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Official Title:	A Phase 2, Open-Label Study of HTX-011 in a Multimodal Analgesic Regimen for Decreased Opioid Use Following Unilateral Open Inguinal Herniorrhaphy
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CLINICAL STUDY PROTOCOL: HTX-011-215

Protocol Title:	A Phase 2, Open-Label Study of HTX-011 in a Multimodal Analgesic Regimen for Decreased Opioid Use Following Unilateral Open Inguinal Herniorrhaphy
Brief Title:	Phase 2 Herniorrhaphy Study for Opioid Elimination
Investigational Products:	HTX-011 (bupivacaine and meloxicam) extended-release solution
Phase of Development:	2
Sponsor:	Heron Therapeutics, Inc. 4242 Campus Point Court, Suite 200 San Diego, CA 92121 1-858-251-4400
Medical Monitor:	[redacted]
Medical Project Leader:	[redacted] Vice President, Clinical Research [redacted]
Protocol Version Date:	31 August 2018

SPONSOR SIGNATURE

Protocol Number: HTX-011-215

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This protocol Version 1 has been reviewed and approved by the Sponsor.

The electronic signature is appended.

[redacted]
VP Clinical Research
Heron Therapeutics, Inc.

INVESTIGATOR AGREEMENT

CLINICAL STUDY PROTOCOL: HTX-011-215

TITLE: A Phase 2, Open-Label Study of HTX-011 in a Multimodal Analgesic Regimen for Decreased 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, Investigator's Brochure, and all other information on the investigational product that were furnished to me by the Sponsor to all physicians and other study personnel responsible to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the investigational product and the conduct of the study.

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

Principal Investigator: _____

Address: _____

Signature: _____

Date: _____

PROTOCOL SYNOPSIS

Sponsor: Heron Therapeutics, Inc.	**Protocol Number:** HTX-011-215
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Name of Active Ingredients: bupivacaine and meloxicam	**Phase of Development:** 2

Study Objectives:

Primary Objective:

- To assess the proportion of subjects who are opioid-free after receiving HTX-011 as part of a multimodal analgesic regimen during the first 72 hours following unilateral open inguinal herniorrhaphy with mesh.

Secondary Objectives:

- To assess the total opioid use following HTX-011 as part of a multimodal analgesic regimen during the first 72 hours following surgery in this study population.
- To assess the proportion of subjects who are opioid-free after receiving HTX-011 as part of a multimodal analgesic regimen during the first 72 hours that remain opioid-free through Day 10 and Day 28.
- To assess the relationship between opioid use and severe pain.

Methodology:

This is a Phase 2, open-label study in subjects undergoing unilateral open inguinal herniorrhaphy.

Cohort 1

Cohort 1 will be composed of approximately 30 subjects. Subjects will be screened within 21 days prior to surgery. Subjects who meet the Screening eligibility criteria will be allowed to participate in the study.

On the day of surgery (Day 1), subjects who continue to meet the eligibility criteria will undergo inguinal herniorrhaphy with mesh under general anesthesia. Spinal, epidural, or regional anesthesia are not allowed. Preoperative nonsteroidal anti-inflammatory drugs (NSAIDs) are not allowed. Approximately 2 hours prior to the start of induction of general anesthesia, subjects are to receive 1 g oral acetaminophen. However, if the start of general anesthesia is delayed by more than 4 hours, the subject must not be enrolled unless the surgery is rescheduled for a later day (if this puts the subject out of the screening window, screening assessments may be re-performed). All subjects will then receive a scheduled postoperative analgesic regimen as follows: start with 600 mg oral ibuprofen once they are able to tolerate oral intake in the postoperative care unit, then 3 hours after the ibuprofen dose administer the first postoperative dose of 1 g oral acetaminophen, then alternate these 2 medications so a dose is delivered every 3 hours.In other words, 3 hours after their first 600 mg oral ibuprofen dose, they will receive a 1 g oral acetaminophen dose, then after 3 more hours another 600 mg oral ibuprofen dose, and so on until the 72-hour postoperative period is complete.

Optional Cohort 2

At the Sponsor's discretion upon completion of Cohort 1, Optional Cohort 2 may be initiated. If conducted, Optional Cohort 2 will be composed of approximately 30 subjects. The same required preoperative, intraoperative, and scheduled postoperative pain medication regimen as in Cohort 1 would

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be required with the intra-operative addition prior to wound closure of 1 dose of intravenous (IV) ketorolac as follows:

- For subjects aged ≥65 years, serum creatinine >1.5, and/or weight <50 kg: 15 mg.
- For subjects aged <65years and/or weight ≥50 kg: 30 mg.

Optional Cohort 3

At the Sponsor's discretion upon completion of Optional Cohort 2, Optional Cohort 3 may be initiated. If conducted, Optional Cohort 3 will be composed of approximately 30 subjects. The specific multimodal analgesic regimen in Optional Cohort 3 will be determined by the Sponsor and included in a protocol amendment.

Inpatient Scheduled Analgesic Regimen (Preoperative, Intraoperative, and Through 72 hours Postoperative) – All Cohorts

Approximately 2 hours prior to the start of induction of general anesthesia, subjects are to receive 1 g oral acetaminophen.

During surgery, the use of IV fentanyl up to 3 μg/kg will be permitted for intraoperative pain control. Just prior to the end of the surgery, all subjects will receive an additional 50 μg IV fentanyl to decrease the inherent variability of intraoperative pain control on immediate postoperative pain. As an example, the maximum total amount of fentanyl used during surgery for a 70 kg subject should not exceed 260 μg (3 μg/kg × 70 kg = 210 μg for intraoperative pain control + 50 μg at the end of the case = 260 μg total).

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

Near the completion of surgery and after final irrigation and suction of each layer have been completed, a single dose of HTX-011 will be given intraoperatively via instillation into the surgical site.

In Optional Cohort 2, subjects will also receive IV ketorolac intraoperatively prior to wound closure.

Following surgery and immediate postoperative recovery, subjects will be transferred to the post-anesthesia care unit (PACU). Subjects will remain in the hospital/research facility for a minimum of 72 hours after administration of HTX-011. During the 72-hour inpatient period, subjects' pain will be assessed via pain Numeric Rating Scale at rest (NRS-R).

During the 72-hour postoperative period, subjects will receive a scheduled postoperative analgesic regimen as follows: start with 600 mg oral ibuprofen once they are able to tolerate oral intake in the postoperative care unit, then 3 hours after the ibuprofen dose administer the first postoperative dose of 1 g oral acetaminophen, then alternate these 2 medications so a dose is delivered every 3 hours. In other words, 3 hours after their first 600 mg oral ibuprofen dose, they will receive a 1 g oral acetaminophen dose, then after 3 more hours another 600 mg oral ibuprofen dose, and so on until the 72-hour postoperative period is complete. These medications are given on a round-the-clock, scheduled basis through the 72-hour postoperative period.

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Inpatient Postoperative Opioid Rescue Medications

During the 72-hour postoperative period, subjects should only receive opioid rescue medication upon request for pain control, as needed. Rescue medication should not be given for pain prophylaxis, but only for treating postoperative pain. Each administration of opioid rescue medication will be recorded.

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

Postoperative rescue medication will consist of oral (PO) immediate-release oxycodone (no more than 10 mg within a 4-hour period as needed) or IV morphine (no more than 10 mg within a 2-hour period as needed). Administration of other opioids or any other analgesics (eg, ketamine, pregabalin), local anesthetics, or anti-inflammatory agents (except as specified by the protocol) 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). Combination opioid/non-opioid products (eg, Percocet) are not allowed.

After the 72-hour inpatient period has been completed, subjects may be discharged. Subjects who are not medically ready for discharge at 72 hours may receive the same scheduled and rescue medications to treat postoperative pain until discharge.

Discharge/Postoperative Analgesic Regimen (following the 72-hour postoperative period to Day 28)

Upon discharge, subjects will be instructed to manage pain with the following regimen:

- 600 mg oral ibuprofen every 6 hours PRN as first-line therapy (before acetaminophen).
- 1g oral acetaminophen every 6 hours PRN as second-line therapy (ie, if ibuprofen has been administered but the subject is still in pain).

If a subject has not received any opioids during the 72-hour postoperative period, they should not receive an opioid prescription on discharge.

If a subject has received any opioids in the 12 hours prior to discharge, the subject should be provided with a paper prescription for oxycodone (up to 5 mg PO q4h, #15, as needed). Pharmacists should be instructed that substitutions with any other opioid-containing product are not permitted, including combination opioid/non-opioid products.

All subjects (whether or not they were discharged with an opioid prescription) will complete a daily diary to record whether they take an opioid medication between 72 hours and Day 28.

Subjects will return to the study site on Days 10 and 28 to complete follow-up assessments.

Number of Planned Subjects: Up to approximately 90 subjects may be enrolled in the study. Approximately 30 subjects will be dosed in Cohort 1; up to 2 additional optional cohorts of approximately 30 subjects each may also be dosed.

Study Sites: Up to 5 sites in the United States (US)

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Study Population:

Inclusion Criteria:

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

1. Is able to provide written informed consent.
2. Is able to adhere to the study visit schedule and complete all study assessments.
3. Is male or female, and ≥18 years of age at screening.
4. Is scheduled to undergo a unilateral open inguinal herniorrhaphy with mesh under general anesthesia.
5. Has an American Society of Anesthesiologists 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 oral contraceptive approved by applicable regulatory authorities for greater than 2 months prior to screening and commits to the use of an acceptable form of birth control for the duration of the study and for 30 days after study drug administration. Note: women in only a same-sex relationship do not need to meet this criterion.

Exclusion Criteria

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

1. Had any prior inguinal hernia repair except as a child (less than 6 years of age).
2. Has a planned concurrent surgical procedure (eg, bilateral herniorrhaphy).
3. Has a pre-existing concurrent acute or chronic painful physical/restrictive condition expected to require analgesic treatment in the postoperative period for pain that is not strictly related to the herniorrhaphy and which may confound the postoperative assessments.
4. Has a contraindication or a known or suspected history of hypersensitivity or clinically significant idiosyncratic reaction to bupivacaine (or other local anesthetics), meloxicam, ibuprofen, and for Optional Cohort 2 ketorolac (or other NSAIDs), oxycodone, morphine, acetaminophen, pregabalin, or fentanyl. Subjects in all cohorts must not have any contraindications to any of the protocol-specified drugs (bupivacaine, meloxicam, fentanyl, ibuprofen, acetaminophen, morphine, or oxycodone). Subjects in Optional Cohort 2 must also not have any contraindications to ketorolac.
5. Has known or suspected daily use of opioids for 7 or more consecutive days within the previous 6 months.

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6. Has taken any NSAIDs (including meloxicam, ibuprofen or, for Optional Cohort 2 ketorolac) within 10 days prior to the scheduled surgery with the exception of subjects on low-dose (≤100 mg) daily acetylsalicylic acid for cardioprotection.
7. Has taken long-acting opioids within 3 days prior to the scheduled surgery.
8. Has taken any opioids within 24 hours prior to the scheduled surgery.
9. Has been administered bupivacaine within 5 days prior to the scheduled surgery.
10. Has been administered any local anesthetic within 72 hours prior to the scheduled surgery, other than for pretreatment prior to a needle placement, to treat an AE that occurs after signing the ICF, or to decrease venous irritation (eg, caused by propofol, in which case no more than a single administration of lidocaine 1% 20 mg IV may be administered).
11. Has initiated treatment with any of the following medications within 1 month prior to study drug administration or is taking any of these medications to control pain: selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin, or cyclooxygenase-2 (COX-2) inhibitors. (Note: If a subject is taking one of these medications for a reason other than pain control, the subject must be on a stable scheduled dose [ie, not "as needed"] for at least 1 month prior to study drug administration.) Anxiolytics prior to surgery are permitted, if necessary.
12. Has been administered systemic steroids within 5 half-lives or 10 days prior to administration of study drug (whichever is longer). Note that for purposes of this exclusion criterion, inhaled, ophthalmic, and over-the-counter steroids are not considered systemic.
13. Has a medical condition such that, in the opinion of the Investigator, participating in the study would pose a health risk to the subject or confound the postoperative assessments. Conditions may include, but are not limited to, any of the following:
    a. History of 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 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 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, and/or having a serum creatinine >2 × ULN.
    f. History of known or suspected coagulopathy or uncontrolled anticoagulation (PLT count <100,000/μL; hemoglobin <12 g/dL; or hematocrit <35%).
    g. Loss of sensation in extremities or significant peripheral neuropathy.
14. As per subject history and/or medical records, has active infection or is currently undergoing

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treatment for Hepatitis B, Hepatitis C, or human immunodeficiency virus (HIV).

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

Investigational Product, Dose, and Mode of Administration:

HTX-011 is a novel, extended-release, fixed-dose combination product that contains bupivacaine and low-dose meloxicam. Bupivacaine is an amide-type local anesthetic and meloxicam is a nonsteroidal anti-inflammatory drug (NSAID). HTX-011 is a solution that is formulated in a proprietary tri(ethylene glycol)-based poly(orthoester) polymer (TEG POE), termed Biochronomer®. HTX-011 will be supplied by the Sponsor.

A single dose of HTX-011 300 mg/9 mg (bupivacaine/meloxicam doses) will be administered via instillation into the surgical site. HTX-011 will be prepared in syringes without a needle using a Luer lock applicator, also supplied by the Sponsor. Following irrigation and suction of each fascial layer, study drug will be administered evenly so that all tissues receive adequate coverage at both the level below and the level above the fascia.

Required Concomitant Medications

Other mandatory medications in this study include oral acetaminophen preoperatively, IV fentanyl intraoperatively, and both oral ibuprofen and oral acetaminophen postoperatively. Additionally, all subjects in Optional Cohort 2 will receive IV ketorolac intraoperatively.

Reference Therapy, Dose, and Mode of Administration:

Not applicable

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Duration of Treatment:

The overall duration of the study is anticipated to be approximately 8 months. The total duration of study participation for each subject (from Screening through the Day 28 follow-up visit) will be up to 53 days.

Criteria for Evaluation:

The start of HTX-011 administration will be considered as Time 0 for all assessment timepoints.

Efficacy Assessments:

- Date, time of administration, amount and type of all opioid rescue medication taken through 72 hours.
- Subject daily diary to record whether any opioids were taken from 72 hours through Day 28.
- Pain intensity scores using NRS-R at 1, 2, 4, 8, 12, 24, 36, 48, 60, 72 hours, and on Day 10.
    - NRS-R: Subjects should be recumbent or lying supine. Measurements should be obtained after the subject is in the resting position for at least 5 minutes.

Safety Assessments:

- AEs from the time the subject signs the ICF through Day 28.
- Clinical safety laboratory tests (hematology and serum chemistry) at the Screening Visit, at 24 hours (hematology only), at 72 hours, and on Day 10.
- Physical examination at Screening Visit and 72 hours; the Screening Visit will also include height, weight, and BMI calculation.
- Wound healing assessment at 72 hours and on Day 10 and Day 28.
- Vital signs (resting heart rate, blood pressure, respiration rate, and body temperature) at the Screening Visit, on Day 1 before surgery, and post-treatment at 60 minutes , 90 minutes, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours.

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Study Endpoints:

Primary Efficacy Endpoint:

- Proportion of subjects receiving no opioid rescue from 0-72 hours.

Secondary Efficacy Endpoints

- Total postoperative opioid consumption (in IV morphine milligram equivalents [IV MME]) through 72 hours.
- Proportion of subjects receiving no opioid rescue over the following time intervals: 0-to 4 hours, 24 to 48 hours, 0 - 48 hours, 24 - 72 hours, 48 - 72 hours.
- Proportion of subjects receiving no opioid rescue from 0 - 72 hours who receive no opioid rescue through Day 10, and through Day 28.
- Proportion of subjects in severe pain (NRS >7) at any point in the first 72 hours postoperatively.

Safety Endpoints

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

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Statistical Methods

All efficacy data will be summarized by treatment group. No statistical hypothesis testing will be performed. For opioid rescue summaries, the proportion of subjects receiving no opioid rescue will be summarized as subjects with a total IV MME dose = 0 over the relevant timeframe.

Handling of Missing NRS Data

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

Safety Analyses

All safety data will be listed and summarized by treatment group; no statistical hypothesis testing will be performed. All TEAEs will be coded and tabulated by System Organ Class and Preferred Term. Incidence of TEAEs, SAEs, and ORAEs will be summarized. Associated laboratory parameters such as hepatic profile, renal function, and hematology values will be grouped and presented together in summary tables. Individual subject values will be listed and values outside of the standard reference range will be flagged. Changes in vital sign parameters and ECG results will be summarized. Wound healing assessment results will be summarized.

Determination of Sample Size

The sample size in this study was selected empirically without a formal statistical assumption.

SCHEDULE OF EVENTS

Assessments	Time Window	Screening	Day 1		Time After Study Drug Administration*													
					60 min	90 min	120 min	4h	8h	12h	24h	36h	48h	60h	72h	D10	D28	ET[a]
		≤21 days	Preop	OR	±5 min	±5 min	±15 min	±15 min	±30 min	±30 min	±1h	±2h	±2h	±4h	±4h	±3d	±4d	
Obtain informed consent		X																
Urine drug screen		X	X															
Urine pregnancy test (WOCBP only)[b]		X	X															
Assess/confirm eligibility		X	X															
Medical history		X																
Demographics		X																
Physical examination		X[c]													X			X[d]
Vital signs[e]		X	X		X	X	X	X	X	X	X	X	X	X	X			X[d]
12-lead ECG (triplicate)[e]		X						X			X		X		X			X[d]
Subject training for pain assessments		X	X															
Hematology and serum chemistry tests		X									X[f]				X	X		
Surgery[g]				X														
Administer study drug				X														
Pain intensity assessment (NRS-R)[h]					X[i]		X	X	X	X	X	X	X	X	X	X	X	X
Wound healing assessment															X	X	X	X
Record opioid use (Diary)[j]															X	X	X	X[k]
Record Scheduled Non-Opioid Pain Meds					←	—	—	—	—	—	—	—	—	—	→			
Record Opioid Pain Meds in hospital					←	—	—	—	—	—	—	—	—	—	→			
Prior and Concomitant medications[l, m]		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[e, n]		←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
OPTIONAL COHORT 2 ONLY - Administer ketorolac[o]				X														

Abbreviations: ECG, electrocardiogram; ET, Early Termination; h, hour; min, minutes; NRS-R, Numeric Rating Scale at rest; OR, operating room; PGA, Patient Global Assessment; Preop, preoperative assessments; WOCBP, women of childbearing potential; D10, Day 10; D28, Day 28.
Note: The start of study drug administration will be considered as Time 0 (T0). For assessments at timepoints when the subject is asleep, an attempt should be made to wake the subject. If there is no response, the assessments at these timepoints may be recorded as "Not Done." Assessments that can be done without waking the subject should be completed. Section 6.0 provides information on study procedures and assessments.

[a] Subjects who withdraw from the study before their Day 28 Visit will be asked to complete Early Termination procedures.

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

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

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

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

[f] Hematology only.

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

[h] 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.

[i] If a subject requires rescue medication before the 1-hour pain intensity assessments, then an unscheduled NRS-R pain score must be obtained before administering the first dose of rescue medication. This does not replace the 1-hour NRS-R assessment.

[j] Subjects will complete a daily diary from 72 hours through Day 28 to record if they take any opioid medication. Subject diary results will be reviewed at the Day 28 Visit.

[k] Only if the subject withdraws after 72 hours.

[l] At the Screening Visit, ensure subject is not taking any prohibited medications. Record all medications taken from the time the subject signs the informed consent form (ICF) through Day 28.

[m] Postoperatively and upon discharge, subjects manage pain with the following regimen: 600 mg oral ibuprofen every 6 hours PRN as first-line therapy before acetaminophen, and 1g oral acetaminophen ibuprofen every 6 hours PRN as second-line therapy.

[n] Adverse events will be collected from the time the subject signs the ICF through Day 28.

[o] Cohort 2 only: IV ketorolac intra-operatively per subject age, weight, and creatinine.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
AUC	Area under the curve
BMI	Body mass index
CFR	Code of Federal Regulations
COX-2	Cyclooxygenase-2
CV	Cardiovascular
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous(ly)
IV MME	IV morphine milligram equivalents
LOCF	Last observation carried forward
NRS	Numeric Rating Scale
NRS-R	NRS scores at rest
NSAID	Nonsteroidal anti-inflammatory drug
ORAE	Opioid-related adverse event
PACU	Postanesthesia care unit
PK	Pharmacokinetic
PO	Oral
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event

Abbreviation	Definition
TKA	Total knee arthroplasty
ULN	Upper limit of normal
US	United States
WOCF	Worst observation carried forward
wWOCF	Windowed worst observation carried forward

1. INTRODUCTION

1.1. Background Information and Study Rationale

Up to 70% of patients have moderate to severe pain after surgery, and the most severe pain occurs within the first 72 hours (Lynch 1997; Svensson 2000; Apfelbaum 2003; Gan 2014; Misiolek 2014; Singla 2014; Meissner 2015). Administering a local anesthetic (eg, bupivacaine, ropivacaine, or levobupivacaine) is a relatively simple and safe means of providing postoperative pain relief. A major limitation of current local anesthetics is their 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 serious manifestation of ineffective pain relief. Exposure to opioids can lead to opioid-related adverse events (ORAEs) resulting in worse patient outcomes and increased hospital costs (Coley 2002; Wheeler 2002; Stephens 2003; Cashman 2004; Shirakami 2005; Jarzyna 2011; Ramachandran 2011; Chan 2013; Kessler 2013; Oderda 2013; Lee 2015; Lee 2016). 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 medical need for safer and more effective clinical alternatives to prescription opioids for management of ambulatory nonmalignant pain.

The development of an extended-release local anesthetic applicable for a broad range of surgeries that could significantly reduce both pain and opioid use after surgery and can be easily administered with a favorable safety profile would address an important public health need.

Heron Therapeutics, Inc. (Heron) is developing HTX-011 for 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 (also referred to as prolonged-release), fixed-dose combination product that contains bupivacaine and low-dose meloxicam. Bupivacaine is the disease-active ingredient and meloxicam enhances the effectiveness of bupivacaine.

HTX-011 is a solution that is formulated in a proprietary tri(ethylene glycol)-based poly(orthoester) polymer (TEG-POE), 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. Unlike other local anesthetics, HTX-011 is not injected; it is applied without a needle using a syringe with a Luer lock applicator attached. After administration, the polymer enables extended release of bupivacaine and meloxicam simultaneously for approximately 3 days. Both bupivacaine and meloxicam are approved in the US, Europe, and other regions, and have a long history of clinical use. Bupivacaine is an amide-type local anesthetic and meloxicam is a nonsteroidal anti-inflammatory drug (NSAID). Inclusion of low-dose meloxicam in HTX-011 reduces local inflammation caused by surgery and normalizes the local pH. This is believed to result in enhanced penetration of bupivacaine into the nerves, thereby potentiating its analgesic effect. Bupivacaine is commercially available as a solution for injection and is approved for surgical anesthesia and for acute pain management (nerve block) in adults and

children (MARCAINE, SENSORCAINE®, and VIVACAINE™). Meloxicam is available as an oral tablet that is approved for the relief of signs and symptoms of osteoarthritis, relief of signs and symptoms of rheumatoid arthritis and relief of the signs and symptoms of pauciarticular or polyarticular course Juvenile Rheumatoid Arthritis in patients who weigh ≥60 kg.

This Phase 2, open-label study is designed to evaluate the safety and analgesic efficacy of HTX-011 administered via instillation into the surgical site of subjects who are undergoing unilateral open inguinal herniorrhaphy.

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

This study is designed to evaluate the effectiveness of HTX-011 to reduce the need for postoperative opioid pain relief in subjects who have undergone herniorrhaphy (primary Cohort 1). 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.

In Optional Cohort 2, the study will evaluate HTX-011 via instillation into the surgical site with the intraoperative addition (prior to wound closure) of 1 dose of intravenous (IV) ketorolac as follows:

- For subjects aged ≥65 years, Creatinine > 1.5, and/or weight < 50 kg: 15 mg.
- For subjects aged < 65 years and/or weight ≥50 kg: 30 mg.

Optional Cohort 3 will be decided upon based upon results of the earlier cohorts.

One dose level of HTX-011 will be evaluated in this study, 300 mg/9 mg (bupivacaine/meloxicam doses) administered via instillation. The dose and administration technique were selected based on a previous Phase 2 dose-finding study in herniorrhaphy (Study 202). In Study 202, HTX-011 doses ranging from 200 mg/6 mg to 400 mg/12 mg via different local administration techniques (injection, instillation, or a combination of the 2 techniques) were evaluated. All doses were determined to be effective at producing postoperative analgesia through 72 hours. Additional study results are provided in Section 1.3. Based on these findings, 300 mg/9 mg administered via instillation was selected for this Phase 2 study.

The primary endpoint for this study, the proportion of subjects receiving no opioid rescue from 0-72 hours post operation, is consistent with the goal of this study to assess whether use of HTX-011 to control pain can eliminate or reduce the need for opioid pain killers. The timepoint of 72 hours selected for this study is considered clinically relevant for patients as literature shows that the most severe postoperative pain occurs within the first 72 hours after surgery (Lynch 1997; Svensson 2000; Apfelbaum 2003; Gan 2014; Misiolek 2014; Singla 2014; Meissner 2015). The numeric rating scale (NRS) was selected as an appropriate measurement because activity is known to be a more sensitive measure of pain control (Breivik 2008), and the prescribed activity reflects a simple daily activity for patients (sitting up from a resting position). All subjects will have a prespecified scheduled non-opioid pain medication routine, and will be able to receive opioid rescue for inadequately controlled pain.

The mean area under the curve (AUC) of the Numeric Rating Scale of pain intensity scores through 72 hours (AUC_{0-72}) was selected based on the United States (US) Food and Drug

Administration (FDA) and Committee for Medicinal Products for Human Use (CHMP) guidances as well as regulatory precedent. Draft FDA Guidance for Industry on Analgesic Indications: Developing Drug and Biological Products (February 2014) states that "pain intensity is the fundamental measure that defines the efficacy of an analgesic drug." In addition, the FDA agreed to a primary endpoint of AUC of the NRS pain intensity scores over the first 24-hour period in a bony model (bunionectomy) for EXPAREL® (EXPAREL USPI 2018).

Given the concern for misuse and abuse of opioids, a reduction in opioid load and an increase in the number of subjects who are opioid-free are clinically meaningful endpoints and are in alignment with the February 2014 FDA Draft Guidance for Industry on Analgesic Indications: Developing Drug and Biological Products. Opioid sparing endpoints were also included in recently approved labels for EXPAREL, OFIRMEV®, and CALDOLOR®, and NAROPIN®.

1.3. Potential Risks and Benefits

As of June 2018, a total of 1077 subjects had received a single dose of the intended commercial formulation 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 the intended commercial formulation of HTX-011 are described for all clinical studies, including the 2 studies in which subjects underwent herniorrhaphy (Study 202 and Study 302).

Safety

In the Phase 1 study in healthy volunteers (Study 102) and the Phase 2a studies in bunionectomy (Study 208), herniorrhaphy (Study 202), and abdominoplasty (Study 203), study drug was administered via subcutaneous injection (Study 102) or via local administration into the surgical site (injection, instillation, a combination of injection and instillation, or injection using a Mayo block) at doses ranging from 30 mg/0.9 mg to 600 mg/18 mg (bupivacaine/meloxicam doses). In Study 102, treatment with HTX-011 400 mg/12 mg was safe and well tolerated. All treatment emergent adverse events (TEAEs) were mild, and the most frequently reported TEAE was injection site bruising in 8 of 10 subjects. No serious adverse events (SAEs) were reported. In the Phase 2a studies, results showed that treatment with HTX-011 was generally well tolerated. The most common TEAEs were nausea, constipation, headache, and dizziness. The majority of TEAEs were mild or moderate in severity and resolved without sequelae. In subjects who received the intended commercial formulation of HTX 011, the incidence of SAEs was low: 2 subjects in Study 202, 1 subject in Study 203, and 1 subject in Study 208. The SAEs in Studies 203 and 208 were considered related to study drug and were, therefore categorized as, serious adverse reactions (SARs).

Safety data from subjects who received HTX-011 via instillation 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 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 combined) compared with active and placebo controls (ie, the total bupivacaine HCl group [50 mg to 125 mg doses combined] 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 (3.7%) and bupivacaine HCl 125 mg group (4.6%). No deaths were reported for subjects who received HTX-011.

The incidences of ORAEs 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. However, the incidences were higher for HTX 011 200 mg/6 mg and 400 mg/12 mg and bupivacaine HCl 125 mg. All except for 2 subjects administered these doses received at least 1 opioid rescue medication.

There were no clinically meaningful differences in laboratory results, vital sign measurements, physical examination findings, or electrocardiogram (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; however, the incidences were higher for the HTX 011 60 mg/1.8 mg and bupivacaine HCl 50 mg groups, which were the doses used in the Phase 3 bunionectomy study (Study 301). Finally, there were no clinically meaningful differences among treatment groups in assessments of wound healing or bone healing (Study 301 and Study 209).

Serious Adverse Reactions

As of 30 May 2018, a total of 3 SARs (SAEs considered related to study drug by the Investigator and/or the Sponsor) have been reported in 3 subjects who received the intended commercial formulation of 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 the Phase 2a study in herniorrhaphy (Study 202), HTX 011 doses ranging from 200 mg/6 mg to 400 mg/12 mg via different local administration techniques (injection, instillation, or a combination of the 2 techniques) were evaluated. All doses were determined to be effective at producing postoperative analgesia through 72 hours. The HTX-011 300 mg/9 mg dose given by local administration via instillation was noted to have similar efficacy to the highest dose tested,

400 mg/12 mg, while demonstrating a good safety profile and improved PK profile (ie, lower systemic exposure). The proportion of subjects who did not require an opioid (ie, were opioid free through 72 hours) was significantly higher in the HTX-011 300 mg/9 mg dose group compared with saline placebo (50.0% vs 7.2%; p = 0.0001) and compared with bupivacaine HCl (50.0% vs 12.5%; p = 0.0108) groups.

The primary and key secondary efficacy endpoints in all 3 adequate and well-controlled studies were achieved for HTX-011.

In the adequate and well-controlled Cohort 2 of the Phase 2b TKA study (Study 209), a bony surgical model, HTX-011 400 mg/12 mg administered with or without low-dose ropivacaine significantly reduced pain over 48 and 72 hours compared with saline placebo. In addition, HTX-011 + low-dose ropivacaine significantly reduced pain over 48 and 72 hours compared with bupivacaine HCl. Furthermore, fewer subjects in the HTX-011 alone group and significantly fewer subjects in the HTX-011 + low-dose ropivacaine group experienced severe pain (NRS of pain intensity score at rest [NRS-R] score ≥7) at any timepoint through 72 hours compared with saline placebo and bupivacaine HCl. Finally, total opioid consumption was lower for HTX-011 and significantly lower for HTX-011 + low dose ropivacaine compared with saline placebo and bupivacaine HCl over 48 and 72 hours.

Efficacy was also demonstrated in the 2 adequate and well-controlled Phase 3 studies in subjects undergoing bunionectomy (Study 301) and herniorrhaphy (Study 302). HTX-011 provided superior, sustained pain relief, reduced opioid intake, and increased the proportion of subjects who were opioid-free over the first 72 hours following study drug administration compared with both bupivacaine HCl and saline placebo in the bony and soft tissue surgical models of postoperative pain. These results are consistent with those from 2 precedent Phase 2a studies (Studies 208 and 202). The proportion of subjects who experienced severe pain (NRS-A score ≥7) at any timepoint during the 72-hour postoperative period was also significantly lower in the HTX-011 groups compared with the saline placebo and bupivacaine HCl groups in both studies. This was consistent with the observed reduction in total opioid consumption and increase in the proportions of opioid-free subjects. Finally, across the 2 studies, >91% of the subjects who received HTX 011 and were opioid-free during the 72-hour postoperative period remained opioid-free through Day 10, and >82% remained opioid free through Day 28.

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 central nervous system toxicity (MARCAINE USPI 2015). Close attention should be given to conditions that may represent reported toxicities associated with bupivacaine including, but not limited to, perioral tingling, metallic taste, visual and auditory disturbances, muscle twitching, seizure, acidosis, shortness of breath, bradycardia (heart rate <50 beats per minute with symptoms), hypotension (systolic blood pressure <90 mmHg or symptomatic decrease from baseline), low oxygen saturation (≤90% for ≥1 minute), and cardiac arrest.

Potential risks for meloxicam include CV adverse reactions, gastrointestinal bleeding, and liver tests elevations (MOBIC 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 gastrointestinal adverse events (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 gastrointestinal events. Borderline elevations of 1 or more liver tests may occur in patients taking NSAIDs, including meloxicam, which may worsen. It is unclear how applicable these potential risks are for meloxicam when given as single dose via local administration (a novel administration method for meloxicam) for postoperative pain as part of a fixed-ratio combination (eg, HTX-011). Any subject in this study with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction.

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

Prior HTX-011 clinical study protocols did not include scheduled preoperative NSAIDs, such as ketorolac.

For more information on HTX-011, refer to the Investigator's Brochure (IB). For more information on the active pharmaceutical ingredients , bupivacaine and meloxicam, refer to the local product labels. Literature reports that intraoperative ketorolac is used in conjunction with postoperative NSAIDs (Kelley 2013; Dalury 2016). The Investigator should also refer to the respective package inserts for information on risks associated with the required concomitant medications (oral acetaminophen, IV fentanyl, oral ibuprofen, and in Optional Cohort 2 ketorolac) as well as midazolam, general anesthetics, anti-emetics, antibiotics, other opioids and any other approved medications likely to be administered while a subject participates in this study.

2. STUDY OBJECTIVES

2.1. Primary Objective

Primary Objective:

- To assess the proportion of subjects who are opioid-free after receiving HTX-011 as part of a multimodal analgesic regimen during the first 72 hours following unilateral open inguinal herniorrhaphy with mesh.

2.2. Secondary Objectives

Secondary Objectives:

- To assess the total opioid use following HTX-011 as part of a multimodal analgesic regimen during the first 72 hours following surgery in this study population.
- To assess the proportion of subjects who are opioid-free after receiving HTX-011 as part of a multimodal analgesic regimen during the first 72 hours that remain opioid-free through Day 10 and Day 28.
- To assess the relationship between opioid use and severe pain.

3. INVESTIGATIONAL PLAN AND ENDPOINTS

3.1. Description of the Study Design

3.1.1. Overall Study Design

This is a Phase 2, open-label study in subjects undergoing unilateral open inguinal herniorrhaphy.

3.1.2. Treatment Groups

Cohort 1

Cohort 1 will be composed of approximately 30 subjects. Subjects will be screened within 21 days prior to surgery. Subjects who meet the Screening eligibility criteria will be allowed to participate in the study.

On the day of surgery (Day 1), subjects who continue to meet the eligibility criteria will undergo inguinal herniorrhaphy with mesh under general anesthesia. Spinal, epidural, or regional anesthesia is not allowed. Preoperative NSAIDs are not allowed. Approximately 2 hours prior to the start of induction of general anesthesia, subjects are to receive 1 g oral acetaminophen. However, if the start of general anesthesia is delayed by more than 4 hours, the subject must not be enrolled unless the surgery is rescheduled for a later day (if this puts the subject out of the screening window, screening assessments may be re-performed). All subjects will then receive a scheduled postoperative analgesic regimen as follows: start with 600 mg oral ibuprofen once they are able to tolerate oral intake in the postoperative care unit, then 3 hours after the ibuprofen dose administer the first postoperative dose of 1 g oral acetaminophen, then alternate these 2medications so a dose is delivered every 3 hours. In other words, 3 hours after their first 600 mg oral ibuprofen dose, they will receive a 1 g oral acetaminophen dose, then after 3 more hours another 600 mg oral ibuprofen dose, and so on until the 72-hour postoperative period is complete.

Optional Cohort 2

At the Sponsor's discretion upon completion of Cohort 1, Optional Cohort 2 may be initiated. If conducted, Optional Cohort 2 will be composed of approximately 30 subjects. Optional Cohort 2 would consist of the same required preoperative, intraoperative, and scheduled pain medication regimen as in Cohort 1 would be required with the intra-operative addition prior to wound closure of 1 dose of IV ketorolac as follows:

- For subjects aged ≥65 years, Serum Creatinine >1.5, and/or weight <50 kg: 15 mg.
- For subjects aged <65 years and/or weight ≥50 kg: 30 mg.

Optional Cohort 3

At the Sponsor's discretion upon completion of Optional Cohort 2, Optional Cohort 3 may be initiated. If conducted, Optional Cohort 3 will be composed of approximately 30 subjects. The specific multimodal analgesic regimen in Optional Cohort 3 will be determined by the Sponsor and included in a protocol amendment.

3.1.3. Inpatient Scheduled Analgesic Regimen (Preoperative, Intraoperative, and Through 72 hours Postoperative) – All Cohorts

Preoperative

Approximately 2 hours prior to the start of induction of general anesthesia, subjects are to receive 1 g oral (PO) acetaminophen.

Intraoperative

During surgery, the use of IV fentanyl up to 3 μg/kg will be permitted for intraoperative pain control. Just prior to the end of the surgery, all subjects will receive an additional 50 μg IV fentanyl in order to decrease the inherent variability of intraoperative pain control on immediate postoperative pain. As an example, the maximum total amount of fentanyl used during surgery for a 70 kg subject should not exceed 260 μg (3 μg/kg × 70 kg = 210 μg for intraoperative pain control + 50 μg at the end of the case = 260 μg total).

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

Near the completion of surgery and after final irrigation and suction of each layer have been completed, a single dose of HTX-011 will be given intraoperatively via instillation into the surgical site.

In Optional Cohort 2, subjects will also receive IV ketorolac intraoperatively prior to wound closure.

Postoperative

Following surgery and immediate postoperative recovery, subjects will be transferred to the postanesthesia care unit (PACU). Subjects will remain in the hospital/research facility for a minimum of 72 hours after administration of HTX-011. During the 72-hour inpatient period, subjects' pain will be assessed via pain NRS-R.

During the 72-hour postoperative period, subjects will receive a scheduled analgesic regimen as follows: start with 600 mg oral ibuprofen once they are able to tolerate oral intake in the postoperative care unit, then 3 hours after the ibuprofen dose administer the first postoperative dose of 1 g oral acetaminophen, then alternate these 2 medications so a dose is delivered every 3 hours. In other words, 3 hours after their first 600 mg oral ibuprofen dose, they will receive a 1 g oral acetaminophen dose, then after 3 more hours another 600 mg oral ibuprofen dose, and so on until the 72-hour postoperative period is complete. These medications are given on a round-the-clock, scheduled basis through the 72-hour postoperative period.

Inpatient Postoperative Opioid Rescue Medications

During the 72-hour postoperative period, subjects should only receive opioid rescue medication upon request for pain control, as needed. Rescue medication should not be given for pain prophylaxis, but only for treating postoperative pain. Each administration of opioid rescue medication will be recorded.

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

Postoperative rescue medication will consist of PO immediate-release oxycodone (no more than 10 mg within a 4-hour period as needed) or IV morphine (no more than 10 mg within a 2-hour period as needed). Administration of other opioids or any other analgesics (eg, ketamine, pregabalin), local anesthetics, or anti-inflammatory agents (except as specified by the protocol) 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). Combination opioid/non-opioid products (eg, Percocet) are not allowed.

After the 72-hour inpatient period has been completed, subjects may be discharged. Subjects who are not medically ready for discharge at 72 hours may receive the same scheduled and rescue medications to treat postoperative pain until discharge.

Discharge/ Postoperative Analgesic Regimen (following the 72-hour postoperative period to Day 28)

Upon discharge, subjects will be instructed to manage pain with the following regimen:

- 600 mg oral ibuprofen every 6 hours PRN as first-line therapy (before acetaminophen).
- 1g oral acetaminophen every 6 hours PRN as second-line therapy (ie, if ibuprofen has been tried but the subject is still in pain).

See Appendix E for instructions on postoperative pain management for subjects medically ready for discharge.

If a subject has not received any opioids during the 72-hour postoperative period, they should not receive an opioid prescription on discharge. If a subject has received any opioids in the 12 hours prior to discharge, the subject should be provided with a paper prescription for oxycodone (up to 5 mg PO q4h, #15, as needed). Pharmacists should be instructed that substitutions with any other opioid-containing product are not permitted, and combination opioid/non-opioid products are not allowed. All subjects (whether or not they were discharged with an opioid prescription) will complete a daily diary to record whether they take an opioid medication between 72 hours and Day 28 and, if yes, reason for taking (relative to surgery or other).

Subjects will return to the study site on Days 10 and 28 to complete follow up assessments per the Schedule of Events.

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

3.2. Study Endpoints

3.2.1. Efficacy Endpoints

3.2.1.1. Primary Efficacy Endpoint

- Proportion of subjects receiving no opioid rescue from 0-72 hours.

3.2.1.2. Secondary Efficacy Endpoints

- Total postoperative opioid consumption (in IV morphine milligram equivalents [IV MME]) through 72 hours.
- Proportion of subjects receiving no opioid rescue over the following time intervals: 0-24 hours, 24-48 hours, 0-48 hours, 24-72 hours, 48-72 hours.
- Proportion of subjects receiving no opioid rescue from 0-72 hours who receive no opioid rescue through Day 10, and through Day 28.
- Proportion of subjects in severe pain (NRS >7) at any point in the first 72 hours postoperatively.

3.2.2. Safety Endpoints

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

3.3. Study Duration

The overall duration of the study is anticipated to be approximately 8 months. The total duration of study participation for each subject (from Screening through the Day 28 follow-up visit) will be up to 53 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

Up to approximately 90 subjects may be enrolled in the study.

Approximately 30 subjects will be dosed in Cohort 1 of this study at up to 5 study sites in the US. An additional 30 subjects may be dosed in the additional optional cohorts using the same study sites.

4.1.1. Inclusion Criteria

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

1. Is able to provide written informed consent.
2. Is able to adhere to the study visit schedule and complete all study assessments.
3. Is male or female, and ≥18 years of age at screening.

4. Is scheduled to undergo a unilateral open inguinal herniorrhaphy with mesh under general anesthesia.
5. Has an American Society of Anesthesiologists 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 oral contraceptive approved by applicable regulatory authorities for greater than 2 months prior to screening and commits to the use of an acceptable form of birth control for the duration of the study and for 30 days after study drug administration. Note: women in only a same-sex relationship do not need to meet this criterion.

4.1.2. Exclusion Criteria

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

1. Had any prior inguinal hernia repair except as a child (less than 6 years of age).
2. Has a planned concurrent surgical procedure (eg, bilateral herniorrhaphy).
3. Has a pre-existing concurrent acute or chronic painful physical/restrictive condition expected to require analgesic treatment in the postoperative period for pain that is not strictly related to the herniorrhaphy and which may confound the postoperative assessments.
4. Has a contraindication or a known or suspected history of hypersensitivity or clinically significant idiosyncratic reaction to bupivacaine (or other local anesthetics), meloxicam, ibuprofen, and for Optional Cohort 2 ketorolac (or other NSAIDs), oxycodone, morphine, acetaminophen, pregabalin, or fentanyl. Subjects in all cohorts must not have any contraindications to any of the protocol-specified drugs (bupivacaine, meloxicam, fentanyl, ibuprofen, acetaminophen, morphine, or oxycodone). Subjects in Optional Cohort 2 must also not have any contraindications to ketorolac.
5. Has known or suspected daily use of opioids for 7 or more consecutive days within the previous 6 months.
6. Has taken NSAIDs (including meloxicam, ibuprofen or, for Optional Cohort 2, ketorolac) within least 10 days prior to the scheduled surgery with the exception of subjects on low-dose (≤100 mg) daily acetylsalicylic acid for cardioprotection.
7. Has taken long-acting opioids within 3 days prior to the scheduled surgery.
8. Has taken any opioids within 24 hours prior to the scheduled surgery.
9. Has been administered bupivacaine within 5 days prior to the scheduled surgery.

10. Has been administered any local anesthetic within 72 hours prior to the scheduled surgery, other than for pretreatment prior to a needle placement, to treat an AE that occurs after signing the ICF, or to decrease venous irritation (eg, caused by propofol, in which case no more than a single administration of lidocaine 1% 20 mg IV may be administered).
11. Has initiated treatment with any of the following medications within 1 month prior to study drug administration or is taking any of these medications to control pain: selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin, or cyclooxygenase-2 (COX-2) inhibitors. (Note: If a subject is taking one of these medications for a reason other than pain control, the subject must be on a stable scheduled dose [ie, not "as needed"] for at least 1 month prior to study drug administration.) Anxiolytics prior to surgery are permitted, if necessary.
12. Has been administered systemic steroids within 5 half-lives or 10 days prior to administration of study drug (whichever is longer). Note that for purposes of this exclusion criterion, inhaled, ophthalmic, and over-the-counter steroids are not considered systemic.
13. Has a medical condition such that, in the opinion of the Investigator, participating in the study would pose a health risk to the subject or confound the postoperative assessments. Conditions may include, but are not limited to, any of the following:
    a. History of 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 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 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, and/or having a serum creatinine >2 × ULN.
    f. History of known or suspected coagulopathy or uncontrolled anticoagulation (PLT count <100,000/μL; hemoglobin <12 g/dL; or hematocrit <35%).
    g. Loss of sensation in extremities or significant peripheral neuropathy.
14. As per subject history and/or medical records, has active infection or is currently undergoing treatment for Hepatitis B, Hepatitis C, or human immunodeficiency virus (HIV).
15. Has uncontrolled anxiety, psychiatric, or neurological disorder that, in the opinion of the Investigator, might interfere with study assessments.
16. Had a malignancy in the last year, with the exception of nonmetastatic basal cell or squamous cell carcinoma of the skin or localized carcinoma in situ of the cervix.
17. Has a known or suspected history of drug abuse, a positive drug screen on the day of surgery, or a recent history of alcohol abuse. Note: Subjects with a positive drug screen

who are taking an allowed, prescribed medication that is known to result in a positive drug test (eg, amphetamine and dextroamphetamine for attention-deficit/hyperactivity disorder, benzodiazepine for anxiety disorder) may be eligible for participation in the study at the discretion of the Sponsor. Subjects taking any marijuana (medical or recreational) are not allowed to participate in the study.

18. Previously participated in an HTX-011 study.
19. Received an investigational product or device in a clinical trial within 30 days or within 5 elimination half-lives (whichever is longer) prior to surgery or is planning to take part in another clinical trial while participating in this study.
20. Has undergone 3 or more surgeries within 12 months prior to signing the ICF, other than for diagnostic procedures (eg, colonoscopy).
21. Has a body mass index (BMI) >39 kg/m^2. (Appendix B provides information about how to determine BMI.)

4.2. Method of Enrolling Subjects

Subjects who meet the screening eligibility criteria will be enrolled across the study sites into the sequential cohorts. No slotting of subjects per site will be implemented.

4.2.1. 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 but who do not meet the eligibility criteria on Day 1 will be withdrawn from the study without receiving study drug. In the event a subject does not meet the eligibility criteria, but is 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

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:

- Adverse event.
- Withdrawal by subject.

- Death.
- Lost to follow up.
- Pregnancy.
- Investigator's decision.
- Sponsor's decision.

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

4.4.2. Subject Replacement

Enrolled subjects who withdraw from study will not be replaced. To account for withdrawal of subjects who are ineligible at Day 1 or are otherwise enrolled but not dosed, enrollment will continue until at least 30 subjects have been enrolled and dosed in each cohort.

5. STUDY TREATMENT

All subjects will receive a single dose of HTX-011 300 mg/9 mg (bupivacaine/meloxicam doses) administered via instillation into the surgical site while undergoing a herniorrhaphy. Study drug is defined as HTX-011 (investigational product).

HTX-011 will be supplied by the Sponsor. Other required medications and rescue medications will be supplied by the sites (eg, fentanyl, ketorolac, ibuprofen, acetaminophen, oxycodone, morphine); HTX-011 is the only medication considered "study drug."

5.1. Description of Investigational Product

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

5.2. Manufacturing, Packaging, and Labeling

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

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

5.3. Storage

At the study site, HTX-011 should be stored at a controlled room temperature of 20 to 25°C (with excursions permitted from 15 to 30°C) and protected from light. A temperature log must be maintained to monitor the room's temperature. Temperature monitoring includes min/max temp over each 24-hour period.

The storage location should be locked with restricted access.

Acetaminophen, ibuprofen, and (for Optional Cohort 2) ketorolac will be stored as per the prescribing information.

5.4. Preparation

Study drug will be prepared at the study site. HTX-011 will be prepared in a group of syringes with a Luer lock applicator attached. Refer to the Pharmacy Manual for details on study drug preparation.

5.5. Study Drug Administration

HTX-011 will be given via instillation into the surgical site after irrigation and suction of each layer are complete and prior to suturing.

5.5.1. Instillation of HTX-011

HTX-011 will be administered via instillation using a Luer lock applicator supplied by the Sponsor. Following irrigation and suction of each fascial layer, the Luer lock applicator should be used to instill HTX-011 evenly to the tissues within the surgical site that could result in pain generation. After the hernia repair is complete, but prior to surgical site closure, apply HTX-011 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).

5.6. Study Drug Compliance

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

5.7. Study Drug Accountability

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

All study drug records must be readily available for inspection by the site's 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 clinical monitor has verified the accuracy of the study drug records at the study site. All returns, disposal, or destruction must be approved by the Sponsor in writing.

6. STUDY PROCEDURES AND ASSESSMENTS

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

6.1. Medical History and Demographics

6.1.1. Medical History

A complete medical history will be obtained before 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, where acceptable by local authorities.

6.2. Prior and Concomitant Therapy

All medications taken by subjects between signing the ICF and Day 28 will be recorded in the subject's eCRF if enrolled.

During the 72-hour postoperative period, the name, dose, and route, as well as the start date and time, of concomitant medications must be recorded. Medications include prescription or

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

After the 72-hour period until the Day 28 Visit, at least the start date of each concomitant medication should be recorded.

6.2.1. Required Concomitant Medications

Other mandatory medications in this study include oral acetaminophen preoperatively, IV fentanyl intraoperatively, and both oral ibuprofen and oral acetaminophen postoperatively. If performed, all subjects in Optional Cohort 2 will receive IV ketorolac intraoperatively in addition to the regimen specified in Cohort 1. The other mandatory medications for Optional Cohort 3 will be defined in a protocol amendment following the results of Cohort 1 and Optional Cohort 2.

Cohort 1

Preoperative Medication:

Approximately 2 hours prior to the start of induction of general anesthesia, subjects are to receive 1 g oral acetaminophen.

Intraoperative medication: All subjects will receive 50 µg IV fentanyl just prior to the end of the surgery.

Postoperative medication: During the 72-hour postoperative period, subjects will receive a scheduled analgesic regimen as follows: start with 600 mg oral ibuprofen once they are able to tolerate oral intake in the postoperative care unit, then 3 hours after the ibuprofen dose administer the first postoperative dose of 1 g oral acetaminophen, then alternate these 2 medications so a dose is delivered every 3 hours. In other words, 3 hours after their first 600 mg oral ibuprofen dose, they will receive a 1 g oral acetaminophen dose, then after 3 more hours another 600 mg oral ibuprofen dose, and so on until the 72-hour postoperative period is complete. These medications are given on a round-the-clock, scheduled basis through the 72-hour postoperative period.

Optional Cohort 2

Preoperative Medication:

Approximately 2 hours prior to the start of induction of general anesthesia, subjects are to receive 1 g oral acetaminophen.

Intraoperative medication:

All subjects will receive 50 µg IV fentanyl just prior to the end of the surgery. In addition, one dose of IV ketorolac will be given intraoperatively prior to wound closure as follows:

- For subjects aged ≥65 years, serum creatinine >1.5 and/or weight <50 kg: 15 mg.
- For subjects aged <65years and/or weight ≥50 kg: 30 mg.

Postoperative medication:

During the 72-hour postoperative period, subjects will receive a scheduled analgesic regimen as follows: start with 600 mg oral ibuprofen once they are able to tolerate oral intake in the postoperative care unit, then 3 hours after the ibuprofen dose administer the first postoperative dose of 1 g oral acetaminophen, then alternate these 2 medications so a dose is delivered every 3 hours. In other words, 3 hours after their first 600 mg oral ibuprofen dose, they will receive a 1 g oral acetaminophen dose, then after 3 more hours another 600 mg oral ibuprofen dose, and so on until the 72-hour postoperative period is complete. These medications are given on a round-the-clock, scheduled basis through the 72-hour postoperative period.

Optional Cohort 3

The required preoperative, intraoperative, and postoperative medications are to be confirmed by protocol amendment.

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 in keeping with the standard of medical care.

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

During surgery, the use of IV fentanyl up to 3 µg/kg is permitted for intraoperative pain control. As an example, the maximum total amount of fentanyl used during surgery for a 70 kg subject should not exceed 260 µg (3 µg/kg × 70 kg = 210 µg for intraoperative pain control + 50 µg at

the end of the case = 260 µg total). As the prescribing information for fentanyl citrate (Fentanyl Citrate USPI 2012) specifies that for intraoperative use a "moderate dose" of 2 to 20 µg/kg IV is necessary in order to allow the anesthesiologist to respond to any signal that the surgical stress is increasing or anesthesia lightening, this dose was chosen to be in the lowermost portion of that range and therefore not interfere with assessment of postoperative opioid load. As clinically appropriate, the minimum possible fentanyl dose should be used.

Inpatient Postoperative Opioid Rescue Medications

During the 72-hour postoperative period, subjects should only receive opioid rescue medication upon request for pain control, as needed. Rescue medication should not be given for pain prophylaxis, but only for treating postoperative pain. Each administration of opioid rescue medication will be recorded.

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

Postoperative rescue medication will consist of PO immediate-release oxycodone (no more than 10 mg within a 4-hour period as needed) or IV morphine (no more than 10 mg within a 2-hour period as needed). Administration of other opioids or any other analgesics (eg, ketamine, pregabalin), local anesthetics, or anti-inflammatory agents (except as specified by the protocol) 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). Combination opioid/non-opioid products (eg, Percocet) are not allowed.

Discharge/ Postoperative Analgesic Regimen (following the 72-hour postoperative period to Day 28)

Upon discharge, subjects will be instructed to manage pain with the following regimen:

- 600 mg oral ibuprofen every 6 hours PRN as first-line therapy (before acetaminophen).
- 1 g oral acetaminophen every 6 hours PRN as second-line therapy (ie, if ibuprofen has been administered but the subject is still in pain).

If a subject has not received any opioids during the 72-hour postoperative period, they should not receive an opioid prescription on discharge.

If a subject has received any opioids in the 12 hours prior to discharge, the subject should be provided with a paper prescription for oxycodone (up to 5 mg PO q4h, #15, as needed). Pharmacists should be instructed that substitutions with any other opioid-containing product are not permitted, including combination opioid/non-opioid products.

All subjects (whether or not they were discharged with an opioid prescription) will complete a daily diary to record whether they take an opioid medication between 72 hours and Day 28 and, if yes, reason for taking (relative to surgery or other).

Appendix E provides information on postoperative pain management for subjects who are medically ready for discharge.

6.2.3. Prohibited Medications

6.2.3.1. Medications Prohibited Prior to Surgery

Refer to exclusion criteria 5 through 12 and 17 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, midazolam, acetaminophen, general anesthetics, anti-emetics, antibiotics, other opioids and any other approved medications likely to 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.

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

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).

Antiemetic medications should not be administered prophylactically, ie, as a routine preventative in the absence of signs or symptoms of nausea or vomiting.

6.2.3.3. Medications Prohibited From Time 0 Through 72 Hours

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

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

6.3. Efficacy Assessments

6.3.1. Use of Opioid Medications

6.3.1.1. Opioid Rescue Medication Through 72 Hours

The name, dose, and route as well as the date and time of administration of any opioid rescue medication must be recorded in the subject's eCRF from Time 0 through 72 hours. 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. Subject Daily Diary of Opioid Use From 72 Hours Through Day 28

Subjects will be provided a daily diary to record if they take any opioid medication from 72 hours through Day 28 (±4 days) (yes or no).

6.3.2. Pain Intensity Assessment

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

Pain intensity scores will be assessed using an 11-point NRS-R (0–10) where 0 represents "no pain" and 10 represents "worst pain imaginable" (Breivik 2008).

For the 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.

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

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 Day 28. Section 8 provides details on safety monitoring and recording.

6.4.2. Physical Examinations

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

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

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

6.4.3. 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 and post-treatment 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. The local ECG tracings will be reviewed by the investigator for safety.

6.4.5. Wound Healing Assessment

Surgical wound healing will be evaluated by the Investigator or other medically qualified clinical site personnel; every attempt should be made by the site to use the same assessor for individual

subject assessments. The findings will be graded according to the Southampton Wound Scoring System (Bailey 1992); Appendix E.

6.4.6. Clinical Laboratory Tests

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

Laboratory results will be reviewed by the Investigator. Any laboratory values outside of the normal reference range will be evaluated for clinical significance. 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 (Central Laboratory):	
Hematology	**Serum Chemistry**
Hematocrit	Alanine aminotransferase
Hemoglobin	Albumin
Red blood cell count	Alkaline phosphatase
Mean Corpuscular Volume White blood cell count (with automated differential) Platelet count	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. See Section 6 for information on study procedures and assessments.

Unless there is a safety concern, every effort should be made to avoid protocol deviations. For pain assessments at timepoints when the subject is asleep, an attempt should be made to wake the subject. If there is no response, the assessments at these timepoints may be recorded as “Not Done.” Assessments that can be done without waking the subject (eg, blood collection for PK)

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

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

- 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).
- Vital signs.
- 12-lead ECG.
- Blood sample collection.
- Physical examination.
- Wound healing assessment.

7.1. Screening Period

After providing written informed consent, potential study subjects will undergo Screening procedures to confirm eligibility to participate in the study. Screening procedures must be performed within 21 days prior to surgery. The Investigator must evaluate the subject's medical history and the results of all Screening assessments to determine study eligibility before the subject is enrolled.

Screening procedures and assessments will include the following:

- Urine drug screen.
- Urine pregnancy test (female subjects of childbearing potential only).
- Medical history.
- Demographic recording.
- Physical examination (including weight, height, and BMI calculation).
- Vital signs measurements.
- 12-lead ECG (in triplicate).
- Blood sample collection for the hematology and serum chemistry.
- Subject training for pain intensity assessments.
- AE recording (from the time the subject signs the ICF).
- Prior medication recording (from the time the subject signs the ICF).

The urine drug screen and urine pregnancy test should be performed first, and the results should be confirmed as negative prior to performing any additional assessments. A subject who fails the drug test may be rescreened once at the discretion of the Investigator. Subjects with a positive drug screen who are taking an allowed, prescribed medication that is known to result in a positive drug test (eg, amphetamine and dextroamphetamine for attention-deficit/hyperactivity

disorder, benzodiazepine for anxiety disorder) may be eligible for participation in the study. Any other screening laboratory test result that does not meet the eligibility criteria may not be repeated without the Sponsor's approval.

All subjects who meet the screening eligibility criteria will be enrolled.

7.2. Treatment and Postoperative Observation Period

7.2.1. Day of Surgery (Day 1)

7.2.1.1.1. Prior to Surgery

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

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

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

7.2.1.2. Surgery and Study Drug Administration

Subjects will undergo an inguinal herniorrhaphy under general anesthesia. Epidural spinal, or regional anesthesia is not permitted. Sites should follow intraoperative safety monitoring in accordance with American Society of Anesthesiologists (ASA) Standards for Basic Anesthetic Monitoring (American Society of Anesthesiologists 2015), which is consistent with the European Board of Anaesthesiology recommendations for minimal monitoring during Anaesthesia and Recovery (for review in 2018) (EBA UEMS 2016). The start and stop time of surgery and additional surgical details (including the length of the surgical incision) should be recorded in the eCRF.

Subjects will be administered study drug unless they experience a clinically significant event during surgery (eg, excessive bleeding, hemodynamic instability) that would render the subject medically unstable or complicate their postoperative course. Study drug will be administered via instillation 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 study drug dosing will be recorded in the eCRF. Details of administration will be recorded on a worksheet, which will be used in the dictation of the surgical notes and will become part of the source document. **Note: The start of study drug administration will be considered as Time 0 for all efficacy 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.

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

7.2.2. Postoperative Assessment Period (Up to 72 Hours)

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

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

- **NRS-R pain intensity assessments:** at 60 minutes (±5 min), 120 minutes and 4 hours (±15 min), 8 and 12 hours (±30 min), 24 hours (±1 h); 36 and 48 hours (±2 h), 60 and 72 hours (±4 h).
  - Note: If a subject requires rescue medication before the 1-hour pain intensity assessments, then an unscheduled NRS-R pain score must be obtained before administering the first dose of rescue medication. This does not replace the 1-hour NRS-R assessment.
- **Vital signs measurements:** 60 minutes (±5 min), 90 minutes(±15 min), 4 hours (±15 min), 8 hours (±30 min), 12 hours (±30 min), 24 hours (±1 h), 36 hours (±2 h), 48 hours (±2 h), 60 hours (±4 h), and 72 hours (±4 h).
- **12-lead ECG (in triplicate)**: 4 hours (±15 min), 24 hours (±1 h), 48 hours (±2 h), and 72 hours (±4 h).
- **Physical examination:** 72 hours (±4 h; height and weight not required).
- **Blood sample for hematology and serum chemistry tests:** 24 hours (±1 h; hematology only) and 72 hours (±4 h; hematology and serum chemistry).
- **Wound healing assessment:** 72 hours (±4 h).
- **AE recording:** (Note: the start date and time of all AEs during this timeframe must be recorded).
- **Concomitant medication recording:** (Note: the start date and time of all concomitant medications during this timeframe must be recorded).

7.2.3. End of the Postoperative Assessment Period

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

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

For subjects who are medically ready for discharge at 72 hours, oral ibuprofen (no more than 600 mg every 6 hours as needed) and oral acetaminophen (no more than 1000 mg every 6 hours as needed) should be recommended for postoperative pain. If a subject received 10 mg or more of any opioids in the 12 hours prior to discharge, the subject should be provided with a prescription for oxycodone (up to 10 mg PO q4h as needed, #15, no substitutions). See Appendix E for instructions on postoperative pain management for subjects medically ready for discharge.

All subjects will be given a diary to complete daily and record whether they take any opioid medication from 72 hours through Day 28. This applies to all subjects.

7.3. Follow-Up Period

7.3.1. Day 10 Visit (±3 Days)

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

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

7.3.2. Day 28 Visit (±4 Days)

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

- NRS-R pain intensity assessment.
- Wound healing assessment.
- Review subject diary results.
- AE recording.
- Concomitant medication recording

7.4. Early Termination Visit

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

- NRS-R pain intensity assessment.
- Vital signs (if withdrew prior to 72 hours).
- Blood sample collection for hematology and serum chemistry (if withdrew prior to 72 hours).
- 12-lead ECG (triplicate) (if withdrew prior to 72 hours).

- Physical examination (if withdrew prior to 72 hours [height and weight not required])
- Wound healing assessment
- Review and record subject diary results in the eCRF (if after the 72-hour discharge but before Day 28)
- AE recording
- Concomitant medication recording

7.5. Unscheduled Visits and Assessments

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

- Vital signs.
- Physical examination.
- ECG.
- Wound healing assessment.
- AE recording.
- Concomitant medication recording.

8. SAFETY MONITORING AND REPORTING

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

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

8.1. Definition of Safety Parameters

8.1.1. Definition of an Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether 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 considered causally associated with the use of the study drug. Any abnormal physical examination findings, laboratory value, vital sign result, ECG finding, or wound healing assessment finding deemed clinically significant by the Investigator, regardless of causal relationship, must be reported as an

AE. A clinical diagnosis, rather than the changes in laboratory analyte or other assessment, should be recorded (eg, anemia rather than low hemoglobin value).

Examples of AEs include the following:

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

The following examples are not considered AEs:

- Medical or surgical procedure (eg, endoscopy, appendectomy), although the condition that leads to the procedure is an AE.
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) (including laboratory values) present or detected at the start of the study that do not worsen.
- The disease or disorder being studied, or expected progression, signs, or symptoms of the disease or disorder being studied, unless they become more severe or occur with a greater frequency than expected for the subject's condition.
- Transient paresthesia that is considered 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 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 HTX-011 based on his/her clinical judgment. The Investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. 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 for enrolled subjects 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 Day 28. Note: the AE start time, as well as the date, must be recorded during the 72-hour postoperative period.

For subjects who received study drug, if an Investigator becomes aware of an SAE that occurs in a subject more than 28 days after study drug administration and the Investigator considers the event to be possibly related to the study drug, the Investigator needs to report the SAE to the Sponsor as described in Section 8.4.1.

8.3.2. Follow-Up of Events

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

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

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

- **Recovered/Resolved:** The event resolved, or the subject recovered without sequelae. An event (either serious or nonserious) occurred and had an endpoint, and the subject experienced no restrictions. Examples include stent placement for coronary artery disease (a device implanted is not a sequela), an appendectomy (a scar is not a sequela), a postoperative wound infection, or an upper respiratory tract infection.
- **Recovered/Resolved with sequelae:** The event has at least one secondary outcome that may result in permanent disability, functional limitation, or both. Such sequelae are usually limited to SAEs. Examples include hip replacement resulting in foot drop (foot drop is not the intended outcome but is a risk of surgery), stroke resulting in paralysis, or emboli formation after a bacterial infection resulting in a renal infarct and loss of renal function.

- **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 this study, regardless of relationship to study drug, he/she must notify the Sponsor by entering the SAE information into the eCRF **within 24 hours of the Investigator becoming aware of the SAE**.

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

Email Address: Heron_PV@ubc.com

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

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

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

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

If the Investigator does not have all information regarding an SAE, he/she must not wait to receive additional information before notifying the Sponsor of the event. The SAE must be

updated when additional information is received. Follow-up information received on all SAEs must be forwarded to the Sponsor using the same timelines as for an initial report.

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

8.4.2. Reporting Unanticipated Problems to the Sponsor

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

Email Address: Heron_PV@ubc.com

The following information will be included with unanticipated problem reporting:

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

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

8.4.3. Regulatory Reporting Requirements

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

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

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

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

8.4.4. Pregnancy Reporting

Pregnancy is not considered an AE; however, any subject who becomes pregnant during the study must be withdrawn from the study immediately. Female subjects who become pregnant within 28 days after receiving study drug should also notify the Investigator. The Investigator must attempt to follow the pregnancy to term or termination 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 Product Safety and Risk Management Committee will monitor safety data on a periodic basis throughout the study (ie, monthly unless more frequent monitoring is necessary due to high enrollment or safety concern), including regular review of ECG findings, AEs, and SAEs.

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

9. OTHER STUDY RESTRICTIONS

9.1. Contraception

Female subjects of 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 oral contraceptive approved by applicable regulatory authorities. Note: The does not apply to women in only a same-sex relationship or women in a monogamous relationship with a surgically sterile partner.

10. STATISTICAL CONSIDERATIONS

10.1. General Considerations

All data will be listed by subject and all safety and efficacy endpoints will be summarized by treatment group. 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

The sample size in this study was selected empirically without a formal statistical assumption.

10.3. Analysis Populations

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

10.4. Statistical Analysis Methods

10.4.1. Disposition and Demographics

The number and percentage of subjects in the Safety Population will be summarized. Subject disposition, including the number of subjects screened, enrolled, dosed, completing the

72-hour postoperative observation period, completing Day 28, and not completing Day 28 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 data will be summarized by treatment group. No statistical hypothesis testing will be performed. For opioid rescue summaries, the proportion of subjects receiving no opioid rescue will be summarized as the proportion of subjects with a total IV MME dose = 0 over the relevant timeframe.

10.4.2.1. Handling of Missing Data

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

10.4.3. Safety Analysis

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

AEs that occur between the time the subject signs the ICF and the start of study drug administration will be considered pretreatment AEs. AEs that start during or after study drug administration, or AEs with an onset prior to study drug administration that worsen after study drug administration will be considered TEAEs. All TEAEs will be coded and tabulated by System Organ Class and Preferred Term. Incidence of TEAEs and SAEs will be summarized and presented in descending order of frequency. AEs leading to study withdrawal, if any, will be listed separately.

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

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

Wound healing assessment results will be summarized at each timepoint.

10.5. Interim Analysis

No formal interim analyses are planned.

11. QUALITY ASSURANCE AND QUALITY CONTROL

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

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

12. REGULATORY AND ETHICAL CONSIDERATIONS

12.1. Regulatory Authority Approval

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

12.2. Ethical Conduct of the Study

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

12.3. Ethics Committee Approval

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

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

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

12.4. Informed Consent Process

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

The Sponsor (or its designee) will provide Investigators with a multicenter ICF for this study. Investigators may adapt the information to suit the needs of their institution, if necessary (although it must reflect the required elements of informed consent specified in 21 CFR

Part 50.25). The final ICF must be accepted by the Sponsor and approved by the EC. Investigators must provide the Sponsor with an unsigned copy of the final ICF before and after it is approved by the EC. If any new information becomes available that might affect subjects' willingness to participate in the study, or if any amendments to the protocol require changes to the ICF, the Sponsor will provide Investigators with a revised ICF.

Prior to participating in any study-related procedure, each subject must sign and date an EC-approved ICF written in a language the subject can understand. The ICF should be as

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

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

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

12.5. Confidentiality

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

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

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

To comply with ICH guidelines for GCP and to verify compliance with this protocol, the Sponsor requires that the Investigator permit its monitor or designee's monitor, representatives

from any regulatory authority, the Sponsor's designated auditors, and the appropriate ECs to review the subject's original medical records (source data or documents), including, but not limited to, clinical laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization by the subject as part of the informed consent process (Section 12.4).

13. STUDY ADMINISTRATION

13.1. Clinical Monitoring

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

13.2. Source Documents and Record Retention

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

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

13.3. Management of Protocol Amendments and Deviations

13.3.1. Protocol Modification

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

13.3.2. Protocol Deviations

Protocol deviations are a change, divergence, or departure from the study design or procedures defined in this protocol. An Important Protocol Deviation is a deviation that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. 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. In the event of an Important Protocol Deviation, the site will notify the Sponsor or designee. The Sponsor is responsible for notifying the regulatory authorities of any protocol deviations, if required.

13.4. Financial Disclosure

Investigators in the US and outside the US 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 US regulations (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 described period.

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

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

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

13.5.1. Suspension of Study

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

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

13.5.2. Termination of Study or Investigational Site

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

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

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

13.6. Publication and Information Disclosure Policy

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

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

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

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

14. REFERENCE LIST

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APPENDIX A. AMERICAN SOCIETY OF ANESTHESIOLOGISTS PHYSICAL STATUS CLASSIFICATION SYSTEM

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

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

APPENDIX B. BMI CALCULATION

Body Mass Index = Weight in kilograms / (height in meters)^2 Meters = inches × 0.0254

Kilograms = pounds × 0.45

Example:

For a man who weighs 165 pounds and is 71 inches tall: 165 lbs. × 0.45 = 74.25 kg

71 in. × 0.0254 = 1.8 m

74.25 / (1.8 × 1.8) = 22.92 kg/m^2

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

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

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

The response must be one of the following:

□0 □1 □2 □3 □4 □5 □6 □7 □8 □9 □10

No Pain Worst Pain

Imaginable

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

APPENDIX D. WOUND HEALING ASSESSMENT – SOUTHAMPTON WOUND SCORING SYSTEM

The single highest grade should be recorded for wound healing assessments. For example, a subject with some bruising and erythema around sutures would be recorded as IIb, not as Ia + IIb.

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

Reference: Bailey, I. (1992). *Community surveillance of complications after hernia surgery*. BMJ 304: 469-471.

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

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

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

While you are at home, if you experience any pain from your operation, please take up to 3 over-the counter 200 mg ibuprofen (eg, Advil) every 6 hours as needed. If this does not control your pain, after 3 hours please take 2 over- the-counter extra-strength (500 mg) acetaminophen tablets (eg, Tylenol, Panadol) every 6 hours as needed. Do not take more than 8 tablets (4000 mg) of acetaminophen in a 24-hour period. If this does not control your pain, please call <<insert name and contact information>> so that we can talk about providing you with a prescription for something stronger, if needed.

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

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

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Approval	Erol Onel Medical 31-Aug-2018 18:56:59 GMT+0000

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