through the Day 15 visit.
- *Secondary*:
  - Proportion of subjects who do not receive an opioid prescription at discharge.
  - Proportion of subjects who do not receive a postdischarge opioid prescription, through the Day 15 visit.
  - Pain intensity scores at the time of discharge.
  - Number of oxycodone pills taken between discharge and the Day 15 visit.
  - Mean TSQM-9 scores

Safety Endpoints:

- Incidences of treatment-emergent AEs (TEAEs) and treatment-emergent SAEs.

STATISTICAL METHODS: Descriptive statistics, including number of subjects, mean, SD, median, minimum, and maximum, will be provided for continuous variables. Numbers and percentages of subjects will be tabulated for discrete and categorical variables.

Determination of Sample Size

The sample size in Part 1 was selected to provide over 80% power to detect a 20% difference between Cohort 1 and Cohort 2, assuming the proportions of subjects who do not receive a postoperative opioid prescription through the Day 15 visit are 10% and 30% in the 2 MMA regimen groups, respectively (Fisher's exact test at $\alpha = 0.2$, 2-sided). The sample size in Part 2 was selected to provide ≥90% probability of obtaining 5% precision regarding the proportion of subjects who do not receive a postoperative opioid prescription through the Day 15 visit, assuming a value of approximately 90% (based on preliminary Part 1 results).

Analysis Population

Safety Population: The Safety Population, which will comprise all subjects who receive HTX-011, will be used for all summaries of efficacy and safety data.

Efficacy Analyses

All efficacy data will be listed and summarized by study part and MMA regimen.

Safety Analyses

All safety data will be listed and summarized by study part and MMA regimen. All TEAEs will be coded and tabulated by System Organ Class and Preferred Term. Incidences of TEAEs and SAEs will be summarized. Changes in vital sign parameters will be summarized.

For Part 1, associated laboratory parameters, such as hepatic profile, renal function, and hematology values, will be grouped and presented together in summary tables. Shift tables will be produced showing the frequency of shifts from Baseline to Day 15, as well as the lowest and the highest postbaseline value in and out of the normal range. Individual subject values will be listed and values outside of the standard reference range will be flagged.

Interim Analysis

No formal interim analysis is planned. Preliminary summary-level efficacy and safety data from Part 1 were reviewed by the Sponsor to inform MMA regimen selection, criteria for prescribing an opioid at discharge for Part 2, and details of the allowed opioid prescriptions.

SCHEDULE OF EVENTS, STUDY PART 1

Assessments	Time: / Window:	Screening ≤28 days	Day 1 Preop	Day 1 OR	Discharge NA	Day 15 ± 2 days	Day 29 ± 4 days	Early Termination[a]
Obtain informed consent		X						
Urine drug screen[b]		X	X					
Urine pregnancy test[b]		X	X					
Demographics		X						
Medical history		X						
Record prior/concomitant medications		X[c]	X	←	→	X	X	X
Vital signs		X	X		X	X		X[d]
12-lead ECG (triplicate)		X						
Hematology and serum chemistry tests (central laboratory)		X				X		X[d]
Physical examination[e]		X						
Assess/confirm eligibility		X	X					
Adverse events[f]		X	X	←	→	X	X	X
Administer PO acetaminophen 1 g and PO ibuprofen 400 mg[g]			X					
Surgery[h]				X				
Administer HTX-011[h]				X				
LAST assessments for any subject with suspected LAST[i]				←	→			
Administer first dose of postoperative MMA regimen once subject is able to tolerate PO intake				X[j]				
Pain intensity (NRS-R and NRS-A)[k]					X			
MMA instructions					X			
Opioid prescription, if indicated[l]					X			
Administer TSQM-9						X		
Record subject-initiated postdischarge contact for postoperative pain and action taken					← →			

Abbreviations: ECG, electrocardiogram; LAST, local anesthetic systemic toxicity; MMA, multimodal analgesic; NA, not applicable; NRS-A, Numeric Rating Scale with activity; NRS-R, Numeric Rating Scale at rest; OR, operating room; PO, oral; Preop, preoperative; TSQM-9, Treatment Satisfaction Questionnaire for Medication (9-question).

Note: The start of study drug administration will be considered as Time 0 (T0). Section 6 provides information on study procedures and assessments.

[a] Subjects who withdraw from the study before their Day 29 Visit will be asked to complete Early Termination procedures.

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

[c] Ensure subject is not taking any prohibited medications.

[d] Clinical laboratory tests and vital signs assessments will be conducted at the Early Termination visit only if the subject withdraws prior to the Day 15 visit.
[e] Includes height, weight, and body mass index calculation.
[f] Adverse events will be collected from the time the subject signs the Informed Consent Form through the Day 29 visit.
[g] Approximately 2 hours prior to the start of induction of anesthesia.
[h] The length of the surgical incision should be recorded.
[i] After HTX-011 administration and until discharge, if the subject has central nervous system or cardiac symptoms that in the opinion of the Investigator may represent LAST (eg, perioral tingling, dizziness, sensory or visual disturbances, fast- or slow-feeling heart rate), then the subject should have vital signs measurements, ECG, and blood draw for bupivacaine plasma concentration performed within 30 minutes of the onset of the symptoms. After discharge and up until the Day 15 visit, any subject with such symptoms should contact the site immediately to discuss the symptoms and determine next steps; if the Investigator decides the subject needs to return to the site for evaluation, these assessments should be performed as soon as possible if LAST is suspected.
[j] The first dose will be administered at the site once the subject is able to tolerate PO intake. The second dose may also be administered at the site, depending upon the regimen and the time of discharge.
[k] NRS-R should be assessed while the subject is recumbent or lying supine; measurements should be obtained after the subject is in the resting position for at least 5 minutes. For NRS-A, subjects should be recumbent or lying supine and instructed to sit up; measurements should be obtained as soon as the subject has sat up from the resting position.
[l] If the subject has an NRS-R pain intensity score of <6 at the time of discharge and has not received a postoperative opioid prior to discharge, a prescription for an opioid medication will not be provided at discharge. Subjects who have an NRS-R score ≥6 at discharge or have received a postoperative opioid prior to discharge, or both, may be provided with a prescription for oxycodone (ten 5 mg pills).

SCHEDULE OF EVENTS, STUDY PART 2

Assessments	Time:	Screening	Day 1		Discharge	Day 15	Day 29	Early Termination[a]
	Window:	≤28 days	Preop	OR	NA	± 2 days	± 4 days	
	Location:	On-Site	On-Site	On-Site	On-Site	On-Site	Via Telephone	On-Site or via Telephone
Obtain informed consent		X						
Urine drug screen[b]		X	X					
Urine pregnancy test[b]		X	X					
Demographics		X						
Medical history		X						
Record prior/concomitant medications		X[c]	X	←	→	X		X
Pain phenotyping questionnaire		X						
Vital signs		X	X		X	X		X
12-lead ECG (triplicate) to assess eligibility		X						
Local laboratory tests to assess eligibility		X						
Physical examination[d]		X						
Assess/confirm eligibility		X	X					
Adverse events[e]		X	X	←	→	X	X	X
Administer PO acetaminophen 1 g and PO ibuprofen 400 mg[f]			X					
Surgery[g]				X				
Administer HTX-011[g]				X				
LAST assessments for any subject with suspected LAST[h]				←	→			
Administer first dose of postoperative MMA regimen once subject is able to tolerate PO intake				X[i]				
Pain intensity (NRS-R)[j]					X			
MMA instructions					X			
Opioid prescription, if indicated[k]					X			
Collect postoperative MMA medication bottles						X		
Administer TSQM-9						X		
Record subject-initiated postdischarge contact for postoperative pain and action taken					← →			

Abbreviations: ECG, electrocardiogram; LAST, local anesthetic systemic toxicity; MMA, multimodal analgesic; NA, not applicable; NRS-R, Numeric Rating Scale at rest; OR, operating room; PO, oral; Preop, preoperative; TSQM-9, Treatment Satisfaction Questionnaire for Medication (9-question).

Note: The start of study drug administration will be considered as Time 0 (T0). Section 6 provides information on study procedures and assessments.

[a] Subjects who withdraw from the study before their Day 29 Visit will be asked to complete Early Termination procedures.

[b] At Screening and Preop, the urine pregnancy test (for women of childbearing potential) and urine drug screen should be performed first. Results, other than for cannabinoids, should be confirmed negative prior to performing any additional assessments and prior to initiation of surgery. A subject who fails the drug test may be rescreened at the discretion of the Investigator. Subjects with a positive drug screen who are taking an allowed, prescribed medication that is known to result in a positive drug test (eg, amphetamine and dextroamphetamine for attention-deficit/hyperactivity disorder, benzodiazepine for anxiety disorder) may be eligible for participation in the study at the discretion of the Sponsor. Subjects taking marijuana (medical or recreational) are allowed to participate in Part 2.

[c] Ensure subject is not taking any prohibited medications. At Day 15, record number of oxycodone pills taken, per subject recall.

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

[e] Adverse events will be collected from the time the subject signs the Informed Consent Form through the Day 15 visit; serious adverse events will be collected through Day 29.

[f] Administer both medications together approximately 2 hours prior to the start of induction of anesthesia.

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

[h] After HTX-011 administration and until discharge, if the subject has central nervous system or cardiac symptoms that in the opinion of the Investigator may represent LAST (eg, perioral tingling, dizziness, sensory or visual disturbances, fast- or slow-feeling heart rate), then the subject should have vital signs measurements, ECG, and blood draw for bupivacaine plasma concentration performed within 30 minutes of the onset of the symptoms. After discharge and up until the Day 15 visit, any subject with such symptoms should contact the site immediately to discuss the symptoms and determine next steps; if the Investigator decides the subject needs to return to the site for evaluation, these assessments should be performed as soon as possible if LAST is suspected.

[i] The first dose will be administered at the site once the subject is able to tolerate PO intake. The second dose may also be administered at the site, depending upon the regimen and the time of discharge.

[j] NRS-R should be assessed while the subject is recumbent or lying supine; measurements should be obtained after the subject is in the resting position for at least 5 minutes.

[k] If the subject has an NRS-R pain intensity score of <6 at the time of discharge and has not received a postoperative opioid prior to discharge, a prescription for an opioid medication will **not** be provided at discharge. Subjects who have an NRS-R score ≥6 at discharge or have received a postoperative opioid prior to discharge, or both, **may** be provided with a prescription for oxycodone (ten 5 mg pills; do not substitute).

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ASA	American Society of Anesthesiologists
BMI	Body mass index
CFR	Code of Federal Regulations
CNS	Central nervous system
CV	Cardiovascular
ECG	Electrocardiogram
eCRF	Electronic case report form
EC	Ethics Committee
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IV	Intravenous(ly)
LAST	Local anesthetic systemic toxicity
MMA	Multimodal analgesic
NRS-A	Numeric Rating Scale with activity
NRS-R	Numeric Rating Scale at rest
NSAID	Nonsteroidal anti-inflammatory drug
PO	Oral
SAE	Serious adverse event
SAR	Serious adverse reaction
TEAE	Treatment-emergent adverse event
TEG-POE	Tri(ethylene glycol) poly(orthoester)
TKA	Total knee arthroplasty
TSQM-9	Treatment Satisfaction Questionnaire for Medication (9-question)
ULN	Upper limit of normal

Abbreviation	Definition
US	United States
USPI	United States Prescribing Information

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

1. INTRODUCTION

1.1. Background Information and Study Rationale

Up to 70% of patients have moderate to severe pain after surgery, and the most severe pain occurs within the first 72 hours (Apfelbaum 2003; Gan 2014; Lynch 1997; Meissner 2015; Misiolek 2014; Singla 2014; Svensson 2000). Administering a local anesthetic (eg, bupivacaine, ropivacaine, or levobupivacaine) perioperatively is a relatively simple and safe means of providing postoperative pain relief. A major limitation of currently available local anesthetics is that their duration of effect is only 6 to 12 hours (Kehlet 2011). Consequently, many patients are given opioids for pain management. The requirement for opioids postoperatively is a manifestation of ineffective pain relief. Exposure to opioids can lead to opioid-related adverse reactions resulting in worse patient outcomes and increased hospital costs (Cashman 2004; Chan 2013; Coley 2002; Jarzyna 2011; Kessler 2013; Lee 2015; Lee 2016; Oderda 2013; Ramachandran 2011; Shirakami 2005; Stephens 2003; Wheeler 2002). Patients can quickly transition from acute opioid use to chronic use. A review of a random sample of records from patients who had at least 1 opioid prescription between 2006 and 2015 showed that the probability of chronic opioid use begins to increase after the third day and rises rapidly thereafter (Shah 2017). Reduced exposure to opioids and better pain management is associated with improved patient outcomes as well as reduced risk for the development of persistent pain and consequent opioid abuse (Barnett 2017). These facts highlight the need for more effective postoperative pain management to reduce the need for opioids.

The development of an extended-release local anesthetic that is applicable for a broad range of surgeries, significantly reduces both pain and opioid use after surgery, can be easily administered, and has 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 for up to 72 hours and the need for opioid analgesics. HTX-011 is a novel, extended-release, dual-acting, fixed-dose combination product that contains bupivacaine and low-dose meloxicam. Bupivacaine, the disease-active ingredient, is an amide-type local anesthetic. Meloxicam, a nonsteroidal anti-inflammatory drug (NSAID), reduces the local inflammation caused by surgery and normalizes the local pH. This is believed to result in enhanced penetration of bupivacaine into the nerves, thereby synergistically potentiating its analgesic effect. Both bupivacaine and meloxicam are approved in the United States (US), Europe, and other regions, and have a long history of clinical use.

HTX-011 is a solution that is formulated in a proprietary tri(ethylene glycol) poly(orthoester) (TEG-POE) polymer, termed Biochronomer®. HTX-011 is administered as a single dose that is applied into the surgical site to coat the affected tissues that could result in pain generation. After administration, the polymer enables extended release of bupivacaine and meloxicam simultaneously for approximately 3 days.

In a previous Phase 3 study in subjects undergoing unilateral open inguinal herniorrhaphy Study 302), HTX-011 300 mg/9 g administered via application into the surgical site provided superior, sustained pain relief over the first 72 hours following surgery, reduced total opioid consumption, and increased the proportion of subjects who did not use any opioid rescue

medication (were "opioid-free"), compared with both saline placebo and bupivacaine HCl (standard of care) 75 mg. Permitted rescue medications, to be administered only upon request by the subject, were oral (PO) immediate-release oxycodone (≤10 mg within a 4-hour period), intravenous (IV) morphine (≤10 mg within a 2-hour period), and/or PO acetaminophen/paracetamol (≤1 g within a 6-hour period). The proportion of subjects in the HTX-011 group who were opioid-free through the 72-hour inpatient postoperative period was 51.2%. Consistent results (50.0% opioid-free) were observed in subjects who received HTX-011 300 mg/9 mg via application into the surgical site in a preceding Phase 2 study in herniorrhaphy with similar opioid and acetaminophen rescue medications (Study 202).

The proportion of subjects who were opioid-free was higher in a recent Phase 2 study (Study 215), in which the safety and analgesic efficacy of HTX-011 in subjects undergoing unilateral open inguinal herniorrhaphy, as part of a multimodal analgesia (MMA) regimen, was evaluated. "Multimodal" refers here to the use of multiple nociceptive agents with different mechanisms of action in order to minimize opioid use (Garimella 2013; Kehlet 1993; Kehlet 2006). Subjects were confined to the site for at least 72 hours and were given PO acetaminophen 1 g approximately 2 hours prior to induction of general anesthesia, HTX-011 300 mg/9 mg via application into the surgical site prior to closure, and the following postoperative MMA regimen: Once subjects were able to tolerate PO intake, they received PO ibuprofen 600 mg every 6 hours. Three hours after the first dose of ibuprofen, they started PO acetaminophen 1 g every 6 hours, alternating the 2 medications so that an analgesic was administered every 3 hours until the 72 hour postoperative period was complete. In Study 215, 90.5% of the subjects who received HTX-011 300 mg/9 mg received no opioids during the 72-hour postoperative period and 87.3% were opioid-free through the Day 10 follow-up visit.

The current study is designed to evaluate, in a more "real-world" context, the effects of 2 different postoperative MMA regimens on opioid use in subjects who have undergone unilateral open inguinal herniorrhaphy and received HTX-011 300 mg/9 mg intraoperatively. Rather than being kept on-site for 72 hours, subjects will be discharged from the site per site practice, and will be given instructions to follow their assigned postoperative MMA regimen at home.

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

In multiple randomized, placebo- and active-controlled clinical trials in subjects undergoing various surgeries, including herniorrhaphy, HTX-011 has been demonstrated to be well tolerated at doses up to 400 mg/12 mg and to effectively reduce postoperative pain for 72 hours and the need for opioids. Over 1,000 subjects have been exposed to HTX-011.

Herniorrhaphy is a well-accepted soft tissue model for acute postoperative pain. Herniorrhaphy produces generally reliable and persistent pain symptoms after surgery, which allows for analysis of acute analgesia over an extended period.

One dose level of HTX-011 will be evaluated in this study: 300 mg/9 mg. The dose and administration technique are the same as those evaluated in an adequate and well-controlled Phase 3 study in herniorrhaphy (Study 302), which demonstrated the safety and efficacy of HTX-011 300 mg/9 mg applied into the surgical site, and in a Phase 2 study in herniorrhaphy (Study 215) that evaluated the same dose of HTX-011 as part of a MMA regimen (Section 1.1).

In the current study, subjects will be discharged from the hospital/facility per site practice and provided with instructions for their assigned postoperative MMA regimen. The study will be conducted in 2 parts. In Part 1, a different postoperative MMA regimen will be evaluated in each of 2 parallel cohorts. In Part 2, the regimens evaluated in Part 1 will be further investigated in a larger subject population.

The postoperative analgesic regimens evaluated in Part 1 were selected based on literature suggesting that using both acetaminophen and ibuprofen, which have different mechanisms of action, can increase effectiveness without increasing risk (Ong 2010). Administering each every 6 hours on a staggered scheduled, such that the subject receives a dose of one or the other every 3 hours, was based on discussions with key opinion leaders, and is consistent with postoperative pain regimens recommended by medical centers (Hallway 2019; University of Michigan 2019); this is the regimen evaluated in Cohort 1 and in the precedent Phase 2 study (Study 215). The Cohort 2 MMA regimen is similar to the Cohort 1 regimen, but was selected because it may be easier for subjects to adhere to.

The primary efficacy endpoint for this study, the proportion of subjects receiving no opioid prescription through the Day 15 visit, is consistent with the study goal of identifying an effective MMA regimen following herniorrhaphy with HTX-011 administration, one that will reduce the need for opioids. Given the public health concerns regarding misuse and abuse of opioids, a reduction in opioid load and an increase in the number of subjects who are opioid-free are clinically meaningful endpoints and are in alignment with the US Food and Drug Administration (FDA) *Draft Guidance for Industry on Analgesic Indications: Developing Drug and Biological Products* (February 2014).

Pain intensity will be assessed at discharge using an 11-point (0–10) Numeric Rating Scale, where 0 represents “no pain” and 10 represents “worst pain imaginable” (Breivik 2008). Pain intensity scores will be obtained using the Numeric Rating Scale at rest (NRS-R) and with activity (NRS-A; Part 1 only). The NRS-R will provide a standard for determining which subjects will receive an opioid prescription at discharge. A score ≥7 is considered indicative of severe pain; NRS-R ≥6 was selected as the criterion for an opioid prescription based on the results of Study 215, in which all subjects who were given opioid rescue medication during the 72-hour inpatient postoperative period had an NRS-R score ≥6 at 2 hours postsurgery and/or received opioid rescue medication within the first 2 hours postsurgery.

The Treatment Satisfaction Questionnaire for Medication (9-question; TSQM-9) is a validated assessment of patient satisfaction with medications, which will be used in this study to assess satisfaction with subjects' assigned MMA regimen (IQVIA 2018).

Safety assessments in the current study include adverse event (AE) and serious AE (SAE) recording, vital signs, and (in Part 1) clinical laboratory tests. More extensive assessments are not considered necessary in this Phase 3b study due to prior demonstration of safety in the Phase 3 program, which included a study in subjects undergoing open inguinal herniorrhaphy. If a subject has central nervous system (CNS) or cardiac symptoms that in the opinion of the Investigator may represent local anesthetic systemic toxicity (LAST), then further safety tests are required, including vital signs, 12-lead electrocardiogram (ECG), and a blood sample to measure the bupivacaine plasma concentration.

Part 2 Study Design Features Informed by Part 1 Results

Based on preliminary results from Part 1 of the study, both regimens were well tolerated and effective and had similar patient satisfaction. Only 3.2% of the subjects (2 subjects in Cohort 1 and 1 subject in Cohort 2) required opioid rescue medication postdischarge. Therefore, both regimens evaluated in Part 1 will also be evaluated in Part 2.

In Part 2, each subject's assignment to one of the regimens will be determined by the Investigator, rather than by randomization. This is a more real-world approach and allows the Investigator to select the best approach for each individual subject.

The criteria for receiving an opioid prescription at discharge will be the same as in Part 1. All three Part 1 subjects who took a postdischarge opioid met the criteria. Of the 86 subjects who did not meet the criteria, none contacted the site postdischarge and none received a postdischarge opioid prescription. As the Part 1 criteria alone were highly predictive of postdischarge opioid use, NRS-A scores will not be collected in Part 2.

Preliminary Part 1 results indicated that the 3 subjects who took postdischarge opioids took 10, 10, and 13 pills, respectively, of oxycodone; therefore, the prescription will remain unchanged in Part 2.

The TSQM-9 was added to Part 2 when it was determined that more than 1 MMA regimen would be evaluated in Part 2.

Part 2 will include a telephone visit on Day 29 to collect limited safety information (deaths, other SAEs, and pregnancies) for a full 4 weeks after administration of study drug in a larger subject population. The HTX-011 safety profile with respect to commonly occurring AEs is well understood based on completed Phase 2 and Phase 3 studies, as well as Part 1 of this study; therefore, a telephone visit is deemed adequate to collect this information while minimizing the burden on the subject and the sites.

A pain phenotyping questionnaire will be used in Part 2 to collect information for analysis of factors that may be predictive of postoperative opioid use.

1.3. Potential Risks and Benefits

1.3.1. HTX-011

As of October 2018, a total of 1,077 adult subjects (1,067 undergoing surgery and 10 healthy volunteers) had received a single dose of HTX-011 in 8 clinical studies. The numbers of subjects exposed to HTX-011 by study phase include 10 in one Phase 1 study, 430 in three Phase 2a studies, 317 in two Phase 2b studies, and 320 in two Phase 3 studies. The potential risks and benefits of HTX-011 are described for all clinical studies.

Safety

Safety data from subjects who received HTX-011 via instillation (referred to as “application” in this document) into the surgical site in the two Phase 2b studies in total knee arthroplasty (TKA; Study 209) and augmentation mammoplasty (Study 211), and from the two Phase 3 studies in bunionectomy (Study 301) and herniorrhaphy (Study 302) were integrated 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, but without the risk of injection-related high

plasma concentrations and resulting toxicities. Specifically, the incidences of any treatment-emergent AE (TEAE) and of any study drug-related TEAE were similar for the total HTX-011 group (60 mg/1.8 mg to 400 mg/12 mg doses pooled) compared with active and placebo controls (ie, the total bupivacaine HCl group [50 mg to 125 mg doses pooled] and the saline placebo group, respectively), and there were no dose-dependent trends in the individual HTX-011 dose groups. The most common TEAEs were nausea, constipation, dizziness, vomiting, and headache. The incidences were generally similar for HTX-011 compared with the controls, and there was no apparent dose-dependent trend in the HTX-011 dose groups. The majority of TEAEs were mild or moderate in severity. The incidence of severe TEAEs was low and similar across all treatment groups, as well as the individual HTX-011 dose groups. The incidences of SAEs were low (1.8% to 2.2%) for the integrated treatment groups, with the highest incidences reported in the HTX-011 400 mg/12 mg group (3.7%) and bupivacaine HCl 125 mg group (4.6%). No deaths were reported for subjects who received HTX-011.

The incidences of prespecified opioid-related TEAEs were similar for the total HTX-011 and control groups (50.5% to 55.5%), and there was no apparent dose-dependent trend in the HTX-011 dose groups. There were no clinically meaningful differences in laboratory results, vital sign measurements, physical examination findings, or ECG findings. There was no evidence of LAST based on a review of potential LAST-related TEAEs, vital signs, ECGs, and bupivacaine plasma concentrations. The incidence of local inflammatory TEAEs was similar for the total HTX-011 group and comparators. Finally, there were no clinically meaningful differences among treatment groups in assessments of wound healing (Studies 209, 211, and 302) or bone healing (Study 301).

Serious Adverse Reactions

As of 23 October 2018, a total of 3 serious adverse reactions (SARs; ie, 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.

Efficacy

In 2 adequate and well-controlled, confirmatory Phase 3 studies in a bony model (Study 301 in bunionectomy) and a soft tissue model (Study 302 in herniorrhaphy), a single dose of HTX-011 provided superior, sustained pain relief, reduced opioid consumption, and increased the proportion of subjects who were opioid-free over the first 72 hours following surgery compared with bupivacaine HCl (standard of care) and saline placebo. The proportion of subjects who experienced severe pain at any time during the 72-hour postoperative period was also significantly lower for HTX-011 compared with saline placebo and bupivacaine HCl. Finally, the proportion of subjects in the HTX-011 group who were opioid-free through the 72-hour postoperative period was 51.2%; >91% of these subjects remained opioid-free through Day 10 and >82% remained opioid-free through Day 28.

Study 302 did not include a scheduled non-opioid postoperative MMA regimen. As described in Section 1.1, the proportion of subjects who were opioid-free was much higher (90.5%) in Study 215, in which subjects undergoing herniorrhaphy followed the same scheduled non-opioid postoperative MMA regimen to be followed by subjects in Cohort 1 of the current study.

Risks

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

Potential risks for bupivacaine include dose-related cardiovascular (CV) and CNS toxicity (MARCAINE USPI 2018). Close attention should be given to conditions that may represent reported toxicities associated with bupivacaine including, but not limited to, perioral tingling, metallic taste, visual and auditory disturbances, muscle twitching, seizure, acidosis, shortness of breath, bradycardia (heart rate <50 beats per minute with symptoms), hypotension (systolic blood pressure <90 mmHg or symptomatic decrease from baseline), low oxygen saturation (≤90% for ≥1 minute), and cardiac arrest.

Cases of methemoglobinemia have been reported in association with local anesthetic use. 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 (MARCAINE USPI 2018).

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

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

For more information on HTX-011, refer to the Investigator's Brochure (IB). For more information on the active ingredients, bupivacaine and meloxicam, refer to the US prescribing information for MARCAINE and MOBIC, respectively.

1.3.2. Other Medications Required in This Study

The Investigator should refer to the respective package inserts for information on risks associated with the required concomitant medications (PO acetaminophen and PO ibuprofen) as well as fentanyl, oxycodone, midazolam, general anesthetics, antiemetics, antibiotics, other opioids, and any other approved medications that may be administered while a subject participates in this study.

1.3.2.1. Ibuprofen

The adverse effects of ibuprofen include ulcers; GI bleeding and/or perforation of the stomach or intestines; an increased risk of blood clots including heart attack and stroke; an increased risk of bleeding by inhibiting clot formation; serious allergic reactions; new high blood pressure or worsening of high blood pressure; heart failure and fluid accumulation; serious skin AEs such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), and all of which can be fatal; and worsening kidney function.

1.3.2.2. Acetaminophen

Subjects should not take more than 4 g of acetaminophen per day because of the risk of liver damage. Acetaminophen is generally considered safe at recommended doses. The most common side effects are nausea, vomiting, headache and insomnia. Serious skin rashes may rarely occur and too high of a dose can result in liver failure.

1.3.2.3. Opioid Rescue Medication

The most common risks associated with oxycodone include nausea, constipation, vomiting, headache, and itchiness. Serious risks include difficulty breathing, respiratory arrest, cardiac arrest, hypotension, and/or shock. Because oxycodone acts on the CNS, concentration and reaction abilities may be decreased. Drinking alcohol may further decrease mental functions and increase the risk of liver damage.

Opioids have the risk of addiction, abuse, and misuse, which can lead to overdose and death.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective in Part 1 is to identify which of 2 postoperative non-opioid MMA regimens, with intraoperative administration of HTX-011 as the foundation, results in the highest proportion of subjects who do not require a prescription for postoperative opioid medication following unilateral open inguinal herniorrhaphy.

The primary objective in Part 2 is to confirm, in a larger study population, the proportion of subjects who do not require a prescription for postoperative opioid medication following unilateral open inguinal herniorrhaphy with intraoperative administration of HTX-011 as the foundation of a non-opioid MMA regimen selected based on the results of Part 1 of the study.

2.2. Secondary Objectives

The secondary objectives are as follows:

- To assess postdischarge opioid consumption.
- To assess subject satisfaction with the postoperative MMA regimen.

3. INVESTIGATIONAL PLAN AND ENDPOINTS

3.1. Description of the Study Design

3.1.1. Overall Study Design

This is a Phase 3b, open-label, study to assess postoperative opioid use in subjects undergoing unilateral open inguinal herniorrhaphy with intraoperative administration of HTX-011 and a postoperative non-opioid MMA regimen. The study will be conducted in 2 sequential parts.

In both parts of the study, subjects will be screened within 28 days of surgery. On the day of surgery (Day 1), subjects who continue to meet the eligibility criteria will undergo open inguinal herniorrhaphy with mesh under general anesthesia; ie, any drug-induced loss of consciousness rendering the patient not arousable, even by painful stimulation. Spinal, epidural, and regional anesthesia are not allowed. Approximately 2 hours prior to the start of induction of anesthesia, subjects will receive both PO acetaminophen 1 g and PO ibuprofen 400 mg together. If the start of anesthesia is delayed by more than 6 hours after taking the preoperative analgesia, the preoperative analgesia should be administered again. If the surgery is rescheduled for more than 10 days later and this puts the subject out of the screening window, then screening assessments should be re-performed. During surgery, the use of IV fentanyl is permitted for intraoperative pain control.

Near the completion of surgery, a single dose of HTX-011 300 mg/9 mg will be applied into the surgical site, as described in Section 5.5. The first dose of the subject's assigned non-opioid postoperative MMA regimen will be administered at the site once the subject is able to tolerate PO intake. The second dose may also be administered at the site, depending upon the regimen and the time of discharge. After surgery and prior to discharge, subjects should receive opioid rescue medication only upon request for pain control, per institutional standard of care.

After viewing an educational video about what to expect after surgery, which includes instructions on their postdischarge MMA regimen, subjects will be discharged per the hospital/research facility practice.

In Part 1, NRS-R and NRS-A pain intensity scores will be obtained at discharge; in Part 2, only NRS-R scores will be obtained. For the NRS-R pain intensity assessment, subjects should be recumbent or lying supine, and measurements should be obtained after the subject is in the resting position for at least 5 minutes. For the NRS-A pain intensity assessment, subjects should be recumbent or lying supine and instructed to sit up; measurements should be obtained as soon as the subject has sat up from the resting position.

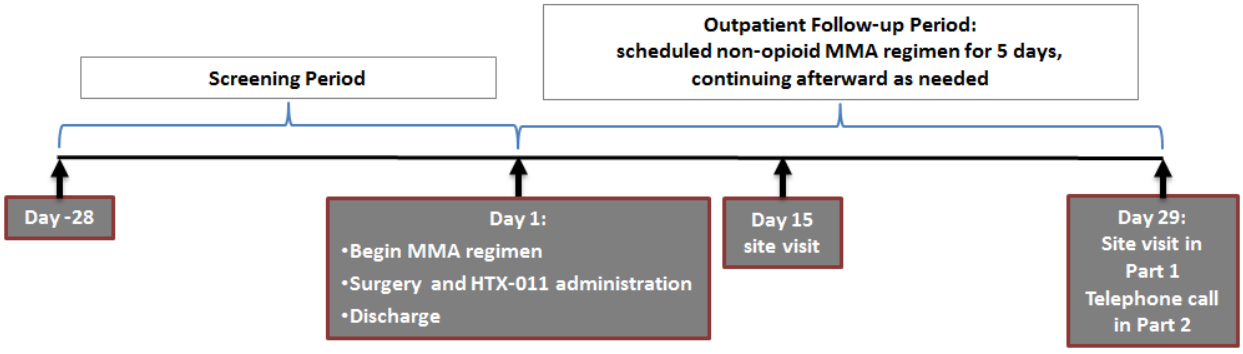
Subjects who have an NRS-R score <6 at discharge and have not received a postoperative opioid prior to discharge will NOT be given an opioid prescription at discharge. A prescription for ten 5 mg pills of oxycodone may be provided at discharge only if the subject has an NRS-R pain intensity score of ≥6 at the time of discharge or had received a postoperative opioid prior to discharge, or both.

In Part 1, subjects will return to the site on Days 15 (± 2 days) and 29 (± 4 days) for follow-up visits. In Part 2, subjects will return to the site only on Day 15 (± 2 days) for a follow-up visit; a Day 29 (± 4 days) safety follow-up visit will be conducted via telephone.

After discharge, up to the Day 15 visit, if a subject contacts the site about postoperative pain related to the surgery, a prescription for oxycodone (ten 5 mg pills; do not substitute) may be provided at the Investigator's discretion. Thereafter, postoperative pain should be addressed per institutional standard of care.

Figure 1 presents an overview of the study design scheme. See Section 6 for more information on the study procedures and assessments. For the timing of procedures and assessments, see Section 7, the SCHEDULE OF EVENTS, STUDY PART 1, and the SCHEDULE OF EVENTS, STUDY PART 2.

Figure 1: Schematic of the Study Design



Abbreviation: MMA, multimodal analgesic.

3.1.2. Treatment Groups (Scheduled Postoperative Non-Opioid MMA Regimens)

3.1.2.1. Part 1

In Part 1, subjects will be randomized to one of 2 parallel cohorts, each with a different postoperative non-opioid MMA regimen. Up to approximately 45 subjects will be included in each cohort.

- Cohort 1 MMA regimen: PO ibuprofen 600 mg every 6 hours, starting once the subject is able to tolerate PO intake. Three hours after the first dose of ibuprofen, start PO acetaminophen 1 g every 6 hours, alternating the 2 medications so that an analgesic is taken approximately every 3 hours.
- Cohort 2 MMA regimen: PO ibuprofen 600 mg and PO acetaminophen 1 g taken together every 6 hours, starting once the subject is able to tolerate PO intake.

Subjects will be instructed to adhere to their assigned non-opioid MMA regimen while awake during the first 5 days after surgery (ie, Days 1 through 6). Upon waking from sleep, if they have missed an analgesic dose(s) (ie, if more than 3 hours [Cohort 1] or more than 6 hours [Cohort 2] 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 their MMA medications as needed but should not exceed ibuprofen 600 mg every 6 hours and/or acetaminophen 1 g every 6 hours.

Note: A proton pump inhibitor (PPI) may also be prescribed at the Investigator's discretion.

3.1.2.2. Part 2

Up to approximately 380 subjects will receive instructions to follow one of the 2 postoperative non-opioid MMA regimens evaluated in Part 1. The regimen will be selected by the Investigator and may reflect subject preference.

3.1.3. Permitted Postoperative, Predischarge, Opioid Rescue Medication

After surgery and prior to discharge, subjects should only receive opioid rescue medication upon request for pain control, as needed, per institutional standard of care. Rescue medication should not be given for pain prophylaxis, but only for treating postoperative pain. Each administration of opioid rescue medication will be recorded.

3.1.4. Permitted Discharge Opioid Prescription

Subjects who have not received a postoperative opioid prior to discharge and have an NRS-R score <6 at discharge will NOT receive an opioid prescription at discharge. Only subjects who have received a postoperative opioid prior to discharge or have an NRS-R score ≥6 at discharge, or both, may receive an opioid prescription (oxycodone, ten 5 mg pills) at discharge; the prescription should specify that substitution with any other opioid-containing product, or with a combination opioid/non-opioid product, is not permitted.

3.1.5. Permitted Postdischarge Opioid Rescue Medication

After discharge, if a subject contacts the site regarding pain related to the surgery, the subject may receive a prescription for opioid rescue medication at the Investigator's discretion. Prior to the Day 15 visit, the prescription should be for oxycodone, ten 5 mg pills; the prescription should specify that substitution with any other opioid-containing product, or with a combination opioid/non-opioid product, is not permitted. After the Day 15 visit, postoperative pain should be addressed per institutional standard of care.

3.2. Study Endpoints

3.2.1. Primary Efficacy Endpoint

- Proportion of subjects who do not receive a postoperative opioid prescription through the Day 15 visit.

3.2.2. Secondary Efficacy Endpoints

- Proportion of subjects who do not receive an opioid prescription at discharge.
- Proportion of subjects who do not receive a postdischarge opioid prescription, through the Day 15 visit.
- Pain intensity scores at the time of discharge.
- Number of oxycodone pills taken between discharge and the Day 15 visit.
- Mean TSQM-9 scores

3.2.3. Safety Endpoints

- Incidences of TEAEs and treatment-emergent SAEs.

3.3. Study Duration

The overall duration of the study is anticipated to be approximately 12 months. The duration of study participation for each subject, from Screening through the final (Day 29) visit, will be up to 61 days.

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

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1. Study Population

Approximately 470 subjects will be enrolled in the study (90 in Part 1 and 380 in Part 2) at up to approximately 50 study sites in the US.

4.1.1. Inclusion Criteria

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

1. Is able to provide written informed consent.
2. Is able to adhere to the study visit schedule and complete all study assessments.
3. Is male or female and ≥18 years of age at Screening.
4. Is scheduled and medically fit to undergo an elective unilateral open inguinal herniorrhaphy with mesh under deep sedation or general anesthesia; no neuraxial technique (eg, no spinal or epidural).
5. Has an American Society of Anesthesiologists (ASA) Physical Status of I, II, or III (Appendix A).
6. Female subjects are eligible only if all the following apply:
    a. Not pregnant (female subjects of childbearing potential must have a negative urine pregnancy test at screening and on Day 1 before surgery).
    b. Not lactating.
    c. Not planning to become pregnant during the study.
    d. Is surgically sterile (eg, has had a bilateral tubal ligation); or is at least 2 years postmenopausal; or is in a monogamous relationship with a partner who is surgically sterile; or is practicing abstinence or agrees to use double barrier contraception in the event of sexual activity; or is using an insertable, injectable, transdermal, or combination PO contraceptive approved by applicable regulatory authorities for greater than 2 months prior to screening and commits to the use of an acceptable form of birth control for the duration of the study and for 30 days after study drug administration. Note: women in only a same-sex relationship do not need to meet this criterion.

4.1.2. Exclusion Criteria

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

1. Has a planned concurrent surgical procedure (eg, bilateral herniorrhaphy).
2. Has a pre-existing concurrent acute or chronic painful physical/restrictive condition, including chronic disability, expected to require analgesic treatment in the postoperative period for pain that is not strictly related to the herniorrhaphy and which may confound the postoperative assessments.

3. Has a contraindication or a known or suspected history of hypersensitivity or clinically significant idiosyncratic reaction (including methemoglobinemia) to bupivacaine (or other local anesthetics), meloxicam, ibuprofen, oxycodone, or acetaminophen.
4. **Part 1 only**: Has known or suspected daily use of opioids for 7 or more consecutive days within the previous 6 months. **Part 2 only**: Has known or suspected history of persistent opioid use, defined as daily, or almost daily, use of opioids for a period of at least 30 days within the previous 6 months.
5. Has taken any opioids within 24 hours prior to the scheduled surgery.
6. 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 asthma or urticarial/ allergic-type reactions after taking aspirin or NSAIDs.
    b. History of clinically significant cardiac abnormality such as myocardial infarction within 6 months prior to signing the Informed Consent Form (ICF), New York Heart Association class III or IV, or clinically significant abnormalities of ECG or cardiac function.
    c. History of coronary artery bypass graft surgery within **12 months (Part 1**) or **6 months (Part 2)** prior to signing the ICF.
    d. History of severe liver function impairment as defined by Child-Pugh Class C, having an aspartate aminotransferase >3 × the upper limit of normal (ULN), or having an alanine aminotransferase >3 × ULN.
    e. History of severe kidney function impairment as defined by creatinine clearance (Cockcroft Gault) <30 mL/min, being on dialysis.
    f. Known history of glucose-6-phosphate dehydrogenase deficiency.
7. Has uncontrolled anxiety, psychiatric, or neurological disorder that, in the opinion of the Investigator, might interfere with study assessments.
8. Has a known or suspected history of drug abuse, has a positive drug screen on the day of surgery (in Part 2, positive result for cannabinoids acceptable), consumes 3 or more alcoholic drinks every day, or has a recent history of alcohol abuse. Note: Subjects with a positive drug screen who are taking an allowed, prescribed medication that is known to result in a positive drug test (eg, amphetamine and dextroamphetamine for attention-deficit/hyperactivity disorder, benzodiazepine for anxiety disorder) may be eligible for participation in the study at the discretion of the Sponsor. **Part 1 only**: Subjects taking any marijuana (medical or recreational) are not allowed to participate in the study.

4.2. Method of Assigning Subjects to MMA Regimen Cohorts

In Part 1, subjects who meet the Screening eligibility criteria (Section 4.1) will be randomized to one of the 2 parallel cohorts within 1 business day prior to surgery, using a computer-generated randomization scheme. No subject may receive study drug prior to randomization.

In Part 2, prior to surgery, the Investigator will select for the subject one of the 2 postoperative MMA regimens (concurrent or alternating), based on Investigator and/or subject preference.

Procedures for Handling Enrolled Subjects Who Do Not Meet the Study Eligibility Criteria:

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

Subjects who meet the Screening eligibility criteria will be reassessed on Day 1 to determine whether they still meet eligibility criteria prior to randomization. Subjects who are randomized 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 immediately. The Sponsor's Medical Monitor and the Investigator will discuss whether to allow the subject to continue in the study.

4.3. Blinding

Not applicable. This is an open-label study.

4.4. Subject Withdrawal and Replacement

4.4.1. Subject Withdrawal

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

Possible reasons for early withdrawal include the following:

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

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

4.4.2. Subject Replacement

Subjects who withdraw early from the study for any reason will not be replaced.

5. STUDY TREATMENT

All subjects will receive a single dose of HTX-011 300 mg/9 mg (bupivacaine/meloxicam doses) administered via application into the surgical site while undergoing herniorrhaphy.

HTX-011 will be supplied by the Sponsor. The Sponsor will supply the sterile devices to be used for preparation and administration of HTX-011, including Luer lock applicators to be used instead of needles.

Postoperative non-opioid MMA medications will be supplied or reimbursed by the Sponsor. Oxycodone will not be supplied by the Sponsor.

Study drug is defined as HTX-011.

5.1. Description of Investigational Product

HTX-011 extended-release solution is a clear, pale yellow to yellow, viscous liquid. HTX-011 is supplied in 20 mL glass vials. The vials serve only as a closed container for the drug product. For administration of study drug, the formulation in the vials will be aseptically transferred to sterile syringes as described in the Pharmacy Manual and, for Part 2, the Instructions for Use.

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. HTX-011 kits will include the sterile devices to be used for preparation and administration of HTX-011, including Luer lock applicators to be used instead of needles.

5.3. Storage

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

Acetaminophen, ibuprofen, and oxycodone will be stored as per the prescribing information.

5.4. Preparation

At the study site, HTX-011 will be prepared in 1 syringe (Part 1) or 2 syringes (Part 2) with attached Luer lock applicator. Refer to the Pharmacy Manual and, for Part 2, the Instructions for Use, for details on study drug preparation.

5.5. Study Drug Administration

After the hernia repair is complete, but prior to surgical site closure, a single dose of HTX-011 300 mg/9 mg (10.5 mL) will be administered without a needle using a Luer lock applicator supplied by the Sponsor. Following final irrigation and suction of each fascial layer, the Luer

lock applicator will be used to apply HTX-011 to the tissues within the surgical site that could result in pain generation, at both the level below and the level above the fascia. Note that the shallow subdermal layer is to be avoided, and that all study drug within the syringe should be utilized (ie, there should be no residual study drug left). Thereafter, skin closure will commence to complete the surgical procedure (ie, there should be no betadine wash until after skin closure at the end of the case).

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

The study drug provided for this study will be used only as directed in the study protocol. In accordance with Good Clinical Practice (GCP), Investigators are required to maintain accurate and up-to-date records of all study 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 unblinded clinical monitor and/or auditor. No study drug can be returned to the Sponsor or designee or disposed of at the study site until the unblinded clinical monitor has verified the accuracy of the study drug records at the study site. All returns, disposal, or destruction must be approved by the Sponsor in writing.

6. STUDY PROCEDURES AND ASSESSMENTS

The following sections describe the study procedures and assessments that will be performed during the study. The timing of procedures and assessments is provided in Section 7, the SCHEDULE OF EVENTS, STUDY PART 1, and the SCHEDULE OF EVENTS, STUDY PART 2.

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.

6.1.2. Demographics

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

6.1.3. Pain Phenotyping Questionnaire

Subjects will provide responses to questions related to nictoine dependence, alcohol use, substance abuse, anxiety, depression, and catastrophizing behavior (Appendix B).

6.2. Prior and Concomitant Therapy

All medications taken by subjects between signing the ICF and the final on-site study visit on Day 29 (Part 1) or Day 15 (Part 2) will be recorded in the subject's eCRF if enrolled. The dosing regimen of "prn" should not be recorded on the eCRF.

While subjects are on-site on Day 1, the name, dose, and route, as well as the start date and time, of concomitant medications must be recorded. Medications include prescription or over-the-counter medications (including herbal products and vitamins). For subjects entering on a stable dose of permitted medication, any change in dose should also be recorded. Note: All medications received during this period must have a start time recorded, except for IV fluids and oxygen during surgery, which do not need to be recorded unless being used to treat an AE.

After discharge until the final on-site study visit on Day 29 (Part 1) or Day 15 (Part 2), at least the start date of each concomitant medication should be recorded.

6.2.1. Required Concomitant Medications

Preoperative Medication: Approximately 2 hours prior to the start of induction of general anesthesia, all subjects are to receive both PO acetaminophen 1 g and PO ibuprofen 400 mg together.

Postoperative MMA Regimen: Subjects will be assigned a postoperative non-opioid MMA regimen as described in Section 4.2.

6.2.2. Allowed Concomitant Medications

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

During surgery, the use of IV fentanyl is permitted for intraoperative pain control per institutional practice.

Information on permitted postoperative opioid rescue medication is provided in Section 3.1.3 (rescue prior to discharge), Section 3.1.4 (discharge prescription), and Section 3.1.5 (postdischarge rescue).

6.2.3. Prohibited Medications

6.2.3.1. Medications Prohibited Prior to Surgery

Refer to exclusion criteria 4 and 5 for medications that are prohibited prior to the scheduled surgery (Section 4.1.2). The Investigator should refer to the respective package inserts for information on risks associated with fentanyl, oxycodone, midazolam, acetaminophen, general anesthetics, antiemetics, antibiotics, other opioids, and any other approved medications that may be administered while a subject participates in this study; medications for any specific subject that would be prohibited based on their package inserts are also prohibited from use in this study.

6.2.3.2. Medications Prohibited During Surgery

Spinal, epidural, or regional anesthesia is not permitted. Intraoperative administration of opioids or any other analgesics (including ketamine), local anesthetics, or anti-inflammatory agents except as specified by the protocol (ie, HTX-011 and fentanyl) is prohibited, unless needed to treat an AE that occurs after signing the ICF, for pretreatment prior to a needle placement, or to decrease venous irritation (eg, caused by propofol, in which case no more than a single administration of lidocaine 1% 20 mg IV may be administered).

6.2.3.3. Postoperative Medications Prohibited

The subject should be instructed not to take any analgesic agents, with the exception of the scheduled non-opioid MMA regimen and permitted opioid rescue medication (Section 3.1), through the Day 15 visit.

6.3. Efficacy Assessments

6.3.1. Use of Opioid Medications

6.3.1.1. Opioid Rescue Medication Prior to Discharge

The name, dose, and route, as well as the date and time of administration, of any postoperative opioid rescue medication administered prior to discharge must be recorded in the subject's eCRF. Information on the procedure for postoperative opioid rescue, as well as the opioid rescue medications that are permitted, is provided in Section 3.1.3.

6.3.1.2. Opioid Prescription Provided at Discharge

If provided, the date and details of the prescription must be recorded in the eCRF. As described in Section 3.1.4, an opioid prescription will NOT be given at discharge to subjects who have not received a postoperative, predischarge opioid and have an NRS-R score <6 at discharge. A prescription for oxycodone (ten 5 mg pills) MAY be provided at discharge only to those subjects who have received a postoperative opioid prior to discharge or have an NRS-R score ≥6 at discharge, or both. The prescription should specify that substitution with any other opioid-containing product, or with a combination opioid/non-opioid product, is not permitted.

6.3.1.3. Opioid Rescue Medication After Discharge

The date and details of any prescription must be recorded in the eCRF. As described in Section 3.1.5, after discharge, subjects may receive a prescription for opioid rescue medication at the Investigator's discretion. Prior to the Day 15 visit, the prescription should be for oxycodone, ten 5 mg pills; the prescription should specify that substitution with any other opioid-containing product, or with a combination opioid/non-opioid product, is not permitted.

6.3.2. Pain Intensity Assessment

In Part 1, subjects will be asked to evaluate their current pain level at discharge, using NRS-R and NRS-A; in Part 2, only NRS-R scores will be obtained. Pain intensity scores will be assessed using an 11-point numeric rating scale where 0 represents "no pain" and 10 represents "worst pain imaginable" (Breivik 2008). See Appendix C.

For the NRS-R assessment, subjects should be recumbent or lying supine; measurements should be obtained after the subject is in the resting position for at least 5 minutes.

For the NRS-A assessment, subjects should be recumbent or lying supine and instructed to sit up; measurements should be obtained as soon as the subject has sat up from the resting position.

6.3.3. Treatment Satisfaction

Subjects will be asked to evaluate their satisfaction with their assigned postoperative MMA regimen at the Day 15 visit, using the TSQM-9. See Appendix E.

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 final on-site study visit (Day 29 in Part 1 and Day 15 in Part 2). In Part 2, information about any deaths and other SAEs will be collected at Day 29 via telephone.

Additional safety information is provided in Section 8. Any abnormal laboratory value or vital sign result deemed clinically significant by the Investigator must be recorded as AE.

6.4.2. Physical Examinations

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

Baseline height and weight measurements will be obtained, and body mass index (BMI) calculated (Appendix D).

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.

6.4.3. Vital Signs

Vital signs will include systolic and diastolic blood pressure, resting heart rate, respiration rate, and body temperature. Subjects should be in a supine position (includes sitting in a recliner chair) for at least 5 minutes before taking vital signs. Clinically significant post-treatment vital sign results should be recorded as AEs.

6.4.4. 12-Lead Electrocardiograms

Screening ECGs will be obtained for all subjects locally. Standard digital 12-lead ECGs will be performed in triplicate by local ECG machines. Subjects should be in the supine position (includes sitting in a recliner chair) for at least 5 minutes before each initial ECG recording.

6.4.5. Clinical Laboratory Tests

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

Laboratory results will be reviewed by the Investigator. Any laboratory values outside of the normal reference range will be evaluated for clinical significance; clinically significant findings after study drug administration will be recorded as AEs.

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

Table 1: Clinical Laboratory Tests

Diagnostic Screening Tests (Local Laboratories):
Urine Pregnancy test: Human chorionic gonadotropin test (female subjects of child-bearing potential only) Drug screen: Amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates/opioids, phencyclidine, propoxyphene, and methadone
Safety Laboratory Tests (Part 1 Only, Central Laboratory):
Hematology: Hematocrit, hemoglobin, red blood cell count, mean corpuscular volume, white blood cell count (with automated differential), platelet count
Serum Chemistry: Alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, direct bilirubin, gamma-glutamyltransferase, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total bilirubin, total protein, uric acid

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. Additional visits and/or assessments are permitted if clinically indicated in the opinion of the Investigator.

Note that at Discharge, the assessments should be performed in the order specified.

7.1. Screening Period (From Day -28 Up 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.

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

- Urine drug screen test (all subjects; note that a positive result for cannabinoids is acceptable in Part 2). 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 at the Sponsor's discretion.
- Urine pregnancy test (female subjects of child bearing potential only).

Additional screening procedures and assessments will include the following:

- Demographics recording.
- Medical history.
- Prior and concomitant medication recording (from the time the subject signs the ICF).
- Pain phenotyping questionnaire.
- Vital signs measurements.
- 12-lead ECG (in triplicate). In Part 2, for study eligibility assessment only.
- Blood sample collection for hematology and serum chemistry. Central laboratory in Part 1, local laboratory (for study eligibility assessment only) in Part 2. Any screening laboratory test result that does not meet the eligibility criteria may not be repeated without the Sponsor's approval.
- Physical examination (including weight, height, and BMI calculation).

- AE recording (from the time the subject signs the ICF).

All subjects who meet the Screening eligibility criteria will be enrolled. In Part 1, randomization may be done up to 1 business day prior to the day of surgery; subjects do not need to be present for randomization to occur.

7.2. Day of Surgery (Day 1)

7.2.1. Prior to Surgery

On Day 1, subjects will be reassessed for study eligibility. Results of the following should be confirmed as negative prior to administering acetaminophen and ibuprofen:

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

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

- Prior and concomitant medication recording.
- Vital signs measurements.
- AE recording.
- Part 2 only: Determine which postoperative MMA regimen (alternating or concurrent) will be assigned to the subject.
- Administer both PO acetaminophen 1 g and PO ibuprofen 400 mg together approximately 2 hours prior to surgery. If the start of anesthesia is delayed by more than 6 hours after taking the preoperative analgesia, the preoperative analgesia should be administered again. If the surgery is rescheduled for more than 10 days later and this puts the subject out of the screening window, then screening assessments should be re-performed.

7.2.2. Surgery and Study Drug Administration

Subjects will undergo open inguinal herniorrhaphy under general anesthesia; ie, any drug-induced loss of consciousness rendering the patient not arousable, even by painful stimulation. Epidural spinal, or regional anesthesia is not permitted. Sites should follow intraoperative safety monitoring in accordance with ASA Standards for Basic Anesthetic Monitoring (American Society Anesthesiologists 2015), which is consistent with the *European Board of Anaesthesiology (EBA) recommendations for minimal monitoring during Anaesthesia and Recovery* (EBA UEMS 2016). The start and stop time of surgery and additional surgical details (including the length of the surgical incision) should be recorded in the eCRF.

Subjects will be administered 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. HTX-011 will be administered via application into the surgical site at the end of the surgical procedure, but prior to wound closure. See Section 5.5 for further details on the study drug administration technique.

The start and stop times of HTX-011 dosing will be recorded in the eCRF. Details of administration will be recorded on a worksheet, which will be used in the dictation of the surgical notes and will become part of the source document. **Note: The start of study drug administration will be considered as Time 0 for all efficacy and safety assessments.** Placement of the last suture will be considered the end of surgery.

Prior and 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.

7.2.3. Postoperative Period (Up to Discharge)

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

- Once the subject is able to tolerate PO intake, administer and record the first postoperative non-opioid MMA dose per the subject's assigned MMA regimen. The second dose may also be administered, depending upon the MMA regimen and the time of discharge.
- AE recording: The start date and time of all AEs must be recorded.
- Recording of concomitant medications, including opioid rescue medication: The start date and time must be recorded.
- If the subject has CNS or cardiac symptoms that in the opinion of the Investigator may represent LAST (eg, perioral tingling, dizziness, sensory or visual disturbances, fast- or slow-feeling heart rate), then the subject should have vital signs measurements, ECG, and blood draw for bupivacaine plasma concentration performed within 30 minutes of the onset of the symptoms.

7.2.4. Discharge

The subject will be discharged per site practice. The time of discharge will be recorded. If discharge is delayed due to an AE, then the AE should be recorded as an SAE.

The following procedures should be completed at discharge**, in the order shown**:

- NRS-R pain intensity assessment (subjects should be recumbent or lying supine; measurements should be obtained after the subject is in the resting position for at least 5 minutes).
- Part 1 only: NRS-A pain intensity assessment (subjects should be recumbent or lying supine and instructed to sit up; measurements should be obtained as soon as the subject has sat up from the resting position).
- Vital signs measurements.
- Provide subject with postoperative MMA medications (ibuprofen and acetaminophen) after subject has viewed an educational video about what to expect after surgery, which includes instructions for their assigned postoperative MMA regimen. In Part 1,

both generic and branded products are acceptable; in Part 2, generic products will be provided.

- Provide subject with opioid prescription, if indicated: Subjects who have not received a postoperative opioid prior to discharge and have an NRS-R score <6 at discharge will NOT receive an opioid prescription at discharge. Only those subjects who have received a postoperative opioid prior to discharge or have an NRS-R score ≥6 at discharge, or both, MAY be provided with a prescription for oxycodone (ten 5 mg pills). The prescription should specify that substitutions with any other opioid-containing product are not permitted, and combination opioid/non-opioid products are not allowed.

7.3. Postdischarge Follow-Up Period

7.3.1. Postdischarge Contacts, Up to the Day 15 Visit

All subject-initiated postdischarge contacts for postoperative pain related to the surgery, up to the Day 15 visit, should be recorded, including the following information:

- Action taken, including whether opioid rescue medication (oxycodone, ten 5 mg pills) is prescribed.
- Any subject with CNS or cardiac symptoms that may represent LAST (eg, perioral tingling, dizziness, sensory or visual disturbances, fast or slow-feeling heart rate) should contact the site immediately to discuss the symptoms and determine next steps; if the Investigator decides the subject needs to return to the site for evaluation, vital signs measurements, ECG, and blood draw for bupivacaine plasma concentration performed should be performed as soon as possible if LAST is suspected.

7.3.2. Day 15 Visit (± 2 Days)

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

- Recording of concomitant medications, including opioids. Number of oxycodone pills taken, per subject recall, will be recorded.
- Part 2 only: Collection of ibuprofen and acetaminophen bottles provided at discharge.
- Vital signs.
- AE recording.
- TSQM-9 (Appendix E).
- Part 1 only: Blood sample collection for hematology and clinical chemistry.

7.3.3. Day 29 Visit (± 4 Days): On-Site in Part 1, via Telephone in Part 2

In Part 1, all subjects will return to the study site and will have the following procedures and assessments:

- Recording of concomitant medications, including opioids.

- AE recording.

In Part 2, the Day 29 visit will be conducted via telephone. Any deaths, other SAEs, and pregnancies will be recorded.

7.4. Early Termination Visit

Subjects who withdraw from the study **before the Day 15 visit** will be asked to complete the following Early Termination procedures:

- AE recording.
- Recording of concomitant medications, including opioids. Number of oxycodone pills taken, per subject recall, will be recorded.
- Vital signs measurements.
- Part 1 only: Clinical laboratory assessments.

Subjects who withdraw from the study **before the Day 29 visit** will be asked to complete the following Early Termination procedures:

- Recording of any deaths, other SAEs, and pregnancies.
- Part 1 only: Recording of any AE.
- Part 1 only: Recording of concomitant medications, including opioids.

7.5. Unscheduled Visits and Assessments

Unscheduled visits should be performed if clinically indicated in the opinion of the Investigator. The results of any assessments, which should include AEs and concomitant medications at a minimum, should be recorded.

8. SAFETY MONITORING AND REPORTING

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

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

8.1. Definition of Safety Parameters

8.1.1. Definition of an Adverse Event

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

An AE may be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not considered causally associated with the use of the study drug. Any abnormal laboratory value or vital sign result deemed clinically significant by the Investigator must be reported as an AE. A clinical diagnosis, rather than the change in a laboratory analyte or vital signs, 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 final on-site study visit (Day 29 in Part 1 and Day 15 in Part 2). Note: the start time of all AEs that begin prior to discharge must also be recorded.

In Part 2, any deaths or other SAEs will be recorded during the Day 29 telephone safety follow-up visit.

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

8.3.2. Follow-Up of Events

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

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

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

- **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 unanticipated problems to the Sponsor and their EC, as required by local regulations.

8.4.3. Regulatory Reporting Requirements

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

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

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

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

8.4.4. Pregnancy Reporting

Pregnancy is not considered to be an AE; however, any subject who becomes pregnant during the study must be withdrawn from the study immediately. Female subjects who become pregnant within 28 days after receiving study drug should notify the Investigator. The Investigator must attempt to follow the pregnancy to term or termination in order to report on outcome and health status of mother and child.

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

Email Address: Heron_PV@ubc.com

8.5. Safety Oversight

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

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

9. OTHER STUDY RESTRICTIONS

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

10. STATISTICAL CONSIDERATIONS

10.1. General Considerations

Unless otherwise specified, Baseline is defined as the last observed measurement, whether scheduled or unscheduled, prior to HTX-011 administration.

Continuous variables will be summarized using the number of subjects with data (n), mean, SD, median, minimum, and maximum. Selected continuous variable summaries will also include the SE. Categorical variables will be summarized using frequency counts and percentages.

10.2. Determination of Sample Size

Part 1: The sample size was selected to provide over 80% power to detect a 20% difference between Cohorts 1 and 2, assuming the proportions of subjects who do not receive a postoperative opioid prescription through Day 15 visit are 10% and 30% in the 2 groups, respectively (Fisher's exact test at $\alpha = 0.2$, 2-sided).

Part 2: The sample size was selected to provide ≥90% probability of obtaining 5% precision regarding the proportion of subjects who do not receive a postoperative opioid prescription through the Day 15 visit, assuming a value of approximately 90% (based on preliminary Part 1 results).

10.3. Analysis Populations

Safety Population: All subjects who receive HTX-011 will be included in the Safety Population. This population will be used for all summaries of efficacy and safety data.

10.4. Statistical Analysis Methods

10.4.1. Disposition and Demographics

Subject disposition, including the number of subjects enrolled, dosed, completing the study, and not completing the study by reason for withdrawal will be summarized. Subject demographics and baseline characteristics will also be summarized and will include age, age category, sex, race, ethnicity, height, weight, and BMI.

10.4.2. Efficacy Analysis

All efficacy analyses will be carried out on the Safety Population. All efficacy data will be listed and summarized by study part and MMA regimen.

10.4.3. Safety Analysis

All safety analyses will be carried out on the Safety Population. All safety data will be listed and summarized by study part and MMA regimen.

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

drug administration, will be considered TEAEs. All TEAEs will be coded and tabulated by System Organ Class and Preferred Term. The incidences of TEAEs and SAEs will be summarized and presented in descending order of frequency. AEs leading to study withdrawal, if any, will be listed separately.

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

In Part 1, 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. Laboratory parameters will be summarized by visit. Shift tables will be produced showing the frequency of shifts from Baseline to Day 15, as well as the lowest and the highest postbaseline value in and out of the normal range.

10.5. Interim Analysis

No formal interim analysis is planned. Preliminary summary-level efficacy and safety data from Part 1 were reviewed by the Sponsor to inform MMA regimen selection, criteria for prescribing an opioid at discharge for Part 2, and details of the allowed opioid prescriptions.

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 Good Clinical Practice 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.

Subject noncompliance with the assigned MMA regimen will not be considered a protocol deviation.

13.4. Financial Disclosure

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

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

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

13.5. Termination of Study or Investigational Site

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

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

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

13.6. Publication and Information Disclosure Policy

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

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

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

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

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APPENDIX A. AMERICAN SOCIETY OF ANESTHESIOLOGISTS PHYSICAL STATUS CLASSIFICATION SYSTEM

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

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

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

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

APPENDIX B. PAIN PHENOTYPING QUESTIONNAIRE

The following questions have been adapted with permission from the PROMIS Cooperative Group Patient-Reported Outcomes Measurement Information System (PROMIS®) Smoking: Nicotine Dependence for All Smokers – Short Form 4a, Alcohol Use – Short Form 7a, Appeal of Substance Use (Past 3 months) v1.0 – Short Form 7a, Anxiety Short Form, and Depression Short-Form; and from the University of Michigan Hospitals and Health Center Department of Anesthesiology AOS II (Analgesic Outcomes Study) Baseline Patient Questionnaire.

1. Do you smoke cigarettes? Yes ☐ No ☐

If "No" move to question #2.

If "Yes," please respond to each statement by marking one box per row.

	Never	Rarely	Sometimes	Often	Always
a. When I haven't been able to smoke for a few hours, the craving gets intolerable.	☐	☐	☐	☐	☐
b. I find myself reaching for cigarettes without thinking about it.	☐	☐	☐	☐	☐
c. I drop everything to go out and buy cigarettes.	☐	☐	☐	☐	☐
d. I smoke more before going into a situation where smoking is not allowed.	☐	☐	☐	☐	☐

2. The following questions ask about your alcohol use and behaviors.

In the past 30 days, did you drink any alcoholic beverage? Yes ☐ No ☐

If "No" move to question #3.

If "Yes," please respond to each statement by marking one box per row. In the past 30 days . . .

	Never	Rarely	Sometimes	Often	Almost always
a. I spent too much time drinking.	☐	☐	☐	☐	☐
b. I drank heavily at a single sitting.	☐	☐	☐	☐	☐
c. I drank too much.	☐	☐	☐	☐	☐
d. I drank more than planned.	☐	☐	☐	☐	☐
e. I had trouble controlling my drinking.	☐	☐	☐	☐	☐
f. It was difficult for me to stop drinking after one or two drinks.	☐	☐	☐	☐	☐
g. It was difficult to get the thought of drinking out of my mind.	☐	☐	☐	☐	☐

3. In the past 3 months, have you used drugs, other than alcohol or your prescribed medications?

Yes ☐ **No** ☐

If "No" move to question #4.

If "Yes," please respond to each statement by marking one box per row. In the past 3 months . . .

	Never	Rarely	Sometimes	Often	Almost always
a. I used drugs to feel more confident.	☐	☐	☐	☐	☐
b. I used drugs to feel good about myself.	☐	☐	☐	☐	☐
c. I used drugs to make it easier to talk to people.	☐	☐	☐	☐	☐

	Not at all	A little bit	Somewhat	Quite a bit	Very much
d. Drugs made me feel like I could do anything.	☐	☐	☐	☐	☐

	Never	Rarely	Sometimes	Often	Almost always
e. I used drugs to change my mood.	☐	☐	☐	☐	☐
f. I used drugs to have a good time.	☐	☐	☐	☐	☐

	Not at all	A little bit	Somewhat	Quite a bit	Very much
g. I used drugs because I liked the feeling.	☐	☐	☐	☐	☐

4. **Please respond to each item by marking one box per row. In the past 7 days . . .**

	Never	Rarely	Sometimes	Often	Always
a. I felt fearful.	☐	☐	☐	☐	☐
b. I found it hard to focus on anything other than my anxiety.	☐	☐	☐	☐	☐
c. My worries overwhelmed me.	☐	☐	☐	☐	☐
d. I felt uneasy.	☐	☐	☐	☐	☐
e. I felt nervous.	☐	☐	☐	☐	☐
f. I felt like I needed help for my anxiety.	☐	☐	☐	☐	☐
g. I felt anxious.	☐	☐	☐	☐	☐
h. I felt tense.	☐	☐	☐	☐	☐

5. **Please respond to each item by marking one box per row. In the past 7 days . . .**

	Never	Rarely	Sometimes	Often	Always
a. I felt worthless.	☐	☐	☐	☐	☐
b. I felt I had nothing to look forward to.	☐	☐	☐	☐	☐
c. I felt helpless.	☐	☐	☐	☐	☐
d. I felt sad.	☐	☐	☐	☐	☐
e. I felt like a failure.	☐	☐	☐	☐	☐
f. I felt depressed.	☐	☐	☐	☐	☐
g. I felt unhappy.	☐	☐	☐	☐	☐
h. I felt hopeless.	☐	☐	☐	☐	☐

6. **Individuals who experience certain symptoms have developed a number of ways to cope with, or deal with, their symptoms. These include saying things to themselves when they experience pain, fatigue, etc. or engaging in different activities. Below is a list of things that patients have reported doing when they feel pain, fatigue, etc. For each item, please indicate, using the scale below, how much you engage in that item when you feel symptoms.**

	Never	Almost Never	Once in a while	Some-times	A lot of the time	Almost always	Always
a. It's terrible, and I feel it's never going to get any better.	☐	☐	☐	☐	☐	☐	☐
b. It's awful, and I feel that it overwhelms me.	☐	☐	☐	☐	☐	☐	☐
c. I feel my life isn't worth living.	☐	☐	☐	☐	☐	☐	☐
d. I worry all the time about whether it will end.	☐	☐	☐	☐	☐	☐	☐
e. I feel I can't stand it anymore.	☐	☐	☐	☐	☐	☐	☐
f. I feel like I can't go on.	☐	☐	☐	☐	☐	☐	☐

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

The following question will be answered by the subject for all 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 HP, Borchgrevink C, Allen SM, Rosseland LA, Romundstad L, Hals EK, Kvarstein G, and Stubhaug A. *Assessment of pain*. Br J Anaesth. 2008;101(1): 17-24.

APPENDIX D. BMI CALCULATION

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

Kilograms = pounds × 0.45

Meters = inches × 0.0254

Example:

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

165 lbs × 0.45 = 74.25 kg

71 in × 0.0254 = 1.8 m

74.25/(1.8 × 1.8) = 22.92 kg/m^2

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

At the Day 15 visit, subjects will complete responses to the TSQM-9 questions, listed below, with reference to their postdischarge, non-opioid, multimodal analgesic (MMA) regimen for the treatment of their herniorrhaphy-related pain.

Effectiveness
How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?
How satisfied or dissatisfied are you with the way the medication relieves your symptoms?
How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?
Convenience
How easy or difficult is it to use the medication in its current form?
How easy or difficult is it to plan when you will use the medication each time?
How convenient or inconvenient is it to take the medication as instructed?
Global Satisfaction
Overall, how confident are you that taking this medication is a good thing for you?
How certain are you that the good things about your medication outweigh the bad things?
Taking all things into account, how satisfied or dissatisfied are you with this medication?

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

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