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Official Title:	A Phase 2, Randomized, Controlled Evaluation of the Efficacy and Safety of HTX-011 or HTX-002 for Post-Operative Analgesia Following Abdominoplasty Surgery
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CLINICAL STUDY PROTOCOL

PROTOCOL NUMBER HTX-011-C2015-203

(PRT-0048)

A Phase 2, Randomized, Controlled Evaluation of the Efficacy and Safety of HTX-011 or HTX-002 for Post-Operative Analgesia Following Abdominoplasty Surgery

U.S. IND Number: 125927

Compound Name:	HTX-011 (extended-release 2.5% bupivacaine and 0.075% meloxicam) HTX-002 (extended-release 2.5% bupivacaine)
Protocol Version:	12
Date of Protocol:	06 February 2017
Previous Versions:	Version 1: 04 December 2015 Version 2: 08 January 2016 Version 3: 21 January 2016 Version 4: 30 March 2016 Version 5: 29 April 2016 Version 6: 08 June 2016 Version 7: 08 August 2016 Version 8: 28 September 2016 Version 9: 30 November 2016 Version 10: 10 January 2017 Version 11: 18 January 2017

SPONSOR DETAILS

Name of Company:	Heron Therapeutics, Inc.
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INVESTIGATOR AGREEMENT

CLINICAL PROTOCOL HTX-011-C2015-203

A Phase 2, Randomized, Controlled Evaluation of the Efficacy and Safety of HTX-011 or HTX-002 for Post-Operative Analgesia Following Abdominoplasty Surgery

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 therein.

I will provide copies of the protocol and all information on the drug relating to the nonclinical and prior clinical experience which 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 drug and the conduct of the study.

I agree to keep records on all subject information (i.e., 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) regulations.

Principal Investigator: _____

Address: _____

Signature: _____

Date: _____

SYNOPSIS

Name of Sponsor/Company: Heron Therapeutics, Inc.	**Protocol Number:** HTX-011-C2015-203
Name of Investigational Product: HTX-011 (extended-release 2.5% bupivacaine and 0.075% meloxicam) • HTX-011-49 • HTX-011-56 HTX-002 (extended-release 2.5% bupivacaine)	**Protocol Title:** A Phase 2, Randomized, Controlled Evaluation of the Efficacy and Safety of HTX-011 or HTX-002 for Post-Operative Analgesia Following Abdominoplasty Surgery
Name of Active Ingredients: Bupivacaine and Meloxicam (HTX-011) Bupivacaine (HTX-002)	**Phase of Development:** 2

Objective:

The primary objective is to evaluate the efficacy and duration of analgesia following administration of HTX-011 or HTX-002 formulations.

The secondary objectives will be:

- To determine the safety and tolerability of HTX-011 and HTX-002 formulations
- To determine the optimum study drug administration technique
- To evaluate the pharmacokinetic (PK) profiles of bupivacaine and meloxicam in HTX-011 formulations and the PK profile of bupivacaine in HTX-002 over 120 hours after study drug administration
- To evaluate the analgesic effects of HTX-011 and HTX-002 formulations over various intervals using a series of secondary efficacy endpoints for pain intensity
- To assess the effects of HTX-011 and HTX-002 formulations on wound healing at 48 hours, at 72 hours, and on Days 10 and 28 post-treatment
- To evaluate nausea at 6, 24, 48, and 72 hours post-treatment
- To evaluate the percentage of subjects who remain pain free over time

Methodology: This is a Phase 2, randomized, controlled evaluation of the efficacy and safety of HTX-011 and HTX-002 for post-operative analgesia following abdominoplasty surgery in adult subjects undergoing abdominoplasty. The total duration of this study for each subject will be a maximum of 88 days that comprise 28-day screening period, 72 hours in-house treatment period, and 25 days post-treatment period involving 4 post-treatment visits to the clinic. Subjects will also receive a phone call from the study site on Day 60.

Up to approximately 523 subjects will be enrolled and studied as follows:

<u>Part A</u>

Part A of the study is the dose-escalation phase of the study. The primary objective of Part A will be to evaluate the efficacy and duration of analgesia following administration of two HTX-011 formulations (HTX-011-49 and HTX-011-56). An optimal formulation/dose will be selected from Part A, and the identified formulation/dose will be utilized for subjects who will be enrolled into Part B. In Part A of the study, the surgical procedure will be restricted to a mini-abdominoplasty, i.e., it will exclude liposuction and/or repositioning of the umbilicus.

Subjects enrolling into Part A will be randomized into each cohort at a ratio of 2:1 to either active or saline.

Enrollment of HTX-011-49 and HTX-011-56 cohorts may occur in parallel.

Approximately 90 subjects will be enrolled into Cohorts 1–6 with approximately 15 subjects per Cohort.

- Cohort 1 will be to evaluate the analgesic efficacy of 6.84 mL (200 mg) of HTX-011-49 compared to saline
- Cohort 2 will be to evaluate the analgesic efficacy of 13.68 mL (400 mg) of HTX-011-49 compared to saline

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- Cohort 3 will be to evaluate the analgesic efficacy of 20.52 mL (600 mg) of HTX-011-49 compared to saline
- Cohort 4 will be to evaluate the analgesic efficacy of 6.84 mL (200 mg) of HTX-011-56 compared to saline
- Cohort 5 will be to evaluate the analgesic efficacy of 13.68 mL (400 mg) of HTX-011-56 compared to saline
- Cohort 6 will be to evaluate the analgesic efficacy of 20.52 mL (600 mg) of HTX-011-56 compared to saline

Note: Dose-escalation to the next cohort will not proceed if any of the following are observed:

- 3 or more subjects experience an SAE reported by the investigator and confirmed by sponsor to be at least possibly related to active study medication.
- 3 or more subjects experience a neurological AE reported by the investigator and confirmed by sponsor to be at least possibly related to active study medication (excluding minor neurologic findings that are not clinically significant, e.g., headache, paresthesia).
- 3 or more subjects experience clinically significant ECG findings reported by the investigator and confirmed by sponsor to be at least possibly related to active study medication.
- 2 or more subjects have PK levels of bupivacaine levels with a C_{max} of $\geq$ 1,000 ng/mL

If any one or more of the dose-escalation rules are triggered in the study of Cohorts 1 or 4, then additional subjects may be enrolled in the affected Cohort to further confirm the tolerability profile of the 200 mg dose.

If any one or more of the dose-escalation rules are triggered in the study of any one of Cohorts 2, 3, 5, or 6, then additional subjects may be enrolled in the affected Cohort to further confirm the tolerability profile of the dose being studied in the affected Cohort.

Specifically, with respect to the rule on PK levels, the dose of Cohort 3 or Cohort 6 can be modified according to the following:

- If 2 or more subjects in Cohort 2 or Cohort 5 have plasma levels of bupivacaine with a C_{max} of $\geq$ 1,000 ng/mL, then an additional 15 subjects will be dosed at 17.10 mL (500 mg) in Cohort 3A or Cohort 6A.
- If 2 or more subjects in Cohort 3 or Cohort 6 who are dosing with 20.52 mL have plasma bupivacaine levels with a C_{max} of $\geq$ 1,000 ng/mL, an additional 15 subjects will be randomly assigned to Cohort 3A to administer 17.10 mL (500 mg) of HTX-011-49 or to Cohort 6A to administer 17.10 mL (500 mg) of HTX-011-56 (10 subjects) or saline (5 subjects).

Part B

Enrollment in Part B will be initiated following the completion of enrollment in Part A and will evaluate HTX-011 compared with HTX-002 or saline. In this part of the study, the surgical procedure allowed will be broadened to accommodate an abdominoplasty that can include liposuction and/or repositioning of the umbilicus.

Part B comprises 3 cohorts enrolling a total of approximately 120 subjects. Subjects will be randomized (1:1;

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active: saline) into each cohort as follows:

- HTX-011-56 13.68 mL (400 mg) via a combination of injection and instillation compared with saline 13.68 mL via injection (mini abdominoplasty)
- HTX-011-002 13.68 mL (400 mg) via a combination of injection and instillation compared with saline 13.68 mL via injection (mini abdominoplasty)
- HTX-011-56 13.68 mL (400 mg) via a combination of injection and instillation compared with saline 13.68 mL via injection (complete abdominoplasty)

Part C

Part C will include subjects undergoing complete abdominoplasty without liposuction. Approximately 30 subjects will be randomized to 1 of the following 2 cohorts in a 1:1 ratio:

- HTX-011-56 13.68 mL (400 mg) via instillation (15 subjects)
- Bupivacaine HCl 0.25% 100 mg (40 mL) via injection (15 subjects)

Part D (Optional)

Part D will include subjects undergoing complete abdominoplasty with liposuction. Approximately 50 subjects will be randomized to 1 of up to 4 cohorts in a 3:3:3:1 ratio:

- HTX-011-56 400 mg (13.68 mL) via instillation and/or injection (as determined by the Sponsor) (15 subjects)
- HTX-011-56 300 mg (10.26 mL) via instillation and/or injection (as determined by the Sponsor) (15 subjects)
- HTX-011-56 200 mg (6.84 mL) via instillation and/or injection (as determined by the Sponsor) (15 subjects)
- Saline (13.68 mL) via injection (5 subjects)

Part E (Optional)

Part E will include subjects undergoing complete abdominoplasty without liposuction. Approximately 48 subjects will be randomized to 1 of up to 5 cohorts in a 2:2:2:1:1 ratio:

- HTX-011-56 400 mg (13.68 mL) via instillation and/or injection (as determined by the Sponsor) and fentanyl 50 µg IV before wound closure (12 subjects)
- HTX-011-56 300 mg (10.26 mL) via instillation and/or injection (as determined by the Sponsor) and fentanyl 50 µg IV before wound closure (12 subjects)
- HTX-011-56 200 mg (6.84 mL) via instillation and/or injection (as determined by the Sponsor) and fentanyl 50 µg IV before wound closure (12 subjects)
- Saline (13.68 mL) via injection and fentanyl 50 µg IV before wound closure (6 subjects)
- Bupivacaine HCl 0.25% 100 mg (40 mL) via injection and fentanyl 50 µg IV before wound closure (6 subjects)

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Part F (Optional)

Part F will include subjects undergoing complete abdominoplasty without liposuction. Approximately 50 subjects will be randomized to 1 of up to 4 cohorts in a 3:3:3:1 ratio:

- HTX-011-56 400 mg (13.68 mL) via instillation and/or injection (as determined by the Sponsor), fentanyl 50 µg IV, and acetaminophen IV (1000 mg) before wound closure (15 subjects)
- HTX-011-56 300 mg (10.26 mL) via instillation and/or injection (as determined by the Sponsor), fentanyl 50 µg IV, and acetaminophen IV (1000 mg) before wound closure (15 subjects)
- HTX-011-56 200 mg (6.84 mL) via instillation and/or injection (as determined by the Sponsor), fentanyl 50 µg IV, and acetaminophen IV (1000 mg) before wound closure (15 subjects)
- Saline (13.68 mL) via injection, fentanyl 50 µg IV, and acetaminophen IV (1000 mg) before wound closure (5 subjects)

Part G (Optional)

Part G will include subjects undergoing complete abdominoplasty with liposuction. Approximately 50 subjects will be randomized to 1 of up to 4 cohorts in a 3:3:3:1 ratio:

- HTX-011-56 400 mg (13.68 mL) via instillation and/or injection (as determined by the Sponsor) and fentanyl 50 µg IV before wound closure (15 subjects)
- HTX-011-56 300 mg (10.26 mL) via instillation and/or injection (as determined by the Sponsor) and fentanyl 50 µg IV before wound closure (15 subjects)
- HTX-011-56 200 mg (6.84 mL) via instillation and/or injection (as determined by the Sponsor) and fentanyl 50 µg IV before wound closure (15 subjects)
- Saline (13.68 mL) via injection and fentanyl 50 µg IV before wound closure (5 subjects)

Part H (Optional)

Part H will include subjects undergoing complete abdominoplasty with liposuction. Approximately 50 subjects will be randomized to 1 of up to 4 cohorts in a 3:3:3:1 ratio:

- HTX-011-56 400 mg (13.68 mL) via instillation and/or injection (as determined by the Sponsor), fentanyl 50 µg IV, and acetaminophen IV (1000 mg) before wound closure (15 subjects)
- HTX-011-56 300 mg (10.26 mL) via instillation and/or injection (as determined by the Sponsor), fentanyl 50 µg IV, and acetaminophen IV (1000 mg) before wound closure (15 subjects)
- HTX-011-56 200 mg (6.84 mL) via instillation and/or injection (as determined by the Sponsor), fentanyl 50 µg IV, and acetaminophen IV (1000 mg) before wound closure (15 subjects)
- Saline (13.68 mL) via injection, fentanyl 50 µg IV, and acetaminophen IV (1000 mg) before wound closure (5 subjects)

Part I (Optional)

Part I will include subjects undergoing complete abdominoplasty without liposuction. Up to approximately

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35 subjects will be randomized to 1 of the following 2 cohorts in a 6:1 ratio:

- HTX-011-56 300 mg (10.26 mL) via instillation and/or injection (as determined by the Sponsor) (30 subjects)
- Saline (10.26 mL) via injection (5 subjects)

Pretreatment Phase (Day -28 to Day -1):

Subjects will be consented and screened.

Treatment and Confinement Phase (Day 0 to Day 5):

Subjects will be re-assessed on Day 0 for eligibility to continue in this study, and will be confined from Day 0 to 72 hours after receiving study medication.

Efficacy evaluations will include collection of Pain Intensity scores and Patient Global Assessment of pain control at pre-defined time intervals throughout the study.

Subject safety will be monitored by regular assessments of vital signs, electrocardiographs (ECGs), physical examination, neurologic exams, clinical laboratory tests, wound healing, and by collection of AEs and concomitant medications.

Blood samples will be obtained to evaluate pharmacokinetic (PK) profiles of bupivacaine and meloxicam.

Subjects will return to the clinic site at 96 and 120 hours post-administration of study drug for safety and efficacy evaluations, as follows:

- 96 Hours: assessments of vital signs, ECG, collection of AEs and concomitant medications, and a blood sample for PK. Efficacy assessments will include collection of Pain Intensity scores and Patient Global Assessment (PGA) evaluations.
- 120 Hours: obtain blood sample for pharmacokinetic analysis, collection of AEs and concomitant medications.

Follow-Up Phase (Days 10, 28, and 60):

Day 10: physical examination, vital signs, ECG, photograph of the surgical intervention area, and assessments of wound healing, AEs, and concomitant medications.

Day 28: assessment of AEs, concomitant medications, wound healing, and photograph of the surgical intervention area.

Day 60: subjects will receive a phone call from the study site to collect follow-up information on post-operative pain and pain medications.

Number of subjects to be enrolled: Up to approximately 523 subjects will be enrolled in this study: 90 in Part A, 120 in Part B, 30 in Part C, 50 in Part D, 48 in Part E, 50 in Part F, 50 in Part G, 50 in Part H, and 35 in Part I. Parts D through I are optional.

Number of study sites: Up to 8

Study country location: United States

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Criteria for inclusion:

Subjects must meet all of the following criteria to be considered eligible to participate in the study:

1. Be scheduled to undergo abdominoplasty surgery that is amenable to treatment with a long acting local anesthetic as per the anesthesia protocol in Section 5.5.1
2. Be American Society of Anesthesiology (ASA) physical Class I or II
3. Subjects 18 years of age or older
4. Have clinical laboratory values that are within normal limits (WNL) or if abnormal, not clinically significant; subjects with AST/ALT < 3 x ULN, and/or creatinine < 2 x ULN are acceptable.
5. Have a body mass index ≤ 30 kg/m^2
6. Female subjects are eligible only if all of the following apply:
   - Not pregnant (female subject of child bearing potential must have a negative serum pregnancy tests at screening and negative urine pregnancy test before surgery)
   - Not lactating
   - Not planning to become pregnant during the study
   - Be surgically sterile; or at least two years post-menopausal; or have a monogamous partner who is surgically sterile; or is practicing double-barrier contraception; or practicing abstinence (must agree to use double-barrier contraception in the event of sexual activity); or using an insertable, injectable, transdermal, or combination oral contraceptive approved by the FDA for greater than 2 months prior to screening visits and commits to the use of an acceptable form of birth control for the duration of the study
7. Male subjects must be surgically sterile (biologically or surgically) or commit to the use of a reliable method of birth control for the duration of the study
8. Does NOT have, as determined by the investigator or the study's medical monitor, a history or clinical manifestations of significant renal, hepatic, cardiovascular, metabolic, neurologic, psychiatric, or other condition that would preclude participation in the study
9. Must be able to understand study procedures and be willing to comply and give informed consent for the conduct of all study procedures, using an IRB approved consent

Criteria for Exclusion:

Subjects who meet any of the following criteria will be excluded from participating in the study:

1. Have a contraindication or be allergic to any medication to be used during the trial period
2. Have another painful physical condition that, in the opinion of the investigator, may confound the assessments of post-operative pain
3. Have a history of migraine or frequent headaches, seizures, or are currently taking anticonvulsants
4. Currently taking analgesics for a chronically painful condition, or has taken long acting opioids within 3 days of surgery, or taken any opioids within 24 hours of surgery
5. Previous abdominal surgery, as determined by the investigator, that would preclude participation in the

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study

6. Subjects that require liposuction as part of the abdominoplasty procedure in Part A, C, E, F, or I of the protocol
7. Subjects that are to have ancillary procedures performed during the abdominoplasty surgery that are unrelated to the abdominal area (breast reduction, breast augmentation, etc.)
8. Subjects unable to discontinue medications that have not been at a stable dose for at least 14 days prior to the scheduled abdominoplasty procedure and before dosing with investigational product
9. Subjects taking the following medications; anticonvulsants, sedatives (including benzodiazepines) corticosteroids (by any means of administration), nonsteroidal anti-inflammatory drugs (NSAIDS) within 24 hours of study drug dosing, morphine, monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), neuroleptics, or serotonin-norepinephrine reuptake inhibitors (SNRIs). Gabapentin and pregabalin are not permitted
10. Have a known or suspected history of alcohol or drug abuse
11. Have positive results on the alcohol breath test indicative of alcohol abuse or urine drug screen indicative of illicit drug use (unless results can be explained by a current prescription or acceptable over-the-counter medication at screening as determined by the investigator). The urine drug screen prior to surgery must be negative
12. Have evidence of a clinically significant 12-lead ECG abnormality according to the judgment of the investigator
13. Have received any investigational product within 30 days before start of study
14. Have previously received HTX-011 in clinical trials
15. Experiences a clinically significant event during surgery prior to the administration of the investigational product (e.g., excessive bleeding, hemodynamic instability) that would render the subject medically unstable, complicate their post-surgical course, or significantly increase the risk of study drug administration as per the judgment of the investigator. This will result in the subject being reported as randomized, not treated.
16. Subjects with sleep apnea or are on home continuous positive airway pressure (CPAP)
17. Subjects who are receiving oxygen therapy at the time of screening

Investigational product: HTX-011 is a sterile, viscous, extended-release fixed-ratio combination of bupivacaine and meloxicam. The term "HTX-011" is used to represent the formulations HTX-011-49 and HTX-011-56. HTX-002 is a sterile, viscous, extended-release formulation identical to HTX-011-56 except that it contains only bupivacaine (at the same concentration) as the active pharmaceutical ingredient. All 3 formulations are to be locally administered into the surgical site for the prevention of post-operative pain.

The vehicle formulation for HTX-011-49, HTX-011-56, and HTX-002 comprises tri[ethylene glycol] based poly[orthoester] polymer with dimethyl sulfoxide, glycerol triacetate, and maleic acid excipients.

The HTX-011 and HTX-002 formulations will be supplied by the sponsor.

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Name of Active Ingredients: Bupivacaine and Meloxicam (HTX-011) Bupivacaine (HTX-002)	**Phase of Development:** 2
Reference therapy: Normal saline and bupivacaine HCl 0.25%. Reference therapy will be sourced and supplied by sites.	
Duration of treatment: Each subject is planned to receive a single dose of study medication.	

Overview: This study is designed to evaluate the safety and analgesic efficacy of up to four dose levels of two HTX-011 formulations and HTX-002 in subjects following abdominoplasty surgery. The study will also evaluate different local administration techniques (injection, instillation, and a combination of the 2 techniques) as well as the effects of a fentanyl and acetaminophen administration at the end of surgery and before wound closure on the analgesic efficacy of HTX-011. Efficacy assessments are intended to characterize the analgesic effect time curve and the magnitude of analgesic effect of HTX-011 and HTX-002 in comparison with saline or bupivacaine HCl. In addition, the study will further characterize the safety and PK profiles of bupivacaine and meloxicam in the HTX-011 formulations and the PK profile of bupivacaine in the HTX-002 formulation.

Subjects will participate in the screening visit within 28 days of the scheduled surgery. ASA classification and inclusion/exclusion criteria for eligibility to participate in the study will be assessed. Medical history, vital signs, physical examination, clinical laboratory tests, drug and alcohol screening, 12-lead ECG, collection of prior/concomitant medications, and a serum pregnancy test will be performed. PONV risk factors will be assessed, and subject will be trained on providing pain intensity assessments.

On the day of surgery, Day 0, subjects will be reassessed for eligibility. No epidural or spinal anesthesia will be allowed, nor will any local anesthetic infiltration other than the administration of the IP or control be permitted. No prophylactic antiemetic, local anesthetics, or analgesic medications are allowed other than those used for inducing general anesthesia or as detailed in the protocol.

Subjects will be assigned randomly to a cohort and dosed as described above. Start and stop time of dosing will be recorded. Dosing stop time will be considered Time 0 (T0).

Subjects will be transferred to the post-anesthesia care area and observed according to institutional standards. While in the post-anesthesia care area, subjects may receive morphine iv rescue medication for pain control, as needed, as per local practice.

Each subject will be sequestered in the post-anesthesia care area at each study center for 72 hours post-Time 0, after which discharge procedures will be performed.

Efficacy analyses:

Pain intensity (PI) scores will be assessed by the subject for their pain according to the Visual Analog Scale (VAS), at 1, 2, 78, 84, and 96 hours after completion of administration of study medication (T0). For the VAS, 0 equates to no pain and 10 equates to the worst pain imaginable.

PI scores will be measured two ways: on movement, and, at rest. PI scores measured *on movement* (i.e., subject sitting up from a supine position) at the following time-points: 4, 6, 8, 10, 12, 14, 18, 24, 30, 36, 42, 48, 54, 60, and 72 hours post-T0.

PI scores *at rest* will be measured at 1, 2, 78, 84, and 96 hours post-T0.

Rescue analgesia (from T0 to T72) will be available to subjects with inadequately controlled pain symptoms.

Pain intensity assessment must be completed prior to administration of any rescue dose administered.

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The approved rescue regimen will be morphine 2 mg iv bolus doses by titration as needed in the post-anesthesia care area. Once effective analgesia has been reached using the morphine administered, subjects will be transitioned to oral oxycodone 10 mg every 2 hours, as needed for analgesia. Additional morphine up to 10 mg iv every 2 hours may be administered for inadequate analgesia with oxycodone. A subject who indicates a PI score that is ≤ 4 may be given acetaminophen 1000 mg for analgesia: however, a daily dose of acetaminophen must not exceed 4 grams (4000 mg). Between T72 and T96, pain medication will be prescribed according to the investigator's discretion and institutional standard of care. After T96, PI scores will not be recorded; subjects may resume standard of care pain medication for inadequately controlled pain, as advised by their surgeon.

Each subject's PGA of pain control will be obtained at 24, 48, 72, and 96 hours post-T0.

Subjects will receive a phone call from the study site on Day 60 and will be asked if they have any current pain related to the operation and to rate their pain intensity over the previous 24 hours using the NRS. Subjects will also be asked about their use of any pain medication over the previous 24 hours to treat pain related to the operation.

Safety analyses:

A neurologic exam and assessment will be completed at the following time points: at Day 0 any time prior to anesthesia induction, and at 24, 48, and 72 hours post-T0. The exam will include awareness and assessment for signs and symptoms of potential bupivacaine toxicity.

Vital signs will be measured at screening, at Baseline (i.e., Day 0, prior to anesthetic pre-operative procedures), and at 1, 2, 4, 6, 12, 18, 24, 36, 48, 60, 72, and 96 hours, and at Day 10 after T0.

Each subject will have a 12-lead ECG performed at screening; at baseline (i.e., Day 0, prior to anesthetic pre-operative procedures); at 1, 2, 3, 4, 5, 6 hours (Parts B through I); at 24, 48, 72, and 96 hours; and at Day 10 post-T0.

Blood samples for clinical laboratory tests will be obtained at screening visit, at Baseline, and at 72 hours post-T0.

Each subject will be assessed for nausea 6, 24, 48, and 72 hours post-T0 using a visual analog scale.

Each subject will be assessed for wound healing at 48 and 72 hours and at Days 10 and 28 post-T0.

A photograph of the surgical intervention area will be taken immediately after surgery, at 48, 72 hours, and at Days 10 and 28 post-T0.

Subjects will be assessed for adverse events and concomitant medications throughout the study.

Pharmacokinetics analyses:

Blood samples for PK analyses will be drawn prior to administration of the investigational product (IP) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 36, 48, 60, 72, 96, and 120 hours post-T0.

Efficacy Endpoints:

Summed pain intensity score (SPI) over the first 24 hours (SPI_{0-24})

Secondary:

Name of Sponsor/Company: Heron Therapeutics, Inc.	**Protocol Number:** HTX-011-C2015-203
Name of Investigational Product: HTX-011 (extended-release 2.5% bupivacaine and 0.075% meloxicam) • HTX-011-49 • HTX-011-56 HTX-002 (extended-release 2.5% bupivacaine)	**Protocol Title:** A Phase 2, Randomized, Controlled Evaluation of the Efficacy and Safety of HTX-011 or HTX-002 for Post-Operative Analgesia Following Abdominoplasty Surgery
Name of Active Ingredients: Bupivacaine and Meloxicam (HTX-011) Bupivacaine (HTX-002)	**Phase of Development:** 2

- SPI at other time points: SPI_{0-6}, SPI_{0-12}, SPI_{12-24}, SPI_{24-48}, SPI_{0-48}, SPI_{48-72}, SPI_{0-72}, $SPI_{72-96,}$ and SPI_{0-96}
- The PGA of pain control at 24, 48, 72, and 96 hours post-T0
- Time to administration of first dose of rescue analgesia
- Total and average daily rescue consumption over 24, 48, 72, and 96 hours post-T0
- The percentage of subjects who remain pain free (VAS score ≤ 1) at 72 hours and at 96 hours after study drug administration

Safety Endpoints:

Safety will be evaluated by assessment of AEs, including SAEs. Additional safety endpoints include the following parameters:

- Nausea assessments
- Wound assessments of the surgical intervention area
- Vital signs
- Neurological examinations
- Clinical laboratory tests (serum chemistry, hematology)
- Electrocardiograms (ECGs)

Pharmacokinetic Endpoints:

- The area under the plasma concentration-time curve from time zero to time t of the last measured concentration above the limit of quantification (AUC_{0-last})
- The area under the plasma concentration-time curve from zero to infinity (AUC_{0-inf})
- The maximum plasma concentration (C_{max})
- The time to reach maximum plasma concentration (T_{max})
- The terminal elimination rate constant (λ_Z) with the respective half-life ($t_{½}$)

Statistical Methodology

The primary efficacy endpoint for this study is the summed pain intensity scores over the first 24 hours (SPI_{0-24}). The primary analysis will be via an analysis of variance for pairwise or pooled group comparisons.

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

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ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
ALT	alanine aminotransferase
APAP	acetyl-para-aminophenol (Acetaminophen)
API	active pharmaceutical ingredient
ASA	American Society of Anesthesiology
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CFR	Code of Federal Regulations
C_{max}	Maximum Plasma Concentration
CPAP	continuous positive airway pressure
DMSO	dimethyl sulfoxide
ECG	Electrocardiogram
eCRF	electronic Case Report Form
ET	early termination
GCP	Good Clinical Practice
FDA	Food and Drug Administration
HEENT	head, eyes, ears, nose and throat
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IP	investigational product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
Kg	Kilogram
L	Liters
LC-MS/MS	liquid chromatography – tandem mass spectrometry
LOCF	last observation carried forward
MAOIs	monoamine oxidase inhibitors
Mg	Milligram

Min	Minute
mITT	modified Intend-to-Treat
NNRS	Nausea Numeric Rating Scale
NRS	Numeric Rating Scale
NSAIDS	non-steroidal anti-inflammatory drugs
PCP	phencyclidine
PGA	Patient Global Assessment
PI	pain intensity
PK	pharmacokinetic
PONV	post-operative nausea and vomiting
PRN	as needed
SAE	serious adverse event
SD	standard deviation
SNRIs	serotonin-norepinephrine reuptake inhibitors
SPI	summed pain intensity
SpO2	peripheral oxygen saturation
SSRI	Selective serotonin reuptake inhibitor
$t_{½}$	half-life
TCAs	tricyclic antidepressants
T_{max}	time to reach maximum plasma concentration
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
VS	Vital signs
WBC	white blood cell
WHO	World Health Organization
WLOCF	Windowed Last Observation Carried Forward
WNL	Within Normal Limits
λZ	terminal elimination rate constant

1. INTRODUCTION

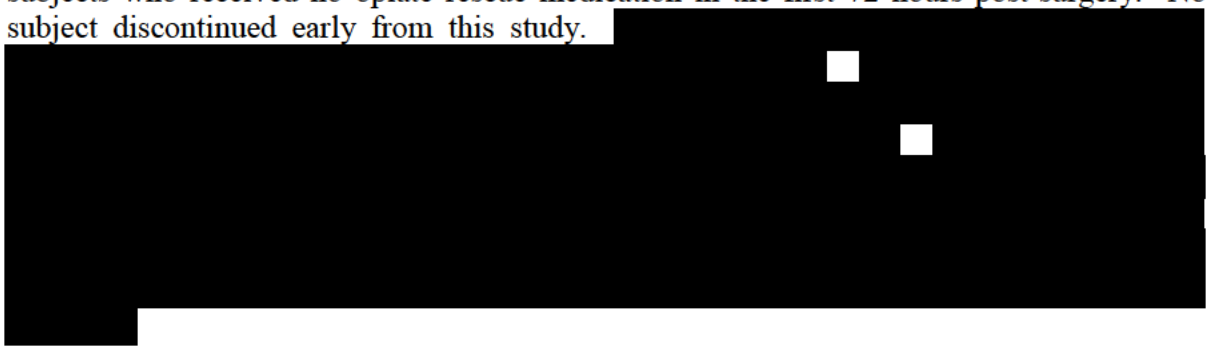
The use of local anesthetics within a surgical wound, i.e., "wound infiltration," has found extensive use in a vast number of patients (Renck 1994). Medical opinion would suggest that such infiltration with local anesthetics may be a relatively simple and safe means to reduce post-operative pain (Moiniche, Mikkelsen et al. 1998). The major limitation of the current local anesthetics used for infiltration is the limited duration of effect (6–12 hours) that is observed following surgery (Kehlet and Andersen 2011). In recent years there has been a dramatic increase in day-case surgery. In this patient population it is estimated that 30 to 40% of the patients suffer from moderate to severe pain during the first 24 to 48 hours. The development of a long-acting local anesthetic formulation for this patient population would be of clinical significance (Rawal 2001).

While non-steroidal anti-inflammatory drugs (NSAIDs) have long been used in the treatment of post-operative pain (Moote 1992), there is early evidence that there may be a synergistic interaction between local anesthetics and non-steroidal anti-inflammatory compounds when locally administered (Ortiz, Castañeda-Hernández et al. 2011). The Sponsor has identified a combination of bupivacaine and low dose meloxicam in two sustained release formulations (HTX-011-49 and HTX-011-56), intended for the management of post-operative pain via wound infiltration, that have demonstrated positive results in a non-clinical model of post-surgical pain. These formulations have been selected for further clinical investigation. Both HTX-011-49 and HTX-011-56 contain bupivacaine and meloxicam as active ingredients and both have vehicle formulations comprising tri[ethylene glycol] based poly[orthoester] polymer with dimethyl sulfoxide (DMSO), glycerol triacetate, and maleic acid. The two formulations differ from each other in their respective quantities of the vehicle excipients.

The Sponsor has also developed a formulation, HTX-002, which is identical in pharmaceutical composition to HTX-011-56 *except* that it contains only bupivacaine as the active pharmaceutical ingredient (API). Therefore, the HTX-002 formulation is a bupivacaine-only comparator to the HTX-011-56 formulation. Exploratory studies evaluating the antinociceptive effect in a post-operative pain model in domestic piglets, and cross-over PK studies in the beagle dogs, demonstrate that the primary pharmacodynamics and pharmacokinetic (PK) characteristics of HTX-002 are similar to that of HTX-011-56. Both the active ingredient (bupivacaine) and the identical biochronomer polymer vehicle have been studied in humans whereas HTX-002 has not yet been studied.

In a placebo-controlled Phase 1 clinical trial, single doses of 1.71 mL, 3.42 mL, and 6.88 mL of HTX-011 were administered subcutaneously to healthy volunteers. HTX-011 achieved the desired PK profile for both bupivacaine and meloxicam. Therapeutically relevant plasma bupivacaine levels were sustained for 2 to 3 days in the absence of the large initial peak that can be observed with commercially available formulations of the drug. The anesthetic effects of HTX-011 persisted through 96 hours, which closely correlated with plasma bupivacaine concentrations. All three doses were well-tolerated with no serious adverse events, clinically relevant ECG or laboratory changes, or premature discontinuations. Mild redness and bruising were seen at some subcutaneous injection sites in this healthy volunteer study.

A placebo-controlled Phase 2 clinical trial in the US, evaluated the efficacy and safety of HTX-011 containing 200 and 400 mg of bupivacaine combined with meloxicam, compared to placebo, in 71 subjects undergoing bunionectomy. The primary endpoint was the difference, as compared to placebo, in pain intensity, as measured by the Summed Pain Intensity score (SPI), in the first 24 hours post-surgery. Other secondary endpoints included: the difference in SPI in the first 48 hours post-surgery; the difference in SPI in the first 72 hours post-surgery; time to the first use of opiate rescue medication; and the percentage of subjects who received no opiate rescue medication in the first 72 hours post-surgery. No subject discontinued early from this study.



This present study is designed to evaluate the safety and analgesic efficacy of HTX-011 and HTX-002 formulations in subjects with acute pain following abdominoplasty surgery. The study will also evaluate different local administration techniques (injection, instillation, and a combination of the 2 techniques) as well as the effects of a fentanyl and acetaminophen administration at the end of surgery and before wound closure on the analgesic efficacy of HTX-011. Efficacy assessments are intended to characterize the analgesic effect-time curve and the magnitude of analgesic effect of doses of HTX-011 and HTX-002 in comparison with saline or bupivacaine HCl. In addition, the study will further characterize the safety and PK profiles of bupivacaine and meloxicam present in HTX-011 and the PK profile of bupivacaine present in HTX-002.

An abdominoplasty procedure involves the cosmetic removal of excess skin, muscle, adipose tissue, and plication of the rectus sheath to narrow the waistline (tightening of the abdominal muscles). Liposuction or repositioning of the umbilicus may or may not be performed. For the purpose of this protocol the procedure will always be referred to as abdominoplasty. However, for Part A, a mini-abdominoplasty will be done which does not contain liposuction and / or repositioning of the umbilicus.

The current edition of the HTX-011 Investigator's Brochure should be consulted for more detailed information on the formulations under investigation (HTX-011 and HTX-002).

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to evaluate the efficacy and duration of analgesia following administration of HTX-011 or HTX-002 formulations.

2.2. Secondary Objectives

The secondary objectives will be:

- To determine the safety and tolerability of HTX-011 and HTX-002 formulations
- To determine the optimum study drug administration technique
- To evaluate the pharmacokinetic (PK) profiles of bupivacaine and meloxicam in HTX-011 formulations and the PK profile of bupivacaine in HTX-002 over 120 hours after study drug administration
- To evaluate the analgesic effects of HTX-011 and HTX-002 formulations over various intervals using a series of secondary efficacy endpoints for pain intensity
- To assess the effects of HTX-011 and HTX-002 formulations on wound healing at 48 hours, at 72 hours, and on Days 10 and 28 post-treatment
- To evaluate nausea at 6, 24, 48, and 72 hours post-treatment
- To evaluate the percentage of subjects who remain pain free over time

3. STUDY ENDPOINTS

3.1. Primary Efficacy Endpoint:

Summed pain intensity score (SPI) over the first 24 hours (SPI_{0-24})

3.2. Secondary Efficacy Endpoints:

- SPI at other time points: SPI_{0-6}, SPI_{0-12}, SPI_{12-24}, SPI_{24-48}, SPI_{0-48}, SPI_{48-72}, SPI_{0-72}, SPI_{72-96}, and SPI_{0-96}
- The PGA of pain control at 24, 48, 72, and 96 hours post-T0
- Time to administration of first dose of rescue analgesia
- Total and average daily rescue consumption over 24, 48, 72, and 96 hours post-T0
- The percentage of subjects who remain pain free (Visual Analog Scale [VAS] score ≤ 1) at 72 hours and at 96 hours after study drug administration

3.3. Safety Endpoints:

Safety will be evaluated by assessment of AEs, including SAEs. Additional safety endpoints include the following parameters:

- Nausea assessments
- Wound assessments of the surgical intervention area
- Vital signs
- Neurological examinations
- Clinical laboratory tests (serum chemistry, hematology)
- Electrocardiograms (ECGs)

3.4. Pharmacokinetic Endpoints:

- The area under the plasma concentration-time curve from time zero to time t of the last measured concentration above the limit of quantification (AUC_{0-last})
- The area under the plasma concentration-time curve from zero to infinity (AUC_{0-inf})
- The maximum plasma concentration (C_{max})
- The time to reach maximum plasma concentration (T_{max})

- The terminal elimination rate constant (λ_Z) with the respective half-life ($t_{½}$)

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is an exploratory Phase 2, randomized, multicenter, observer-blind, controlled, evaluation of the efficacy and safety of HTX-011 in adult subjects undergoing abdominoplasty surgery. The study is planned to be conducted in up to 9 parts and to enroll up to approximately 523 subjects total: approximately 90 in Part A, 120 in Part B, 30 in Part C, 50 in Part D, 48 in Part E, 50 in Part F, 50 in Part G, 50 in Part H, and 35 subjects in Part I. Parts D through I are optional. Additional subjects may be added for reasons defined in Section 5.3.2.

The design of each study part is as follows:

Part A

Study Part A comprises 6 study cohorts enrolling approximately 90 subjects (approximately 15 subjects per cohort). Subjects enrolling into Part A will be randomized (2:1; active: saline) into each cohort to receive any one of HTX-011-49, HTX-011-56, or normal saline. For study Part A, the surgical procedure will be restricted to a mini-abdominoplasty, i.e., it will exclude liposuction and/or repositioning of the umbilicus.

Enrollment to the separate HTX-011-49 and HTX-011-56 cohorts may occur in parallel; however, escalation from one cohort to the next for each respective formulation is subject to meeting certain safety criteria as described further below in Section 4.1.1.

Cohorts 1 to 6 in study Part A will be as follows:

- Cohort 1 will evaluate the analgesic efficacy of 6.84 mL (200 mg) of HTX-011-49 compared to saline
- Cohort 2 will evaluate the analgesic efficacy of 13.68 mL (400 mg) of HTX-011-49 compared to saline
- Cohort 3 will evaluate the analgesic efficacy of 20.52 mL (600 mg) of HTX-011-49 compared to saline
- Cohort 4 will evaluate the analgesic efficacy of 6.84 mL (200 mg) of HTX-011-56 compared to saline
- Cohort 5 will be to evaluate the analgesic efficacy of 13.68 mL (400 mg) of HTX-011-56 compared to saline
- Cohort 6 will be to evaluate the analgesic efficacy of 20.52 mL (600 mg) of HTX-011-56 compared to saline

Part B

Enrollment in Part B will be initiated following completion of enrollment in Part A and will evaluate HTX-011 compared with HTX-002 or saline. The surgical procedure allowed will be broadened to accommodate an abdominoplasty that can include liposuction and/or repositioning of the umbilicus.

Part B comprises 3 cohorts enrolling a total of approximately 120 subjects. Subjects will be randomized (1:1; active: saline) into each cohort as follows:

- HTX-011-56 13.68 mL (400 mg) via a combination of injection and instillation compared with saline 13.68 mL via injection (mini-abdominoplasty)
- HTX-011-002 13.68 mL (400 mg) via a combination of injection and instillation compared with saline 13.68 mL via injection (mini-abdominoplasty)
- HTX-011-56 13.68 mL (400 mg) via a combination of injection and instillation compared with saline 13.68 mL via injection (complete abdominoplasty)

Part C

Part C will include subjects undergoing complete abdominoplasty without liposuction. Approximately 30 subjects will be randomized to 1 of the following 2 cohorts in a 1:1 ratio:

- HTX-011-56 13.68 mL (400 mg) via instillation (15 subjects)
- Bupivacaine HCl 0.25% 100 mg (40 mL) via injection (15 subjects)

Part D (Optional)

Part D will include subjects undergoing complete abdominoplasty with liposuction. Approximately 50 subjects will be randomized to 1 of up to 4 cohorts in a 3:3:3:1 ratio:

- HTX-011-56 400 mg (13.68 mL) via instillation and/or injection (as determined by the Sponsor) (15 subjects)
- HTX-011-56 300 mg (10.26 mL) via instillation and/or injection (as determined by the Sponsor) (15 subjects)
- HTX-011-56 200 mg (6.84 mL) via instillation and/or injection (as determined by the Sponsor) (15 subjects)
- Saline (13.68 mL) via injection (5 subjects)

Part E (Optional)

Part E will include subjects undergoing complete abdominoplasty without liposuction. Approximately 48 subjects will be randomized to 1 of up to 5 cohorts in a 2:2:2:1:1 ratio:

- HTX-011-56 400 mg (13.68 mL) via instillation and/or injection (as determined by the Sponsor) and fentanyl 50 µg IV before wound closure (12 subjects)

- HTX-011-56 300 mg (10.26 mL) via instillation and/or injection (as determined by the Sponsor) and fentanyl 50 µg IV before wound closure (12 subjects)

- HTX-011-56 200 mg (6.84 mL) via instillation and/or injection (as determined by the Sponsor) and fentanyl 50 µg IV before wound closure (12 subjects)

- Saline (13.68 mL) via injection and fentanyl 50 µg IV before wound closure (6 subjects)

- Bupivacaine HCl 0.25% 100 mg (40 mL) via injection and fentanyl 50 µg IV before wound closure (6 subjects)

Part F (Optional)

Part F will include subjects undergoing complete abdominoplasty without liposuction. Approximately 50 subjects will be randomized to 1 of up to 4 cohorts in a 3:3:3:1 ratio:

- HTX-011-56 400 mg (13.68 mL) via instillation and/or injection (as determined by the Sponsor), fentanyl 50 µg IV, and acetaminophen IV (1000 mg) before wound closure (15 subjects)

- HTX-011-56 300 mg (10.26 mL) via instillation and/or injection (as determined by the Sponsor), fentanyl 50 µg IV, and acetaminophen IV (1000 mg) before wound closure (15 subjects)

- HTX-011-56 200 mg (6.84 mL) via instillation and/or injection (as determined by the Sponsor), fentanyl 50 µg IV, and acetaminophen IV (1000 mg) before wound closure (15 subjects)

- Saline (13.68 mL) via injection, fentanyl 50 µg IV, and acetaminophen IV (1000 mg) before wound closure (5 subjects)

Part G (Optional)

Part G will include subjects undergoing complete abdominoplasty with liposuction. Approximately 50 subjects will be randomized to 1 of up to 4 cohorts in a 3:3:3:1 ratio:

- HTX-011-56 400 mg (13.68 mL) via instillation and/or injection(as determined by the Sponsor) and fentanyl 50 µg IV before wound closure (15 subjects)

- HTX-011-56 300 mg (10.26 mL) via instillation and/or injection (as determined by the Sponsor) and fentanyl 50 µg IV before wound closure (15 subjects)

- HTX-011-56 200 mg (6.84 mL) via instillation and/or injection (as determined by the Sponsor) and fentanyl 50 µg IV before wound closure (15 subjects)

- Saline (13.68 mL) via injection and fentanyl 50 µg IV before wound closure (5 subjects)

Part H (Optional)

Part H will include subjects undergoing complete abdominoplasty with liposuction. Approximately 50 subjects will be randomized to 1 of up to 4 cohorts in a 3:3:3:1 ratio:

- HTX-011-56 400 mg (13.68 mL) via instillation and/or injection (as determined by the Sponsor), fentanyl 50 µg IV, and acetaminophen IV (1000 mg) before wound closure (15 subjects)

- HTX-011-56 300 mg (10.26 mL) via instillation and/or injection (as determined by the Sponsor), fentanyl 50 µg IV, and acetaminophen IV (1000 mg) before wound closure (15 subjects)

- HTX-011-56 200 mg (6.84 mL) via instillation and/or injection (as determined by the Sponsor), fentanyl 50 µg IV, and acetaminophen IV (1000 mg) before wound closure (15 subjects)

- Saline (13.68 mL) via injection, fentanyl 50 µg IV, and acetaminophen IV (1000 mg) before wound closure (5 subjects)

Part I (Optional)

Part I will include subjects undergoing complete abdominoplasty without liposuction. Approximately 35 subjects will be randomized to 1 of the following 2 cohorts in a 6:1 ratio:

- HTX-011-56 300 mg (10.26 mL) via instillation and/or injection (as determined by the Sponsor) (30 subjects)

- Saline (10.26 mL) via injection (5 subjects)

Adult subjects ≥ 18 years old who require abdominoplasty will be screened for participation at the study sites within 28 days before surgery. During the screening visit, after signing the informed consent, subjects will be assessed for ASA classification, medical history and prior/concomitant medications, vital sign measurements, physical examination, clinical laboratory tests, drug and alcohol screen tests, 12-lead electrocardiogram (ECG), serum pregnancy test (as appropriate). Post-operative nausea and vomiting (PONV) risk factors will be assessed, and subjects will be trained on providing pain assessments.

On the day of surgery (Day 0), subjects will undergo abdominoplasty under a standardized general anesthesia regimen. The abdominoplasty procedure types will be documented on the eCRF.

A single dose of the study drug (i.e., either HTX-011-49, HTX-011-56, HTX-002, saline, or bupivacaine HCl, according to a randomization schedule) will be administered intra-operatively (as detailed in the Pharmacy Manual). The operating surgeon and the

attendant surgical staff will not be blinded to the study medication because HTX-011 and HTX-002 are colored preparations, whereas normal saline and bupivacaine HCl are not.

Following the completion of surgery and immediate post-operative recovery, subjects will be transferred to the post-anesthesia care area. Staff members in the post-anesthesia care area will be blinded to study treatment administered, as well as the investigator assessing the AEs. Subjects will stay in the post-anesthesia care area for 72 hours after completion of the administration of study medication (i.e., T0), prior to discharge from the study center. Each subject will return to the study center 96 hours elapsed time (T96) after T0 to complete additional assessments. After completion of the 96-hour assessments, subjects will be scheduled to return to the study center on Days 10 and 28 for study specific assessments; each subject will be asked to return to the study center specifically for a PK blood sample draw at 120 hours (T120) post-T0. Subjects will also receive a phone call from the study site on Day 60 to collect follow-up information on post-operative pain and pain medications.

Efficacy assessments will include pain intensity scoring using the Visual Analog Scale (VAS), use of rescue medication, and Patient Global Assessment (PGA) of pain control.

Blood samples will be obtained to assess meloxicam and bupivacaine pharmacokinetics out to 120 hours post-T0.

Safety assessments will include AEs, concomitant medications, physical examinations, neurologic assessments (including neurological/cardiovascular assessments for potential bupivacaine toxicity), vital sign measurements, clinical laboratory tests, ECGs, nausea assessments (using a VAS for nausea), and wound healing assessments and photographs of the surgical invention area.

4.1.1. Dose Escalation and Dose Modification Rules for Study Part A

Enrollment to the next cohort in each of the parallel formulation study cohorts will not proceed if any of the following are observed:

- 3 or more subjects experience an SAE reported by the investigator and confirmed by sponsor to be at least possibly related to active study medication
- 3 or more subjects experience a neurological AE reported by the investigator and confirmed by the sponsor to be at least possibly related to active study medication (excluding minor neurologic findings that are not clinically significant, e.g., headache, paresthesia).
- 3 or more subjects experience clinically significant ECG changes reported by the investigator confirmed by the sponsor to be at least possibly related to study medication
- 2 or more subjects have plasma bupivacaine levels with a C_{max} of $\geq$ 1,000 ng/mL

If any one or more of the dose escalation rules are triggered in the study of Cohorts 1 or 4, then additional subjects may be enrolled in the affected Cohort to further confirm the tolerability profile of the 200 mg dose.

If any one or more of the dose escalation rules are triggered in the study of any one of Cohorts 2, 3, 5 or 6, then additional subjects may be enrolled in the affected Cohort to further confirm the tolerability profile of the dose being studied in the affected Cohort. Specifically, with respect to the rule on PK levels, the dose of Cohort 3 or Cohort 6 can be modified according to the following:

- If 2 or more subjects in Cohort 2 or Cohort 5 have plasma levels of bupivacaine with a C_{max} of $\geq$ 1,000 ng/mL, then an additional 15 subjects will be dosed at 17.10 (500 mg) mL in Cohort 3A or Cohort 6A.

- If 2 or more subjects in Cohort 3 or Cohort 6 who are dosed with 20.52 mL have plasma bupivacaine levels with a C_{max} of $\geq$ 1,000 ng/mL, an additional 15 subjects will be randomly assigned to 17.10 mL (500 mg) of HTX-011-49 or 17.10 mL (500 mg) of HTX-011-56 (10 subjects) or saline (5 subjects) – these subjects will be designated as Cohorts 3A and 6A, respectively, if applicable.

The following sections summarize the three phases of activities for this study: 1) Pretreatment Phase, 2) Treatment and Confinement Phase, and 3) Follow-up Phase.

4.1.2. Pretreatment Phase (Day -28 to Day -1)

Subjects will be consented and screened during this phase by assessments as described in Section 6.5.1. The screening period will be at any time between Day -28 and Day -1.

4.1.3. Treatment and Confinement Phase (Day 0 Through Day 5)

a. Pre-surgery (Day 0): Subjects will be admitted to the surgical unit and reassessed for eligibility to continue participating in the study. Standard pre-surgery activities will be conducted once eligibility has been re-confirmed.

b. Surgery (Day 0): Subjects will undergo an abdominal surgical procedure under general anesthesia. A standard anesthetic regimen will be followed for all subjects as outlined in the anesthesia protocol (Section 5.5.1). A single dose of the study drug (either HTX-011-49, HTX-011-56, HTX-002, saline, or bupivacaine HCl, according to a randomization schedule) will be administered by local infiltration intra-operatively and/or by instillation, and upon completion of the surgery, in accordance with instructions provided in the Pharmacy Manual. Start and stop times of dose administration will be recorded. Dosing stop time will be considered T0.

c. Post-operative Period (Days 0–5): Following surgery, subjects will be transferred to the post-anesthesia care area where, over the next 72 hours, they will undergo efficacy (see Section 3.1) and safety (see Section 3.3) assessments, and collection of blood samples for PK analyses (see Section 6.4.6). Treatments allowed during

the post-operative period will include rescue analgesia medications for inadequately controlled pain, as described in Section 5.16. Subjects will be discharged from the clinic unit after completion of the 72 hour assessments. Efficacy assessments scheduled at 78 and 84 hours and will be completed at home and information recorded on paper diaries.

Subjects with inadequately controlled pain symptoms may request rescue analgesia. Efforts should be made to encourage subjects to wait at least 60 minutes after the end of surgery before receiving rescue analgesic medication. **Pain intensity assessment must be completed prior to administration of any rescue dose administered.** Subjects do not need to have a qualifying score to receive rescue analgesia; however, whenever possible staff should try to ensure that rescue analgesia is administered only when a Visual Analog Scale for Pain score of ≥ 4.0 cm is recorded. Pain intensity assessments (Visual Analog Scale for Pain) will be completed prior to each dose of rescue medication.

4.1.4. Follow-Up (Day 10 ± 2, Day 28 ± 2, and Day 60 ± 7)

Subjects will return to the clinical site on Days 10 and 28 post-T0 for safety assessments.

Subjects will also receive a phone call from the study site on Day 60 to collect follow-up information on post-operative pain and pain medications.

4.2. Rationale for Study Design and Control Groups

This study will evaluate the efficacy and safety of two HTX-011 formulations of the combination of a known local anesthetic, bupivacaine, and a known anti-inflammatory drug, meloxicam. A bupivacaine-only formulation, HTX-002, will also be evaluated. Previous research has demonstrated the safety and sustained concentrations over 96 hours of single doses of 100 mg, 200 mg, and 400 mg of HTX-011 when administered subcutaneously to healthy subjects.

This study will explore the analgesic effects of dosing with HTX-011 and HTX-002 in an accepted model of post-operative pain. Abdominoplasty surgery produces generally reliable and persistent pain symptoms for a period typically lasting over 72 hours from the surgical insult, which will allow for analysis of acute analgesic effect of HTX-011 over an extended period of time. Efficacy measures will be collected so as to gain a better knowledge of the analgesic effect-time curve of HTX-011 and HTX-002 compared with saline or bupivacaine HCl, and will examine the effects of fentanyl and acetaminophen administration following a surgical procedure. In addition, the study will further characterize the safety and pharmacokinetic profiles of bupivacaine and meloxicam. Based on the overall PI, PK, and safety data from the study cohorts in Part A, the optimum dose(s)/formulation(s) of HTX-011 to be studied in Parts B through I of this study will be decided: the methodology will be detailed in the statistical analysis plan for this study. Normal saline and bupivacaine HCl are employed in this study as controls for efficacy and safety evaluations.

[redacted]

5. STUDY POPULATION

5.1. Inclusion Criteria

Subjects must meet all of the following criteria to be considered eligible to participate in the study:

1. Be scheduled to undergo abdominoplasty surgery that is amenable to treatment with a long acting local anesthetic as per the anesthesia protocol in Section 5.5.1
2. Be American Society of Anesthesiology (ASA) physical Class I or II
3. Subjects 18 years of age or older
4. Have clinical laboratory values that are within normal limits (WNL) or if abnormal, not clinically significant; subjects with AST/ALT < 3 x ULN and/or creatinine < 2 x ULN are acceptable.
5. Have a body mass index ≤ 30 kg/m^2
6. Female subjects are eligible only if all of the following apply:
    - Not pregnant (female subject of child bearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test before surgery)
    - Not lactating
    - Not planning to become pregnant while participating during the study
    - Be surgically sterile; or at least two year post-menopausal; or have a monogamous partner who is surgically sterile; or is practicing double-barrier contraception; or practicing abstinence (must agree to use double-barrier contraception in the event of sexual activity); or using an insertable, injectable, transdermal, or combination oral contraceptive approved by the FDA for greater than 2 months prior to screening visits and commits to the use of an acceptable form of birth control for the duration of the study and for 30 days from completion of the study
7. Male subjects must be surgically sterile (biologically or surgically) or commit to the use of a reliable method of birth control for the duration of the study
8. Does NOT have, as determined by the investigator or the study's medical monitor, a history or clinical manifestations of significant renal, hepatic, cardiovascular, metabolic, neurologic, psychiatric, or other condition that would preclude participation in the study
9. Must be able to understand and agree to comply with all study procedures and voluntarily provide written informed consent to participate in the study.

5.2. Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participating in the study:

1. Have a contraindication or be allergic to any medication to be used during the trial period

2. Have another painful physical condition that, in the opinion of the investigator, may confound the assessments of post-operative pain
3. Have a history of migraine or frequent headaches, seizures, or are currently taking anticonvulsants
4. Currently taking analgesics for a chronically painful condition, or has taken long acting opioids within 3 days of surgery, or taken any opioids within 24 hours of surgery
5. Previous abdominal surgery, as determined by the investigator, that would preclude participation in the study
6. Subjects that require liposuction as part of the abdominoplasty procedure in Part A, C, E, F, or I of the protocol
7. Subjects that are to have ancillary procedures performed during the abdominoplasty surgery that are unrelated to the abdominal area (breast reduction, breast augmentation, etc.)
8. Subjects unable to discontinue medications that have not been at a stable dose for at least 14 days prior to the abdominoplasty surgery procedure and before dosing with investigational product
9. Subjects taking the following medications; anticonvulsants, sedatives (including benzodiazepines) corticosteroids (by any means of administration), nonsteroidal anti-inflammatory drugs (NSAIDS) within 24 hours of study drug dosing, morphine, monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), neuroleptics, or serotonin-norepinephrine reuptake inhibitors (SNRIs). Gabapentin and pregabalin are not permitted
10. Have a known or suspected history of alcohol or drug abuse
11. Have positive results on the alcohol breath test indicative of alcohol abuse or urine drug screen indicative of illicit drug use (unless results can be explained by a current prescription or acceptable over-the-counter medication at screening as determined by the investigator). The urine drug screen prior to surgery must be negative
12. Have evidence of a clinically significant 12-lead ECG abnormality according to the judgment of the investigator
13. Have received any investigational product within 30 days before start of study
14. Have previously received HTX-011 in clinical trials
15. Experiences a clinically significant event during surgery prior to the administration of the investigational product (e.g., excessive bleeding, hemodynamic instability) that would render the subject medically unstable, complicate their post-surgical course, or significantly increase the risk of study drug administration as per the judgment of the investigator. This will result in the subject being reported as randomized, not treated
16. Subjects with sleep apnea or are on home continuous positive airway pressure (CPAP)
17. Subjects who are receiving oxygen therapy at the time of screening

5.3. Discontinuation of Subjects

5.3.1. Procedures for Withdrawal

A subject may be discontinued 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. Any

subject who withdraws consent to continue treatment or who is discontinued from the study before completing the protocol specified duration of treatment should be encouraged to complete the early termination assessments. All subjects will be encouraged to agree to be followed for up to 28 ± 2 days after completion of study medication administration. The date at which the subject is withdrawn, and the primary reason for discontinuation, will be recorded in the subject's electronic case report form (eCRF).

5.3.2. Replacement of Subjects

Subjects who discontinue from this study up to 96 hours post-T0 may be replaced in this study, after discussion with the investigator and at the discretion of the Sponsor.

Protocol violations or subjects not administered with study drug according to protocol, or any other inadvertent events, that lead to a subject not completing the study as planned may result in a replacement subject being enrolled, at the discretion of the Sponsor.

Any subject who is randomly assigned to study drug but who discontinues the study prior to the study drug administration will be replaced by the next study subject who meets the study entry criteria. The replacement subject will be assigned to the same study drug that was intended for the subject being replaced.

Additional subjects may also be added to a cohort for any one of the following reasons, but not limited to:

- Better define drug administration techniques
- Better characterize PK profile
- Better characterize potential safety signals

5.4. Lifestyle Guidelines During Confinement

Bathroom privileges will be restricted during the post-operative period. Following completion of the surgery, subjects will be restricted to use of a bedpan, bedside commode or bathroom privileges via wheelchair through completion of 12 hour assessments; bathroom privileges may be loosened at any time at the discretion of the investigator. While confined in the post-anesthesia care area following surgery, subjects will be required to remain resting in bed at least 30 minutes prior to any pain intensity assessment. Subjects will be encouraged to maintain a semi-recumbent position while in bed. Subjects will be allowed to ambulate according to standard post-operative care instructions.

5.4.1. Diet

While confined at the research unit, subjects may receive the diet normally provided by the institution for post-operative patients.

5.5. Surgical Procedure

On the day of surgery (Day 0), subjects will undergo an abdominoplasty surgical procedure. Surgery should be scheduled to accommodate induction of anesthesia so that all surgical procedures to be completed by approximately 5:00 pm on the day of surgery.

5.5.1. Anesthesia Protocol and Administration of Study Medication

5.5.1.1. Anesthesia for Surgery

The anesthetic protocol described below is a guide that should be followed to minimize inter-subject variability to the greatest extent possible. However, it is understood that hemodynamic fluctuations and other intraoperative events may necessitate some deviation from the standard regimen to ensure that necessary measures are undertaken to preserve subject safety.

Subjects will undergo an abdominal procedure under general anesthesia. Epidural or spinal anesthesia is also not allowed. Midazolam up to 5 mg IV may be administered pre-operatively for anxiolysis. Propofol induction may include a small dose of lidocaine (up to 5 mL of 1% lidocaine without epinephrine) to minimize injection discomfort. In mini-abdominoplasty, up to 100 μg IV of fentanyl may be administered during surgery, and general anesthesia will be maintained with a volatile anesthetic agent. In complete abdominoplasty, the use of fentanyl and the maintenance of gaseous general anesthesia shall be in accordance with the institutional practice. In addition, subjects in Parts E, F, G and H will be administered 50 μg IV of fentanyl at the end of the surgery and before wound closure. Subjects in Part F and H will also receive 1000 mg IV acetaminophen at the end of surgery and before wound closure. Should intubation be required, rocuronium should be used for muscle relaxation. Muscle relaxation to be reversed per standard dosing. Succinylcholine to be avoided if possible. One dose of ondansetron may be administered with induction.

Agents for nausea prophylaxis, including other 5-HT3 receptor blockers (e.g., ondansetron), scopolamine, dexamethasone, or haloperidol are not allowed during or upon completion of the surgical procedure. Anti-nausea medication will only be administered during the post-operative period for any of the following: (1) subject records a score of ≥ 5 on the Visual Analog Scale for Nausea; (2) subject is actively vomiting; (3) subject requests anti-nausea medication.

5.5.1.2. Study Drug Administration

For all study drug administration techniques, start and stop time of dosing will be recorded; dosing stop time will then be considered Time 0 (T0). Details of an 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.

Infiltration Dosing Technique for Mini-Abdominoplasty

Study medication will be administered intra-operatively by infiltration in equally divided volumes for injection.

- After the plication is completed, approximately one third of the total volume will be administered to the plication area of the posterior rectus sheath via approximately 5 injections.

- Another one-third of the study drug volume will be administered just above and below the external fascial layers of the rectus and external oblique muscles via approximately 10 injections at a 45-degree angle in two tracks parallel on either side of the central midline of the abdomen (i.e., the semilunaris). The trajectory of the needle should be visualized throughout the entire length by the translucency of the fascia, to avoid inadvertent injection deep in the abdomen or in the muscle itself.

- Lastly, prior to skin closure, the remaining third of study drug will be administered via injections into the upper third of the subcutaneous tissue along the upper and lower abdominal incision within the bikini line.

Combined Infiltration and Instillation Dosing Technique for Mini-Abdominoplasty

Study medication will be administered in equally divided volumes.

- After the plication is completed, approximately one third of the total volume will be administered via infiltration to the plication area of the posterior rectus sheath via approximately 5 injections.

- Another one-third of the study drug volume will be administered via infiltration just above and below the external fascial layers of the rectus and external oblique muscles via approximately 10 injections at a 45-degree angle in two tracks parallel on either side of the central midline of the abdomen (i.e., the semilunaris). The trajectory of the needle should be visualized throughout the entire length by the translucency of the fascia to avoid inadvertent injection deep in the abdomen or in the muscle itself.

- Lastly, prior to skin closure, the remaining third of study drug will be administered via instillation along the upper and lower abdominal incision within the bikini line where the subcutaneous fascia emerges from the deeper tissue.

Combined Infiltration and Instillation Dosing Technique for Complete Abdominoplasty

- After plication is completed, approximately 1/3 of the total study drug volume will be administered *via infiltration* to the entire plication area of the posterior rectus sheath via approximately 8 injections.

- Another 1/3 will be administered *via infiltration* just above and below the external fascial layers of the rectus and external oblique muscles via approximately 12 injections at a 45 degree angle in two tracks parallel on each side of the central midline of the abdomen (ie, the semilunaris). The trajectory of the needle should be visualized throughout the entire length by the translucency of the fascia, to avoid inadvertent injection deep in the abdomen or in the muscle itself.

- If the procedure involved relocation of the umbilicus, a small amount of study drug is to be administered *via infiltration* around the pedicle of the relocated tissue.

- Prior to skin closure, the remaining 1/3 of study drug will be administered *via* instillation*, after removing the needle from the syringe* into the subcutaneous tissue along the upper and lower abdominal incision within the bikini line where the subcutaneous fascia emerges from the deeper tissue.

Instillation Only Dosing Technique for Complete Abdominoplasty

- Approximately 1/3 of the total study drug volume will be administered via instillation (i.e., without a needle on the syringe) to the entire plication area of the posterior rectus sheath; it is critical that the agent be applied to the posterior sheath rather than just the anterior sheath. Note that an acceptable way of administering the product to the posterior sheath on either side of the linea alba would be prior to the plication.

- Another 1/3 will be administered via instillation just above and below the external fascial layers of the rectus and external oblique muscles at a 45 degree angle in two tracks parallel on each side of the central midline of the abdomen (i.e., the semilunaris).

- If the procedure involved relocation of the umbilicus, a small amount of study drug is to be instilled around the pedicle of the relocated tissue.

- Lastly, prior to skin closure, the remaining 1/3 of study drug will be administered via instillation to the subcutaneous tissue along the upper and lower abdominal incision within the bikini line where the subcutaneous fascia emerges from the deeper tissue.

Dosing Technique for Administering Saline and Bupivacaine HCl Controls in Complete Abdominoplasty

Administer saline and bupivacaine HCl 0.25% intra-operatively by infiltration in equally divided volumes for injection.

- After the plication is completed, administer approximately one third of the total volume of study drug to the plication area of the posterior rectus sheath via approximately 5 injections.

- Administer another one-third of the study drug volume just above and below the external fascial layers of the rectus and external oblique muscles via approximately 10 injections at a 45-degree angle in two tracks parallel on either side of the central midline of the abdomen (i.e., the semilunaris). The trajectory of the needle should be visualized throughout the entire length by the translucency of the fascia, to avoid inadvertent injection deep in the abdomen or in the muscle itself.

- If the procedure involved relocation of the umbilicus, a small amount of study drug is to be administered around the pedicle of the relocated tissue.

- Lastly, prior to skin closure, administer the remaining third of study drug via injections into the upper third of the subcutaneous tissue along the upper and lower abdominal incision within the bikini line.

Fentanyl IV Administration for Part E, F, G, and H

For Part E, F, G, and H a dose of 50 μg fentanyl IV will be administered at the conclusion of surgery and before wound closure. Fentanyl will be administered per the product label instructions.

Acetaminophen IV Administration for Part F and H

For Part F and H, a dose of 1000 mg acetaminophen IV will be administered at the conclusion of surgery and before wound closure. Acetaminophen IV will be administered per the product label instructions.

5.6. Identity of Study Medication

Study drug in this study is defined as HTX-011 (an extended-release, fixed-ratio combination of bupivacaine and meloxicam), HTX-002 (an extended-release bupivacaine formulation), normal saline, or bupivacaine HCl. The HTX-011 formulations that will be used for this study are HTX-011-49 and HTX-011-56. HTX-011 and HTX-002 are sterile viscous injectable formulations to be administered intraoperatively by local infiltration for the prevention of postoperative pain. HTX-011 and HTX-002 are colored preparations, whereas the controls (normal saline and bupivacaine HCl) are not.

The excipients in the vehicle formulation for HTX-011-49, HTX-011-56, and HTX-002 are tri[ethylene glycol] based poly[orthoester] polymer with dimethyl sulfoxide (DMSO), glycerol triacetate, and maleic acid.

Each mL of HTX-011-49 contains 29.25 mg bupivacaine base and 0.88 mg of meloxicam. The proposed drug product contains 2.50% w/w bupivacaine base, 0.075% w/w meloxicam, in 54.275% w/w AP135, 0.15% w/w maleic acid, 8.00% w/w DMSO, and 35% w/w glycerol triacetate (or triacetin).

One mL of HTX-011-56 contains 29.25 mg bupivacaine base and 0.88 mg of meloxicam. The proposed drug product contains 2.50% w/w bupivacaine base and 0.075% w/w meloxicam in 62.375% w/w AP135, 0.05% w/w maleic acid, 10.00% w/w DMSO, and 25.00% w/w glycerol triacetate.

HTX-002 is an identical formulation as that of HTX-011-56 except that it contains only bupivacaine as the API.

HTX-011-49, HTX-011-56, and HTX-002 will be supplied by the sponsor. Normal saline, bupivacaine HCl 0.25%, fentanyl and acetaminophen will be sourced and supplied by the site.

5.7. Method of Assigning Subjects to Treatment Groups

A computer generated randomization scheme for each part of the study will be prepared prior to study initiation. Subjects will be identified by a 7 digit number, ABC-DEFG: ABC-Site number, DEFG-sequential subject number starting at 0001 (e.g. 001-0001).

For Part A of the study, subjects will be randomly assigned to treatment with any one of HTX-011-49, HTX-011-56, or saline in a 2:1 ratio (active:saline) according to the randomization scheme.

For Part B of the study, subjects will be randomly assigned to treatment with HTX-011-56 or saline in a 1:1 ratio (active:saline) according to the randomization scheme.

For Part C of the study, subjects will be randomly assigned to treatment with HTX-011-56 or bupivacaine HCl in a 1:1 ratio (active:active control) according to the randomization scheme.

For Part D of the study, subjects will be randomly assigned to treatment with HTX-011-56 or saline in a 3:3:3:1 ratio (active:saline) according to the randomization scheme.

For Part E of the study, subjects undergoing complete abdominoplasty without liposuction will be randomly assigned to treatment with HTX-011-56 and fentanyl 50 µg IV before wound closure, saline and fentanyl 50 µg IV before wound closure, or bupivacaine HCl and fentanyl 50 µg IV before wound closure in a 2:2:2:1:1 ratio (active:saline or active control) according to randomization scheme.

For Part F of the study, subjects undergoing complete abdominoplasty without liposuction will be randomly assigned to treatment with HTX-011-56, fentanyl 50 µg IV, and 1000 mg acetaminophen IV before wound closure or saline, fentanyl 50 µg IV, and 1000 mg acetaminophen IV before wound closure in a 3:3:3:1 ratio (active:saline) according to randomization scheme.

For Part G of the study, subjects undergoing complete abdominoplasty with liposuction will be randomly assigned to treatment with HTX-011-56 and fentanyl 50 µg IV before wound closure or saline and fentanyl 50 µg IV before wound closure in a 3:3:3:1 ratio (active:saline) according to randomization scheme.

For Part H of the study, subjects undergoing complete abdominoplasty with liposuction will be randomly assigned to treatment with HTX-011-56, fentanyl 50 µg IV, and 1000 mg acetaminophen IV before wound closure or saline, fentanyl 50 µg IV, and 1000 mg acetaminophen IV before wound closure in a 3:3:3:1 ratio (active:saline) according to randomization scheme.

For Part I of the study, subjects undergoing complete abdominoplasty without liposuction will be randomly assigned to treatment with HTX-011-56 or saline in a 6:1 ratio (active:saline) according to randomization scheme.

Site staff involved in the post-surgical assessments of safety and efficacy will not have access to the randomization scheme and will be blinded to treatment.

5.8. Selection of Doses

In a placebo-controlled Phase 1 clinical trial, single doses of 100 mg, 200 mg, and 400 mg of HTX-011-19 (another different formulation of the HTX-011 combination of bupivacaine and meloxicam), and single doses of 100 mg and 200 mg of HTX-011-49 were administered to healthy adult volunteers. HTX-011 elicited the desired pharmacokinetic profile for both bupivacaine and meloxicam. Therapeutically relevant plasma bupivacaine levels were sustained for 2 to 3 days in the absence of large initial peak plasma concentrations that can be observed with commercially available formulations of the drug. The analgesic effects of HTX-011 persisted through 96 hours, which closely correlated with plasma bupivacaine concentrations. All five doses were well-tolerated with no serious adverse events, clinically relevant ECG or laboratory changes, or premature discontinuations. Mild redness and bruising were seen at some injection sites due to the subcutaneous administration of the product in this healthy volunteer study.

To further demonstrate analgesic efficacy and to better understand the analgesic effect-time curve of the two HTX-011 formulations, this study will evaluate the analgesic effects of HTX-011 and HTX-002 in subjects with acute pain following abdominoplasty surgery.

5.9. Blinding and Unblinding of Study Medications

Because HTX-011 and HTX-002 formulations are colored and viscous in contrast to normal saline and bupivacaine HCl, this renders obsolete any double-blinded study drug administration. Therefore, the site's surgical and pharmacy staff will not be blinded to the study medication administered. However, the conduct of the study will be observer blind. Once surgery is completed and subjects have been transferred to the post-anesthesia care area, all site staff in the post-anesthesia care area as well as study center staff involved in the assessment of safety and efficacy will be blinded to the treatment assignment and (s)he will remained masked to treatment assignments throughout the conduct of the study.

The study blind may be broken only if the safety of a subject is at risk and the treatment plan for that subject depends on which study medication he or she received. If knowledge of the treatment assignment is absolutely necessary for the management of a subject's safety, then the investigator must contact the medical monitor for unblinding information. If a subject's treatment assignment is unblinded without the prior knowledge of the Sponsor, the investigator must notify the Sponsor as soon as possible and no later than the next business morning. All circumstances leading to a premature unblinding must be clearly documented.

5.10. Treatment Compliance

Because the study medication is being administered as a component of the surgical procedure, a lack of treatment compliance is not expected. The exact date, start and stop time, and dose of study medication administration will be recorded in the subject's eCRF. It is important that all study medication is administered and that the dosing syringes are completely emptied as part of the study drug infiltration procedure.

5.11. Drug Accountability

The investigator (or designee) will sign for the study medications when they are received at the site. The study medication must be handled and stored as described in the pharmacy manual and dispensed only to those subjects formally entered and assigned randomly into a study cohort.

At the completion of the study, and after reconciliation of all delivery and usage records, any unused study medication supplied by the sponsor will be returned to the sponsor (or designee) or destroyed per written instructions from the Sponsor.

5.12. Packaging, Labeling, and Storage

All active HTX-011 and HTX-002 study medication will be prepared (i.e., packaged and labeled in individual doses) by the sponsor or the sponsor's designee. Normal saline, bupivacaine HCl, fentanyl and acetaminophen will be sourced and supplied by the study site. All study medication will be dispensed and administered by the unblinded staff.

5.12.1. Study Drug Packaging

HTX-011 and HTX-002 will be packed and dispatched in refrigerated shipping containers with a temperature monitor enclosed. The lot number and a manufacturing date will be provided.

5.12.2. Study Drug Labeling and Storage

HTX-011 and HTX-002 labeling will comply with the applicable laws and regulations. At the minimum, the following information will be provided:

- Study number (HTX-011-C2015-203)
- Drug identification
- Name, address, and telephone number of sponsor or manufacturer
- Lot number
- Content of package
- Storage conditions
- CAUTION: New Drug – Limited by United States Law to Investigational Use Only

All HTX-011 and HTX-002 formulations at the study site(s) should be stored in a refrigerator at 2–8^{o}C. The refrigerator should be in a locked area with restricted access. A daily temperature log or chart should be maintained to monitor the refrigerator temperature at the study site.

Please refer to the study Pharmacy Manual for complete storage, preparation, and administration instruction.

5.13. Prior and Concomitant Medications

All medications taken by subjects within 14 days before dosing and administered during the study conduct will be recorded in the eCRF.

Unless a medication has been prescribed at a stable dose for at least 30 days prior to the scheduled abdominoplasty, it will be prohibited for administration before the surgical procedure within 5 half-lives of that specific medication, or, if half-life is unknown, within 48 hours.

5.14. Prohibited Medications

The following medications are prohibited throughout the study: anticonvulsants, corticosteroids (by any means of administration), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), neuroleptics or norepinephrine reuptake inhibitors (SNRIs), gabapentin, and pregabalin, and, administration of any of these agents while participating in the study, will disqualify the subject from the efficacy evaluation.

Selective serotonin reuptake inhibitor (SSRI) treatments are allowed if taken for at least 30 days before the screening period of the study at an unchanged stable dose.

Analgesic medications other than those pre-specified for post-randomization rescue use (Section 5.16) are prohibited during the period from T0 to T72, and the prohibited medications include, but are not limited to: hydrocodone, codeine, fentanyl, meperidine, tramadol, opioid combinations and NSAIDS. Aspirin (acetylsalicylic acid) is also prohibited excluding low dose aspirin for cardiac prophylaxis.

Sedatives (including benzodiazepines) used as minor tranquilizers or hypnotics are not allowed unless approved by the investigator and the Sponsor medical monitor.

Agents for post-surgical nausea prophylaxis, including 5-HT3 receptor blockers (e.g., ondansetron), scopolamine, dexamethasone, or haloperidol are prohibited during or upon completion of the surgical procedure.

5.15. Concomitant Interventions and Procedures

All interventions or procedures that occur in a study subject, whether diagnostic or therapeutic, will be recorded in the eCRF, along with time, date, and reason for the intervention or procedure. If an intervention or procedure is implemented to treat an AE, then the event must be recorded as an AE, along with all relevant information.

5.16. Analgesia Rescue Medication

Study investigators will review the HTX-011/HTX-002 Investigator's Brochure so as to be aware of the safety related events which may be anticipated with its use. Investigators will

be versed in the latest standard of care guidelines. A fully stocked emergency crash cart, oxygen, and personnel trained in emergency resuscitation will be available at the post-anesthesia care area at all times during the confinement period.

Rescue analgesia (from T0 to T72) will be available to subjects with inadequately controlled pain symptoms. Pain intensity (PI) assessments must be completed prior to administration of any rescue analgesia dose. The approved rescue regimen will be morphine 2 mg iv bolus doses by titration as needed in the post-anesthesia recovery area. Once effective analgesia has been reached using the morphine administered, subjects will be transitioned to oral oxycodone 10 mg every 2 hours, as needed for analgesia. Additional morphine up to 10 mg IV every 2 hours as needed may be administered for inadequate analgesia with oxycodone. A subject who indicates a PI score that is ≤ 4 may be given acetaminophen 1000 mg for analgesia; however a daily dose of acetaminophen must not exceed 4 grams (4000 mg). For subjects in Parts F or H, the fact that they received 1000 mg IV acetaminophen in the operating room must be accounted for so their daily consumption of acetaminophen on Day 0 must not exceed an additional 3000 mg in the 24 hours following surgery.

Efforts should be made to encourage subjects to wait at least 60 minutes after the end of surgery to receive rescue medication. **Pain intensity assessment must be completed prior to administration of any rescue dose administered**. Subjects do not need to have a qualifying pain score to receive rescue analgesia; however, whenever possible staff should try to ensure that rescue analgesia is administered only when PI prior to rescue is a Visual Analog Scale for Pain of ≥ 4.0 cm. Pain Intensity will also be assessed within 5 minutes prior to administration of each dose of rescue analgesia.

Between T72 (i.e., after discharge from the research unit) and T96, pain medication (if needed) will be prescribed according to the investigator's discretion and institutional standard of care. The name, dose, reason, route, and time of administration of analgesics consumed after T72 will be recorded in a subject diary and presented at the time of the T96 visit to the study center.

After T96, PI scores will not be recorded: subjects may resume standard of care pain medication as advised by their surgeon. This may include, but is not limited to: ibuprofen, acetaminophen, or opiate/APAP combo medication, if still needed. The name, dose, reason, route, and time of administration of analgesics consumed after T96 will be recorded at the time of Day 10 visit to the study center.

Subjects who do not receive adequate analgesia from the rescue regimen or experience intolerable opioid related side effects can be administered the standard of care analgesics. The subjects will not be evaluable for efficacy; however, the subject must remain in the study for all planned visits (i.e., safety evaluations and for obtaining PK blood samples) until completion of participation in the study or early termination from the study for any other reason.

6. STUDY PROCEDURES

A schedule of study procedures for overall study assessments and day-of-dosing assessments is provided in Appendix A.

6.1. Order of Study Procedures

The order of the procedures to be performed at any scheduled time will be as follows (where appropriate):

1. Pain Intensity Score
2. Patient Global Assessment
3. Nausea assessment
4. Vital signs
5. 12-Lead ECG
6. Physical Examination (± 30 minutes at 72 hours)
7. Neurologic Exam
8. Blood draw for PK and clinical laboratory assessments
9. Surgical Wound site assessment (Appendix F)
10. Photography of wound
11. Adverse events
12. Concomitant medications

Study procedures have a ± 15 minutes window unless otherwise stated.

6.2. Demographic and Efficacy Assessments

6.2.1. Demographics

Demographic information will be collected during screening visit including age, sex, ethnicity, race, weight, (also measured at Day 0 and at any early termination from the study) height, and BMI (see Appendix D).

6.2.2. Medical History

The investigator or designee will document each subject's medical history (including PONV risk factors; Appendix C-2) during the screening visit. Medical history will be obtained through subject interview. The review of subject's medical records from their primary care physician will not be conducted. Medical history will be updated on Day 0 when the subject reports for surgery and the subject will be interviewed to confirm that they continue to meet the required study inclusion and exclusion criteria.

6.2.3. Physical Examination

The investigator or designee will perform a physical examination (HEENT, cardiovascular, respiratory, abdominal, gastrointestinal, neurological, dermatologic, and musculoskeletal systems) during the screening visit, at admission (Day 0) to the study site on the day of

surgery, at 72 hours post-dosing, and at the Day 10 visit. Body weight and height will be measured, and BMI (Appendix D) will be calculated during the screening visit. Weight does not need to be measured at 72 hours after administration of study medication.

The study investigator may perform a physical examination (the extent of which is determined by the study investigator) at any time during the study if indicated by change in a subject's medical history or condition.

6.3. Efficacy Assessments

At screening visit, each subject will be trained with how to provide pain intensity assessments as determined by the VAS. A refresher training will be provided when subject returns to study center on Day 0 prior to surgery.

6.3.1. Pain Intensity (PI)

PI will be assessed by the subject for their current pain according to the Visual Analog Scale for Pain where 0 equates to no pain and 10 equates to the worst pain imaginable. PI scores will be measured two ways: on movement and at rest. A ± 15 minute window allowed for the collection of each PI assessment. PI assessments must be collected, even if subjects are asleep at the time of the assessment.

PI scores will be solicited at the following time points: 1, 2, 4, 6, 8, 10, 12, 14, 18, 24, 30, 36, 42, 48, 54, 60, 72, 78, 84, and 96 hours post study drug administration. The level of pain experienced will be measured in two ways: when subject is at rest, and when subject makes a deliberate movement. Assessments performed at 78 and 84 hours will be performed by subjects at home using a patient diary.

PI scores will be measured *at rest* at the following time-points after time T0: 1, 2, 78, 84, and 96 hours after the administration of study medication.

Pain scores will be measured *on movement* (i.e., sitting up from a supine position) at the following time-points after time T0: 4, 6, 8, 10, 12, 14, 18, 24, 30, 36, 42, 48, 54, 60, and 72 hours. A PI assessment will first be obtained at rest. Then a second PI assessment will be obtained after the subject sits up.

PI will also be assessed within 5 minutes prior to administration of each dose of rescue analgesia, and at time of early discontinuation in the event it occurs, and only if the subject is discontinued prior to T96.

6.3.2. Patient Global Assessment of Pain Control (PGA)

Subjects will be asked to evaluate the performance of their study medication as a pain treatment in response to the following inquiry: "Overall, please rate how well your pain has been controlled during the last 24 (48, 72, 96) hours since you received study medication: 0-poor, 1-fair, 2-good, 3-very good, or 4-excellent."

The PGA of pain control will be completed at 24, 48, 72, and 96 hours after study medication (i.e., T0) administration, and at time of early discontinuation if it should occur and only if the subject is discontinued prior to T96.

6.3.3. Analgesia Rescue Medication Usage

All subjects will be monitored for analgesia rescue medication administration/usage beginning at T0 and ending at T96. The medication name, dose, reason, route, and time of administration will be recorded in the subject's eCRF.

The total and average daily rescue analgesic consumption over 24, 48, 72, and 96 hours post-T0 will be calculated for each subject.

6.4. Safety Assessments

6.4.1. Clinical Laboratory Tests

During the screening visit, on Day 0 during check-in, and at 72 hours following study drug administration, and in the event of subject early discontinuation, subjects will have blood samples collected for routine clinical laboratory testing as follows:

- hematology: complete blood count consisting of white blood cell (WBC) and red blood cell count, platelet count, hemoglobin, hematocrit, and differential counts (total neutrophils, eosinophils, basophils, lymphocytes, and monocytes)

- clinical chemistry tests: urea, glucose, creatinine, sodium, potassium, chloride, bicarbonate, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, direct bilirubin, gamma-glutamyltransferase, lactate dehydrogenase, calcium, total protein, magnesium, phosphate, albumin, and uric acid

Additional urine or blood samples will be collected and tested as follows:

- urine drug screen and alcohol breath test at the screening visit, and during admission to the study unit on Day 0. Urine drug screen will include screening of (at minimum): cocaine, marijuana, opiates, amphetamines, methamphetamines, phencyclidine (PCP), benzodiazepines, barbiturates, tricyclic antidepressant, methylenedioxymethamphetamine, methadone, and oxycodone.

- serum pregnancy testing at the screening visit, and urine pregnancy testing at check-in on Day 0 (female subjects of child bearing potential only).

Screening laboratory results will be used for assessing eligibility for study randomization. Clinical laboratory test data from Day 0 prior to surgery will be used as "baseline" reference for study analysis and not for assessing study randomization eligibility. Blood samples for baseline laboratory samples must be collected prior to the first surgical incision.

6.4.2. Nausea Assessment

Nausea will be assessed during the study using the Visual Analog Scale for Nausea where 0 equates to no nausea and 10 equates to the worst nausea imaginable. Assessment of nausea will be completed by subjects at the following time points: 6, 24, 48, and 72 hours within a ± 15 minute window and at the time of early discontinuation, if it should occur and only if a subject is discontinued prior to T96.

6.4.3. Vital Sign Measurements

Resting vital signs will include resting blood pressure, resting pulse, respiratory rate, oral temperature, and peripheral oxygen saturation (SpO2). Resting tests must be obtained after resting (seated/supine) for ≥ 5 minutes.

After the administration of study medication (i.e. post-T0), subjects will have vital signs (resting only) measured and recorded at the following times: 1, 2, 4, 6, 12, 18, 24, 36, 48, 60, 72, and 96 hours and at the Day 10 visit, and at time of early discontinuation, if any. Vital signs will have a collection window of ± 15 minutes for 1 through 72 hours and ± 2 hours for 96 hours and for Day 10 (± 2 days).

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.

6.4.4. 12-Lead Electrocardiogram (ECG)

A 12-lead ECG will be performed after the subject has been supine for at least 5 minutes and will be completed for all subjects at screening, at check-in on Day 0 (if screening ECG was done > 7 days prior to Day 0), and at the following post-T0 time-points: 24, 48, 72, and 96 hours, and at the Day 10 visit and at time of early discontinuation. ECG intervals, notably qTC, will be analyzed in the context of time matching to peak PK values.

For subjects enrolled in Parts B through I, additional ECGs will be performed post–T0 timepoint at 1, 2, 3, 4, 5, and 6 hours. Data from the 12-lead ECG will be used to exclude a subject from participation in the study at screening or Day 0 if (s)he has a clinically significant abnormal ECG.

The findings (i.e., classification as "normal," "abnormal, not clinically significant," or "abnormal, clinically significant [including heart block]") will be recorded in the subject's eCRF. ECGs that are "abnormal clinically significant" may be collected; otherwise a copy of actual ECG tracings will not be collected for Data Management purposes.

6.4.5. Surgical Wound Healing Evaluation and Photographs

The wound evaluator will be a blinded investigator, or other medically qualified clinical site personnel, who will assess the surgical site to determine if healing is normal or abnormal at 48 hours, 72 hours, Day 10, Day 28, and at time of early discontinuation (if applicable), and who will record observations (Appendix F) on the appropriate source document and eCRF.

If a wound is assessed as abnormal and unexpected post-surgical finding(s), then the finding(s) will be recorded as an AE.

Photographs of the subject's abdomen/surgical intervention site will be taken immediately after surgery and at following time-points after T0: 72 hours, Day 10, Day 28, and at time of early discontinuation (if applicable) (Appendix G).

6.4.6. Blood Sampling for Bupivacaine/Meloxicam Pharmacokinetics Analysis

Blood samples for the pharmacokinetic analysis of bupivacaine and meloxicam concentrations will be collected at the following times: prior to anesthesia induction for surgery, and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 36, 48, 60, 72, 96, and at 120 hours after study medication administration (± 15 minutes for all draws from 1 hour through 36 hours, ± 1 hour for 48 hours through 72 hour draws, and ± 4 hours at 96 and 120 hours). Please refer to the PK lab manual for the procedures for blood sample collection and handling.

6.4.6.1. Bioanalysis of Bupivacaine and Meloxicam

The concentrations of bupivacaine and meloxicam in plasma will be determined using validated LC-MS/MS assays. Concentrations will be calculated by interpolation from a calibration curve. Quality control samples will be analyzed throughout the study. Their measured concentrations will be used to determine between-run, overall precision, and accuracy of the analyses.

6.4.7. Neurologic Exam and Assessment

The neurologic examination includes a mental status exam and evaluation of cranial nerve, motor, sensory, and cerebellar function. The potential for bupivacaine toxicity will be assessed during the neurologic exam and may include (but not necessarily limited to) any of the following: perioral tingling, strange taste, muscle twitching, ringing in ears, seizure, bradycardia and cardiac arrest.

Neurologic examinations should be completed by a physician or other health professional qualified to perform such examinations, *and*, if possible, the same individual should perform the neurologic exam throughout the study. The findings will be summarized in a neurologic assessment. The examiner will be asked to record whether the subject's overall neurologic status is better, worse, or the same.

The neurologic exam/assessment will be completed at the following time points: at Day 0 any time prior to anesthesia induction, and at 24, 48, and 72 hours post-T0 within a ± 15 minute window. A neurologic exam and assessment will also be completed at early termination from the study if it occurs at ≤ T72.

6.4.8. Assessment of Adverse Events and Prior/Concomitant Medications

Prior/concomitant medications and AE assessments will be conducted throughout the study conduct after Day 0 until Day 28 post-T0 from the study. Serious AEs will be recorded if

they occur at any time after study drug administration through to Day 28 post-T0. SAEs that occur before study drug administration will be reported only if considered related to study participation. Physical examinations including neurologic and cardiovascular evaluations will be performed to determine if there are any changes in the patient's condition from baseline as noted in the schedule of events.

Close attention should be given to conditions that may represent reported toxicities associated with bupivacaine including, but not limited to perioral tingling, strange taste, visual and auditory disturbances, muscle twitching, seizure, acidosis, shortness of breath, bradycardia (heart rate < 50 bpm with symptoms), hypotension (BP < 90 mmHg or symptomatic decrease from baseline), low oxygen saturation (≤ 90% for ≥ 1 minute), and cardiac arrest.

Adverse events and any interventions associated with AEs will be documented in the eCRF.

6.4.8.1. Treatment of Bradycardia, Hypotension, and Low Oxygen Saturation

If a subject's heart rate drops < 50 beats/minutes, with symptoms of bradycardia present, then interventions can be made in accordance with the investigator's discretion and following standard of care guidelines.

If a subject's systolic blood pressure drops < 90 mm Hg or has a symptomatic decrease from baseline (pre T0 value), then interventions can be made in accordance with the investigator's discretion and following standard of care guidelines.

If a subject's peripheral oxygen saturation drops to ≤ 90% for ≥ 1 minute, then treatment with oxygen via nasal cannula can be initiated at the discretion of the investigator, with a target saturation of 95% or a return to baseline levels.

All interventions should be recorded in the subject's eCRF.

6.5. Assessments by Visit

6.5.1. Screening Visit

Subjects meeting the eligibility criteria listed in Sections 5.1 and 5.2 may be enrolled in the study after the nature and purpose of the protocol have been explained to them and they have voluntarily granted written informed consent to participate. All subjects will have a screening evaluation within 28 days before surgery (Day 0). After informed consent is obtained, the following procedures will be performed at the screening visit for all subjects:

- Demographics
- ASA classification
- Review of medical history and the inclusion/exclusion for study eligibility
- Measurement of resting vital signs

- 12-lead ECG
- Physical examination including height, weight, and BMI
- Clinical laboratory tests
- Urine drug screen and alcohol breath test
- Serum pregnancy test for women of childbearing potential
- Assessment of PONV risk factors
- Training on reporting pain intensity assessments
- Record prior and concomitant medications
- Record SAEs after informed consent signature (only if considered related to study participation)

6.5.2. Day 0 Check-In and Surgery

The following assessments will be conducted on the day of admission (Day 0, prior to surgery) for all subjects:

- Review of inclusion/exclusion criteria eligibility
- Medical history update
- Measurement of resting vital signs
- 12-lead ECG (if screening ECG was > 7 days prior to Day 0)
- Physical examination, including weight only
- Neurologic Exam
- Clinical laboratory tests
- Urine drug screen and alcohol breath test
- Urine pregnancy test for women of childbearing potential
- Training reminders on pain assessments and placebo response
- Blood draw for PK analysis of bupivacaine and meloxicam (‘baseline’ PK sample)
- Record prior and concomitant medications

- Record SAEs
- Study drug administration

Subjects who continue to meet eligibility criteria will undergo an abdominoplasty surgical procedure. Subjects who don't experience a clinically significant event during surgery (e.g., excessive bleeding, hemodynamic instability) that would render the subject medically unstable or complicate their post-surgical course will be administered study medication according to the randomization scheme.

6.5.3. Day 0 (Treatment) – Day 5

The following assessments will be conducted during the treatment phase on Days 0 – 5 subsequent to the administration of study medication:

- PI assessments
- PGA for pain control
- Assessment of VAS for nausea
- Measurement of resting vital signs
- 12-lead ECG
- Blood samples for PK analysis of bupivacaine and meloxicam (through 120 hours)
- Physical examination (72 hour only)
- Clinical laboratory tests (72 hour only)
- Record AEs/SAEs and concomitant medications
- Monitor and record use of analgesia rescue medication
- Wound Healing Assessment (48 hour and 72 hour)
- Photograph of surgical intervention site (Day 0 immediately post surgery, 48 hour and 72 hour)
- Neurologic assessment (24, 48, 72 hours)

One hour after administration of study medication (T1) assessments will be completed if the subject is awake and alert.

Rescue analgesia will be available to subjects with inadequately controlled pain symptoms during the treatment phase on Days 0 – T72. After T72, subjects may resume standard of care pain medication as advised by their surgeon.

6.5.4. Day 10 ± 2 and Day 28 ± 2 (Follow-Up Procedures)

The following procedures will be conducted for all subjects during the Day 10 and 28 visits.

- Physical examination, including weight only (Day 10 only)
- 12-lead ECG (Day 10 only)
- Vital signs (Day 10 only)
- Record analgesic medications usage
- Record AEs/SAEs and concomitant medications
- Assessment of wound healing
- Photograph of surgical intervention site

Clinically significant adverse events, examination, or test results will be followed until appropriate resolution can be documented.

6.5.5. Day 60 Follow-Up Phone Call (±7 days)

Subjects will receive a phone call from the study site. Subjects will be asked if they have any current pain related to the operation. Subjects will also be asked to think about the previous 24 hours and to rate their pain intensity related to the operation using the NRS, and to report any medication(s) to treat the pain (name, dose, and route). See Appendix H for details on the information to be collected. The results will be recorded in source documents.

6.5.6. Early Termination (ET) Procedures

Subjects who discontinue participation or who are discontinued prior to completing the Day 28 visit will be asked to complete ET procedures, which will include:

- Pain intensity assessment (only if the subject was discontinued prior to 96 hour)
- PGA assessment (only if the subject was discontinued prior to 96 hour)
- Assessment of nausea VAS (only if the subject was discontinued prior to 96 hour)
- Measurement of resting vital signs
- 12-lead ECG
- Physical examination, including weight only
- Clinical laboratory tests

- Assessment of AEs and review of concomitant medications
- Assessment wound healing
- Photograph of abdominal wound
- Neurologic assessment (only if subject was discontinued prior to 72 hours)

6.5.7. Unscheduled Visits

Unscheduled visits should be performed on an "as-needed" basis if a subject's medical situation warrants it. For each unscheduled visit, the following will be recorded:

- Assessment of any new AEs.
- Assessment of concomitant medications.
- A blood sample draw (to be used for determination of bupivacaine levels) when the unscheduled visit(s) is precipitated by AE(s) associated with neurologic or cardiac symptoms.

6.6. Appropriateness of Assessments

The efficacy measures utilized in this study are commonly used in clinical studies performed in acute post-operative pain populations. The timing of assessments is intended to evaluate the time to onset of analgesia, duration of effect, and magnitude of benefit.

Safety measures used in this study are standard for clinical trials of investigational medications.

7. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND SERIOUS SUSPECTED ADVERSE REACTIONS

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE, SAE, or serious suspected adverse reaction as provided in this protocol. During the study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

7.1. Definition of an Adverse Event

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

An AE may be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study medication, whether or not considered causally associated with the use of the study medication. Any abnormal laboratory value deemed clinically significant by the investigator, regardless of causal relationship, must be reported as an AE.

Examples of an AE include the following:

- significant or unexpected worsening or exacerbation of the condition or indication under study
- exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency or intensity of the condition (e.g., 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 medication or a concurrent medication (overdose per se should not be reported as an AE or SAE, unless nonserious or serious sequelae occur)

The following examples are not considered AEs:

- medical or surgical procedure (e.g., endoscopy, appendectomy), although the condition that leads to the procedure is an AE
- anticipated day to day fluctuations of preexisting 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's that are considered to be clinically normal (would be expected to occur as a long-acting local anesthetic wears off)

All AEs, whether volunteered, elicited, or noted on physical examination and regardless of causality or seriousness, will be assessed and recorded in the eCRF beginning after administration of study medication through the Day 28 study visit.

7.2. Definition of a Serious Adverse Event

An SAE is defined as any event that meets the following criteria:

- It results in death or is life-threatening (i.e., presents 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.)

- It results in persistent or substantial disability or incapacitation. (This criterion is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, diarrhea, or sprained ankle.)

- It results in hospitalization.

- It results in prolongation of an existing hospitalization.

- It is a congenital anomaly or birth defect.

- It requires medical or surgical intervention to prevent any of the above outcomes.

Medical and scientific judgment should be exercised in determining whether an AE is serious when considering important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent any of the other outcomes listed. Examples of such medical events that may also be considered serious include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline does not meet the definition of an SAE.

Social or convenience admission to a hospital or prolongation of a hospitalization for social or convenience reasons not associated with the occurrence of an AE does not meet the definition of an SAE.

7.2.1. Serious Adverse Events That Occur Before Administration of Study Medication

Before administration of study medication, only SAEs assessed by the investigator as related to study participation (e.g., related to study procedures or a change in existing therapy) will be transcribed onto the SAE reporting form and reported to the sponsor.

7.2.2. Serious Adverse Events That Occur After Study Completion

If an investigator becomes aware of an SAE or death that occurs in a subject more than 30 days of the subject's last study visit and that investigator considers the event to be related to the study medication, the investigator is obligated to report the SAE to the sponsor as outlined in Section 7.7.

7.3. Definition of a Suspected Adverse Reaction

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the adverse event was caused by the study drug. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.4. 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 7.2; i.e., death, life-threatening, causes or prolongs inpatient hospitalization, causes a persistent of significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital abnormality/birth defect.

7.5. Recording and Evaluating Adverse Events and Serious Adverse Events

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, or other clinical information. In such cases, the diagnosis, not the individual signs or symptoms, should be documented as the AE or SAE.

7.5.1. Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study, using his or her clinical judgment. The intensity of each AE and SAE recorded in the eCRF should be assigned to one of the following categories:

- mild: an event that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities
- moderate: an event that is sufficiently discomforting to interfere with normal everyday activities
- severe: an event that prevents normal everyday activities

An AE that is assessed as severe should not be confused with an SAE. Severity is a term used to describe the intensity of a specific event, and both AEs and SAEs can be assessed as severe. The event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as serious, which is based on the subject's or event's

outcome or on action criteria usually associated with events that pose a threat to a subject's life or functioning (see Section 7.2).

7.5.2. Assessment of Causality

The investigator is obligated to use his or her clinical judgment to assess the relationship between the study medication and the occurrence of each AE or SAE. The investigator will assess the relationship to the study medication by using the following criteria:

- Definitely Related: An AE has a strong temporal relationship to the study drug. The AE is most likely explained by study drug. Dechallenge and rechallenge (if possible) are positive. The AE is consistent with a known response to the study drug. Another etiology is unlikely or significantly less likely.

- Probably Related: An AE has a strong temporal relationship to the study drug. The AE is more likely explained by study drug than by another cause. Dechallenge (if performed) is positive.

- Possibly Related: An AE has a reasonable temporal relationship to study drug. The AE could have been due to another equally likely cause. Dechallenge is positive.

- Unlikely Related: An AE does not follow a temporal relationship to study drug. The AE can be explained due to study factors.

- Not Related: The subject did not receive the study drug OR the AE has no temporal relationship to study drug OR the AE has a much more likely alternate etiology OR the AE is due to an underlying or concurrent illness or effect of another drug.

Even in situations in which minimal information is available for the initial SAE report, it is important that the investigator always make an assessment of causality for every event before transmitting the SAE reporting form and completing the AE eCRF page(s). 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 reporting form and AE eCRF page(s) accordingly.

7.5.3. Assessment of Outcome

All SAEs must be followed until they are resolved, the condition stabilizes, the events are otherwise explained, or the subject is lost to follow-up. The investigator will assess the outcome of the event by using the following terms:

- 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 post-operative wound infection, or an upper respiratory tract infection.

- 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 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.

- Death

7.6. Follow-Up of Adverse Events and Serious Adverse Events

Nonserious AEs will be followed after the last scheduled study visit, until an appropriate resolution can be documented.

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 are designated as ongoing and will be reviewed at subsequent visits or contacts.

SAEs will be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost to follow-up. 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 on the originally completed SAE reporting form and entered into the eCRF pages, with all changes signed and dated by the investigator. The updated SAE reporting form should be resubmitted to the sponsor within the time frames outlined in Section 7.7.

7.7. Prompt Reporting of Serious Adverse Events to the Sponsor

Once the investigator determines that an event meets the protocol definition of an SAE, he or she must notify the sponsor within 24 hours of being informed about the event.

ANY SAE OR ANY OUTCOME OF DEATH DUE TO ANY CAUSE WHICH OCCURS DURING THE COURSE OF THIS STUDY, REGARDLESS OF RELATIONSHIP TO STUDY MEDICATION, MUST BE REPORTED TO THE SPONSOR IMMEDIATELY (within 24 hours).

COMPLETE THE SAE DETAILS REPORTING FORM AND FORWARD BY E-MAIL TO THE FOLLOWING SPONSOR CONTACT:

Htx011safety@herontx.com

In the initial e-mail, 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, photographs, or medical reports relevant to the SAE.

E-mail transmission is the preferred method to transmit SAE information. In rare circumstances and in the absence of e-mail 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 reporting form and eCRF pages within the time frames outlined.

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

7.8. Regulatory Reporting Requirements

The investigator must promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 7.7, "Prompt Reporting of Serious Adverse Events to the Sponsor." 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 medication, 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 IRB or IEC.

7.9. Precautions

Any subject who becomes pregnant during the study must be discontinued immediately but should be followed through delivery or termination of the pregnancy. A subject should also notify the investigator if she becomes pregnant within 30 days after receiving study medication. The sponsor must be notified of all pregnancies reported to the investigator (see Section 7.7 for contact information).

8. STATISTICAL METHODOLOGY

8.1. Determination of Sample Size

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

8.2. Study Endpoints

See Section 3 for efficacy, safety, and PK endpoints.

8.3. General Considerations for Statistical Analysis

8.3.1. Software and General Statistical Methods

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.2 or higher) for Windows. If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

For continuous variables, summary statistics including number of subjects with data, mean, standard deviation (SD), median, minimum, and maximum will be provided. For categorical variables, the number of subjects and percentage for each category will be presented.

8.3.2. Analysis Datasets

Intent-to-Treat (ITT) Analysis Set: The ITT set will include all subjects who are randomized to receive study medication.

Efficacy Set: The efficacy analysis set will include all subjects who are randomized to receive study medication and have recorded at least one post-dosing PI scores. This analysis set is noted as the modified Intend-to-Treat (mITT) set.

Safety Set: The safety set will include all treated subjects and will be used for safety and tolerability assessments.

8.3.3. Test Hypothesis and *P* Value Justification

The null hypothesis is that there is no difference between each comparison (pairwise or pooled group comparisons). The alternative hypothesis is that there is a difference for the comparison.

Each pairwise or pooled group comparison will be evaluated via 2-sided 2-sample t-test at the 0.05 level of significance. Nominal p-value will be reported without adjustment for multiplicity.

8.3.4. Procedures for Handling Missing Data

Unless indicated otherwise (see Section 8.3.4.1 and 8.3.4.2), no imputation will be done for missing data.

8.3.4.1. PI Score Before and After Analgesic Rescue Medication

All subjects are expected to assess their post-operative pain intensity according to the pain intensity schedule; those PI assessments are referenced as the scheduled PIs. Subjects who require rescue analgesia are expected to report their pain intensity immediately before taking the rescue medication; this PI is referenced as the pre-rescue PI. The duration of analgesic effect will be determined for the rescue medication (e.g., the analgesic window for one oxycodone 10 mg Q2 hours); this analgesic duration is referenced as the analgesic window of this rescue medication. When the assessment of a scheduled PI is done after the rescue medication and the time is within the analgesic window (inclusive) of the rescue medication, the scheduled PI score will be replaced by the pre-rescue PI score for the purpose of efficacy analysis. This method is referenced as the Windowed Last Observation Carried Forward (WLOCF). The original scheduled PI scores will be displayed on data listing along with the "imputed" PI score.

8.3.4.2. Other Missing PI Score(s)

After the scheduled PI scores are appropriately replaced by the pre-rescue PI score for all subjects who had rescue medication based on the WLOCF method, if there are additional time points where the PI scores are missing, the standard LOCF method will be used to impute the missing PI score. All imputed PI scores will be clearly marked on data listings.

Additional missing data imputation methods may be used to assess the robustness of the efficacy data. The details will be discussed in the statistical analysis plan for the study.

8.3.5. Derived Variables

Prior to data base lock, a complete statistical analysis plan will be developed which will describe in detail the calculation of all efficacy variables.

8.3.5.1. Study Population Summaries

Population summaries will be provided for the safety analysis set included in this study.

8.3.6. Disposition

The summary tables will provide frequency counts for subject disposition (all treated subjects, subjects who completed the study, subjects who discontinued from the study, and reason for discontinuation) by treatment group and study overall.

Disposition in terms of number of subjects excluded from each analysis sets (mITT, safety) will also be provided by treatment groups and study overall.

8.3.7. Demographics

The demographic summary will include descriptive statistics for age, sex, race, weight, height, and BMI for the overall and by treatment group.

8.3.8. Protocol Violations

All protocol violations and deviations will be identified. Tabulation may be provided if data are warranted.

8.3.9. Treatment Compliance

Since study medication is administered intra-operatively, no formal summary of treatment compliance will be produced.

8.3.10. Prior and Concomitant Medications

All prior and concomitant medications will be tabulated for the overall study population. Prior and concomitant medications will be coded to the therapeutic drug classes and generic drug names using the World Health Organization (WHO) drug classifications version 1Q2013 or higher.

8.4. Efficacy Analysis

8.4.1. SPI and PI Analyses

The analyses of the primary and all secondary endpoints will be described in the statistical analysis plan. The basic analysis plan will be an Analysis of Variance with the contrasts to test for differences between the cohorts.

8.4.2. Time to First Dose of Rescue Medication

A description of the analysis of time to first dose of rescue medication will be presented in the Statistical Analysis Plan.

8.4.3. Patient Global Assessment (PGA) of Pain Control

Number and percent of subjects in each global pain control category (0-poor, 1-fair, 2-good, 3-very good, or 4-excellent) will be tabulated by treatment group. The difference between the groups in global pain control will be evaluated based on proportion of subjects rated their pain control as good, very good, or excellent using Fisher's exact test.

8.4.4. Proportion of Subjects Requiring Rescue Medication

The analysis will evaluate the relative risk (HTX-011 or HTX-002 vs. saline or bupivacaine HCl) to require rescue medications during the treatment phase of the study. Proportion of subjects that used rescue medications at least once will be tabulated by treatment group; difference between HTX-011, HTX-002, saline, and bupivacaine HCl will be assessed as described in the statistical analysis plan.

8.4.5. Opioid Consumption and Symptoms Associated With Opioid Use

Average daily opioid use will be calculated for each 24 hour period post study medication administration. Subjects who did not use any opioid during a period will be assigned to "0." Average daily opioid data will be tabulated by treatment group with descriptive statistics.

8.4.6. Subgroup Analyses for Efficacy

No subgroup analysis for efficacy endpoints is planned.

8.5. Safety and Tolerability Evaluations

8.5.1. Adverse Events

The Medical Dictionary for Regulatory Activities (Version 16 or higher) will be used to classify all AEs with respect to system organ class and preferred term.

Three types of summaries will be produced for the AE summary:

1. an overall summary of AEs: number of subjects with at least one event and number of events for all AEs, and SAEs
2. a summary table of AEs and SAEs by system organ class and preferred term and severity
3. a summary table of AEs and SAEs by preferred terms in descending order of total incidence

AEs will be tabulated by treatment group. AEs that lead to premature discontinuation from the study or to death will be listed separately via data listings.

8.5.2. Nausea Assessments

The mean nausea assessment scores at 6, 24, 48, and 72 hours will be calculated, and the analysis of the data will be described in the Statistical Analysis Plan.

8.5.3. Clinical Laboratory Tests

Laboratory values will be collected at screening, Day 0 during check-in, 72 hours, and ET. Observed values at each time point and change from baseline (Day 0) at the end of study will be summarized for the by treatment group without formal statistical testing.

8.5.4. Vital Sign Measurements

Resting vital sign values at each time point collected will be summarized by treatment without formal statistical testing.

8.5.5. Electrocardiograms

The number and proportion of subjects with abnormal ECG findings at each time point collected will be tabulated by treatment group. A data listing will be provided for subjects

with changes from normal at baseline to abnormal and clinically significant after baseline by treatment.

8.5.6. Subgroup Analyses for Safety Endpoints

No subgroup analysis is planned for safety endpoints.

8.6. Interim Evaluation

An evaluation of the data in Part A will be used to determine the optimal HTX-011 formulation(s) and dose(s) for Part B.

9. STUDY ADMINISTRATION

9.1. Regulatory and Ethical Considerations

9.1.1. 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.

9.1.2. Ethical Conduct of the Study and Ethics Approval

This study will be conducted according to GCP; US 21 Code of Federal Regulations (CFR) Part 50 (Protection of Human Subjects); US 21 CFR Part 56 (IRBs); US 21 CFR Part 54 (Financial Disclosure); International Conference on Harmonization (ICH) Guidance for Industry, E6 GCP: Consolidated Guidance; the Nuremberg Code; and, where applicable the principles of the Declaration of Helsinki (Recommendations guiding Medical Doctors in Biomedical Research Involving Human Subjects), and with the NH&MRC National Statement on Ethical Conduct in Human Research (2007).

9.1.2.1. Ethics Committees

The investigator (or sponsor, where applicable) is responsible for ensuring that this protocol, the site's informed consent form, and any other information that will be presented to potential subjects (e.g., advertisements or information that supports or supplements the informed consent form) are reviewed and approved by the appropriate IRB or IEC. The investigator agrees to allow the IRB or IEC direct access to all relevant documents. The IRB or IEC must be constituted in accordance with all applicable regulatory requirements. The sponsor will provide the investigator with relevant documents or data needed for IRB or IEC review and approval of the study. Before investigational products can be shipped to the site, the sponsor must receive copies of the IRB or IEC approval, the approved informed consent form, and any other information that the IRB or IEC has approved for presentation to potential subjects. The study agreement must also be fully executed.

If the protocol, the informed consent form, or any other information that the IRB or IEC has approved for presentation to potential subjects is amended during the study, the investigator is responsible for ensuring that the IRB or IEC reviews and approves, where applicable, these amended documents. The investigator must follow all applicable regulatory requirements pertaining to the use of an amended informed consent form, including obtaining IRB or IEC approval of the amended form, before new subjects consent to take part in the study using the new version of the form. The investigator must promptly forward to the sponsor copies of the IRB or IEC approval of the amended informed consent form or other information and the approved amended informed consent form or other information. IRB or IEC approval of the consent forms must be obtained in addition to the approval given for the clinical study. Regulatory review and approval may be required in some countries before IRB or IEC approval can be sought.

9.1.2.2. General Considerations

The ethical standards defined within GCP are intended to ensure the following:

- Human subjects are provided with an adequate understanding of the possible risks of their participation in the study, and they have a free choice to participate or not.
- The study is conducted with diligence and in conformance with the protocol in such a way as to ensure the integrity of the findings.
- The potential benefits of the research justify the risks.

Heron Therapeutics, Inc. is the sponsor of study HTX-011-C2015-203. The sponsor (or its designee) is responsible for all of the following:

- selecting qualified investigators
- providing investigators with the information they need to conduct the investigation properly
- ensuring proper monitoring of the investigation
- ensuring that appropriate regulatory agencies and all participating investigators are properly informed of significant new information regarding AEs or risks associated with HTX-011 or HTX-002.

9.1.3. Informed Consent

The sponsor (or its designee) will provide investigators with a multicenter informed consent form 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 informed consent form must be accepted by the sponsor and approved by the IRB or IEC. Investigators must provide the sponsor with an unsigned copy of the final informed consent form before and after it is approved by the IRB or IEC. 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 informed consent form, the sponsor will provide investigators with a revised informed consent form. The IRB or IEC must provide written approval of any revisions to the informed consent form in advance of its use.

Investigators must provide subjects 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, and possible risks.

All information in the informed consent form should be provided in a language (whether written or spoken) that is as nontechnical as practical and that is understandable to the subjects.

Before written 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 (or his or her legally authorized representative).

Before a subject undergoes procedures specific to the protocol, the informed consent form must be signed and dated by the subject (or his or her legally authorized representative) and any other signatories as required by the IRB or IEC.

If a subject (or legally authorized representative) cannot read, a short form approved by the IRB or IEC may be used. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign the copy of the summary in accordance with 21 CFR 50.27 (b2).

After all required signatures have been obtained, a copy of the informed consent form should be provided to the subject, and the original must be kept on file at the site and made available for review by the sponsor. Documentation of the informed consent discussion must be noted in the subject's case history.

9.1.4. Investigator Reporting Requirements

The investigator is responsible for completing and maintaining adequate and accurate eCRFs and source documentation. Source documentation constitutes original records (first point of entry, either hard copy or electronic), which may include progress notes, medication administration records, operation reports, laboratory reports, discharge summaries, and so on.

9.2. Study Monitoring

The sponsor (or its designee) is responsible for ensuring the proper conduct of the study with regard to subject protection, ethics, protocol adherence, site procedures, and integrity of the data. At regular intervals during the study, the sponsor's study monitors will contact the study site via visits to the site, telephone calls, and letters in order to review study progress and eCRF completion and to address any concerns or questions regarding the study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: subjects' informed consent documents, subject recruitment procedures, subjects' compliance with the study procedures, source-data verification, drug accountability, use of concomitant therapy by subjects, AE and SAE documentation and reporting, and quality of data.

9.3. Quality Assurance

The sponsor, a regulatory authority, or an IRB representative may visit the study site at any time during the study or after completion of the study to perform audits or inspections. The purpose of a sponsor audit or regulatory inspection is to examine systematically and independently all study related activities and documents to determine whether these activities were conducted according to the protocol, GCP, ICH guidelines, and any other applicable regulatory requirements. Investigators should contact the sponsor immediately if contacted by a regulatory agency about an inspection at their site.

9.4. Study and Site Closure

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 the study site should be closed, this action may be taken after appropriate consultation between the sponsor and investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study
- submission of knowingly false information from the research facility to the sponsor, study monitor, or regulatory agencies
- failure of the investigator to comply with GCP (e.g., ICH guidelines, regulatory agency guidelines)
- insufficient adherence to protocol requirements or an unacceptably high rate of missing, erroneous, or improperly collected data
- evidence from the blinded data of sufficient technical problems with the study that one could believe with a high degree of certainty that subjects are being exposed to the investigational drug without a realistic expectation of evaluable data
- a decision on the part of the sponsor to suspend or discontinue testing evaluation or development of the product
- failure of the investigator to enroll subjects into the study at an acceptable rate

9.5. Records Retention

9.5.1. Health Insurance Portability and Accountability Act of 1996

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subjects' health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR Parts 160 and 164 (the Health Insurance Portability and Accountability Act of 1996 privacy regulation). 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 and in a form satisfactory to the sponsor.

9.5.2. Financial Disclosure

Financial disclosure is required for this study.

9.5.3. Access to Original Records

Regulatory authorities expect that monitors, auditors, and representatives of national and international government regulatory agency bodies have access to original source documentation (see examples in Section 9.1.4) to ensure data integrity. "Original" in this context is defined as the first documentation of an observation and does not differentiate between hard copy and electronic records.

9.5.4. Archiving of Study-Related Documents

Records related to this clinical study must be retained either 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. The sponsor will notify the investigator as to when these documents no longer need to be retained for this use.

9.6. Provision of Study Results and Information to Investigators

When a clinical study report is completed, the sponsor will provide the major findings of the study to the investigators.

In addition, details of the study treatment assignment will be provided to the investigators to enable them to review the data to determine the outcome of the study for their subjects.

The sponsor may list and summarize the results from coded samples by subject number in the clinical study report. In this event, the investigator and study staff would have access to the research results and would be able to link the results to a particular subject. The investigator and study staff would be directed to hold this information confidentially.

9.7. Information Disclosure and Inventions

9.7.1. Ownership

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.

All rights, title, and interests in any inventions, know how, or other intellectual or industrial property rights that are conceived or reduced to practice by site staff during the course of or as a result of the study are the sole property of Heron Therapeutics, Inc. and are hereby assigned to Heron Therapeutics, Inc.

9.7.2. 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 other 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. 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 IEC or IRB 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 9.7.3. 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.

9.7.3. Publication

For multicenter studies, the first publication or disclosure of study results shall be a complete, joint, multicenter publication or disclosure coordinated by Heron Therapeutics, Inc. Thereafter, any secondary publications will reference the original publication(s). If no multicenter publication is submitted for publication within 18 months of study database hard lock, then the site shall be free to disclose its own results, subject to sponsor rights under Section 9.7.1.

Before submitting material for publication, presentation, or use for instructional purposes, or before otherwise disclosing the study results generated by the site (collectively, a "publication"), the investigator shall provide Heron Therapeutics, Inc. with a copy of the proposed publication and allow Heron Therapeutics, Inc. a period of at least 120 days to review the proposed publication. Proposed publications shall not include either Heron Therapeutics, Inc. confidential information (other than the study results) or the personal data (such as name or initials) of any subject.

At Heron Therapeutics, Inc.'s request, the submission or other disclosure of a proposed publication will be delayed a further 90 days to allow Heron Therapeutics, Inc. to seek patent or similar protection of any inventions, know-how, or other intellectual or industrial property rights disclosed in the proposed publication.

9.7.4. Data Management

The investigator (or designee) will enter subject data by using the eCRF defined by Heron Therapeutics, Inc. or its designee. Clinical data management will be performed in accordance with applicable Heron Therapeutics, Inc. standards and data cleaning procedures. Database freeze will occur when data management quality-control procedures are completed.

In addition, validated clinical and PK laboratory data will be transmitted electronically from the clinical laboratory to Heron Therapeutics, Inc. or its designee.

The investigator or designee must record all required data using the previously specified data collection method defined by Heron Therapeutics, Inc. or its designee. An explanation must be documented for any critical data points. The investigator must sign and date a declaration in the eCRF attesting that he or she is responsible for the quality of all data recorded and that the data represent a complete and accurate record of each subject's participation in the study.

9.7.5. Data Security

Access to the data will be strictly controlled.

9.8. Subject Tracking

Drug accountability logs, a subject identification log (to be retained by the investigator only), and a subject enrollment log will be used to track subject participation in the study.

10. REFERENCES

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Moote, C. (1992). "Efficacy of nonsteroidal anti-inflammatory drugs in the management of postoperative pain." Drugs **44 Suppl 5**: 14-29; discussion 29-30.

Ortiz, Mario I., Gilberto Castañeda-Hernández, Jeannett A. Izquierdo-Vega, et al. (2011). "Peripheral synergistic interaction between lidocaine and lumiracoxib on the 1% formalin test in rats." The Open Pain Journal **4**: 8-14.

Rawal, N. (2001). "Analgesia for day-case surgery." Br J Anaesth **87**(1): 73-87.

Renck, H. (1994). "Wound infiltration with local anaesthetics." Acta Anaesthesiol Scand **38**(1): 2-6.

11. APPENDICES

Appendix A: OVERVIEW OF STUDY SCHEDULE

Table 1: SCREENING

Procedure	Day -28 to -1
	Screening
Informed Consent	X
Eligibility Assessment	X
Demographics and Medical History	X
Assessment of PONV Risk Factors	X
Physical Examination [e]	X
Serum Pregnancy Test (female subjects of child bearing potential only)	X
Urine Drug Screen	X
Alcohol Breath Test	X
Clinical Laboratory Tests [a]	X
Vital Signs [b]	X
BMI Determination	X
12-lead ECG	X
Subject Pain Training	X
Prior and Concomitant Medication [c]	X
Serious Adverse Event Monitoring [d]	X

[a] Laboratory tests will include hematology and chemistry. Results will determine subject eligibility for the study.
[b] Resting vital signs (VS) will be collected at screening. Resting VS include: resting blood pressure, resting pulse, respiratory rate, oral temperature and SpO2. Resting tests must be obtained after resting (seated/reclined) for ≥ 5 minutes.
[c] Concomitant medications taken within 14 days before dosing will be recorded on the eCRF.
[d] SAEs will be reported if considered related to study participation.
[e] PE will include weight, height, and BMI.

Appendix A: OVERVIEW OF STUDY SCHEDULE

Table 2: DAY 0 PRIOR TO SURGERY AND SURGERY

	Day 0	
	Prior to Surgery	**Surgery**
Eligibility Assessment	X	
Demographics and Medical History	X	
Physical Examination [c]	X	
Urine Pregnancy Test (female subjects of child bearing potential only)	X	
Urine Drug Screen	X	
Alcohol Breath Test	X	
Clinical Laboratory Tests [a]	X [d]	
Vital Signs [b]	X	
12-lead ECG	X [e]	
Subject Pain Training	X	
Blood Draw for PK	X [d]	
Neurologic Exam	X	
Abdominoplasty Procedure		X
Study Drug Administration		X
Prior and Concomitant Medication	X	X
Serious Adverse Event Monitoring [f]	X	X
Post-surgical Photograph of Abdominal Wound		X

[a] Laboratory tests will include hematology and chemistry and will be used as baseline reference and not for determining subject eligibility.
[b] Resting vital signs (VS) will be collected at screening and check-in only, all other assessments will include resting VS only. Resting VS include: resting blood pressure, resting pulse, respiratory rate, oral temperature and SpO2. Resting tests must be obtained after resting (seated/reclined) for ≥ 5 minutes. VS will have a ± 15 minute window.
[c] Physical examination will include weight only but not height or BMI.
[d] Baseline laboratory samples can be collected prior to surgery.
[e] If screening 12-lead ECG was done > 7 days prior to Day 0.
[f] SAEs that occur before study drug administration will be reported only if considered related to study participation. After study drug administration, all SAEs that occur through Day 28 must be reported.

Appendix A: OVERVIEW OF STUDY SCHEDULE

Table 3: POST STUDY MEDICATION ADMINISTRATION (DAYS 0 – 5)

			Day 0 to 5																					
			Post Study Drug Administration Time Points (hrs)																					
	0.5	1[f]	1.5	2	2.5	3	4	5	6	8, 10, 12	14	18	24	30	36	42	48	54	60	72	78	84	96[h]	120[h]
Confinement	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Physical Examination [c]																				X[g]				
Clinical Laboratory Tests [a]																				X				
Vital Signs [b]		X		X			X		X	X (hr 12 only)		X	X		X		X		X	X			X	
12-lead ECG		X[i]		X[i]		X[i]	X[i]	X[i]	X[i]				X				X			X			X	
Pain Intensity (PI) At Rest		X		X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pain Intensity (PI) on Movement							X		X	X	X	X	X	X	X	X	X	X	X	X				
PGA of Pain Control													X				X			X			X	
Use of Rescue Medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]			X[e]	
PK Blood Draws (± 15 min 1 hr through 36 hr, ± 1 hr 48-72 hrs, ± 4 hrs 96 + 120 hrs)	X	X	X	X	X	X	X	X	X	X		X	X	X	X		X		X	X			X	X
Nausea Assessment									X				X				X			X				
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of Wound Healing																	X			X				
Abdominal Photographs																	X			X				
Neurologic Exam and Assessment													X				X			X				
Adverse Event Monitoring [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Laboratory tests will include hematology and chemistry.
[b] Resting VS only. Resting VS include: resting blood pressure, resting pulse, respiratory rate, oral temperature and SpO2. Resting tests must be obtained after resting (seated/supine) for ≥ 5 minutes.
[c] Physical examination will include weight only, but not height or BMI. Weight not required at 72 hour exam.
[d] AEs will be monitored after administration of study medication through the Day 28 study visit. SAEs will be monitored from screening through Day 28.
[e] Subjects may resume standard of care pain medication as advised by their surgeon after the 72 hour study visit.
[f] 1 hour assessments to be completed if subject is awake and alert.
[g] ± 30 minutes.
[h] ± 4 hours, except for vital signs, which will be measured at ± 2 hours.
[i] Parts B, C, D, E, F, G, H, and I.

Table 4: POST STUDY MEDICATION ADMINISTRATION (FOLLOW-UP)

	Post Study Drug Administration Time Points			
	Day 10 (± 2 days)	**Day 28 (± 2 days)**	**Day 60 (± 7 days)**	**Early Termination**
Physical Examination	X[c]			X
Clinical Laboratory Tests [a]				X
Vital Signs [b]	X			X
12-lead ECG	X			X
Pain Intensity (PI)				X[e]
PGA of Pain Control				X[e]
Nausea Assessment				X[e]
Concomitant Medications	X	X		X
Assessment of Wound Healing	X	X		X
Abdominal Photographs	X	X		X
Neurologic Exam and Assessment				X[f]
Adverse Event Monitoring [d]	X	X		X
Phone Call [g]			X	

[a] Laboratory tests will include hematology and chemistry.
[b] Resting VS only. Resting VS include: resting blood pressure, resting pulse, respiratory rate, oral temperature and SpO2. Resting tests must be obtained after resting (seated/supine) for ≥ 5 minutes.
[c] Physical examination will include weight only, but not height or BMI.
[d] AEs will be monitored after administration of study medication through the Day 28 study visit. SAEs will be monitored through from screening to Day 28.
[e] PI, PGA, and nausea assessments are only required at the Early Termination Visit if the subject discontinues before T96.
[f] Neurologic examination and assessment is only required at the Early Termination Visit if the subject discontinues before T72.
[g] Subjects will receive a phone call from the study site on Day 60 (±7 days). Subjects will be asked if they have any current pain related to the operation. Subjects will also be asked to think about the previous 24 hours and to rate their pain intensity related to the operation using the NRS and to report any medication(s) to treat the pain (name, dose, and route).

Appendix B: INVESTIGATOR OBLIGATIONS

As an investigator, you are responsible for ensuring that the study is conducted according to the protocol, the signed Statement of Investigator, and all applicable regulations.

Debarment

Individuals ineligible to conduct or be involved with clinical studies, including those ineligible as a result of debarment under the Generic Drug Enforcement Act of 1992, will not be allowed to conduct or work on studies sponsored by Heron Therapeutics, Inc. You are required to disclose immediately to the sponsor, in writing, if any person involved in the conduct of the study is debarred pursuant to a hearing by FDA under this antifraud law or if any proceeding for debarment is pending or is (to the best of your knowledge) threatened.

Institutional Review Board

You are required to obtain initial and continuing review and approval by an IRB or IEC that complies with the requirements specified in 21 CFR Part 56. Before initiating the trial, you must have written approval from the IRB or IEC for the protocol, informed consent form, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to the subjects. You must submit the Investigator's Brochure and any updates to the IRB or IEC for review. The IRB or IEC must also provide written approval of any amendments to the protocol that affect the conduct of the study and any changes to the informed consent form in advance of use. If the duration of the study is longer than 1 year, reapproval by the IRB or IEC must be obtained on a yearly basis (or at more frequent intervals if required by the IRB or IEC). All IRB or IEC approvals must be forwarded to the sponsor.

You must provide reports of all SAEs from your site to the IRB or IEC. You are also responsible for providing the IRB or IEC with Safety Reports of any SAEs from any other study conducted with the study medication. The latter will be provided to you by the sponsor.

Confidentiality and Safety of Subjects

You are responsible for protecting the rights, safety, and welfare of subjects under your care and for the control of the drug(s) under investigation.

You are responsible for keeping a record of all screened subjects, including full names and last known addresses. All subjects will be identified on the eCRFs by initials and subject numbers. Demographic information including date of birth, sex, and race will also be recorded on the eCRFs. Confidentiality of subject data will be maintained in accordance with local laws.

In addition to your responsibilities for reporting AEs identified during the course of a subject's participation in the study, you must also report any SAEs that occur within 30 days after the last dose of study medication (regardless of relationship to study medication) and

any serious adverse drug reactions (SAEs for which you consider that there is a reasonable possibility that the study medication caused the response) that you become aware of at any time (even if the event occurs more than 30 days after the subject's last exposure to study medication). This obligation is in addition to any protocol-specified requirement for reporting AEs occurring after the last dose of study medication. Please refer to Sections 7.7 and 7.8 of this protocol for contact information and SAE reporting requirements.

Study-Related Records

You are required to maintain complete and accurate study documentation in compliance with current GCP standards and all applicable federal, state, and local laws, rules, and regulations related to the conduct of a clinical study.

You are required to make all study documentation promptly available for inspection, review, or audit at your study site upon request by the sponsor, its representatives, or any appropriate regulatory agencies.

Accountability of the Investigational Product

You or your designee (i.e., the pharmacist) is responsible for accountability of the investigational product at the site. You or your designee must maintain records of the product's delivery to the site, inventory at the site, use by each subject, and the return to the sponsor or alternative disposition of any unused product. These records must include dates; quantities; batch, serial, or lot numbers; and expiration dates (if applicable).

You should ensure that the investigational product is used only in accordance with the protocol.

Appendix C: STUDY-SPECIFIC INFORMATION

Appendix C-1: Patient Global Assessment (PGA) of Pain Control

The following question will be answered by the patient 24, 48, 72, and 96 hours after study treatment initiation:

"Overall, please rate how well your pain has been controlled during the last 24 (48, 72, 96) hours since you received study medication?"

Response to each question will be: (Check (√) one box)

☐ Poor (0)

☐ Fair (1)

☐ Good (2)

☐ Very Good (3)

☐ Excellent (4)

Appendix C-2: Risk Factors for Post-Operative Nausea and Vomiting

- Past history of post-operative nausea and vomiting and/or motion sickness
- Habitual nonsmoking status
- Female gender
- Expected to receive opioid analgesia post-operatively

Appendix D: BMI CALCULATION

Body Mass Index Calculations

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 E: AMERICAN SOCIETY OF ANESTHESIOLOGISTS PHYSICAL STATUS CLASSIFICATION SYSTEM

I Normal healthy patient

II Patient with mild systemic disease; no functional limitation – e.g. smoker with well-controlled hypertension

III Patient with severe systemic disease; definite functional impairment – e.g. diabetes and angina with relatively stable disease, but requiring therapy

IV Patient with severe systemic disease that is a constant threat to life – e.g. diabetes and angina and congestive heart failure; patients with dyspnea on mild exertion and chest pain

V Unstable moribund patient who is not expected to survive 24 hours with or without operation

VI Brain dead patient whose organs are removed for donation to another

E Emergency operation of any type, which is added to any of the above six categories, an in ASA II E

Appendix F: WOUND ASSESSMENT

WOUND SITE EVALUATION

Timepoint: ☐ Post-Surgical ☐48 Hour ☐ 72 Hour ☐ Day 10 ☐ Day 28

WOUND SITE EVALUATION NOT DONE ☐

	Normal (Expected Post-Surgical Findings)	***Abnormal**	***Abnormal findings which are to be recorded on the CRF as Adverse Events** If observations are mild they should **not** be recorded on the CRF as Adverse Events. Please describe below any other wound abnormalities that are not listed in boxes below.
Wound Site:	☐	☐	
Other, *specify in the boxes below*:	☐	☐	

Wound Description	**Normal**	***Abnormal**	**Not present**
Wet	☐	☐	☐
Dehiscence	☐	☐	☐
Erythema	☐	☐	☐
Drainage ☐ **Blood** ☐ **Serous** ☐ **Purulent** ☐ **Other (specify)** _____	☐	☐	☐
Bruising	☐	☐	☐
Swelling	☐	☐	☐

Appendix G: PHOTOGRAPHY INSTRUCTIONS

INSTRUCTIONS FOR TAKING PHOTOGRAPHS OF ABDOMINOPLASTY SURGICAL WOUND

Materials

- Camera (type and model to be specified) Identify camera settings
- Memory card
- Background cloth
- ID tag: Complete for **Protocol #, Subject #, Study Hour or Day, Date, Time, and what is being photographed (i.e., abdomen)**

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1. Ensure the batteries in the camera are charged. If low, replace the batteries prior to using the camera.
2. Place the memory card in the camera.
3. Expose the entire abdomen to be photographed and place the background cloth under the area to be photographed.
4. Remove any dressing and place the completed ID tag adjacent to the area to be photographed taking care not to obscure any area of the wound itself to be photographed.
5. Ensure that **Protocol #**, **Subject #, Study Hour or Day, Date, Time, and what is being photographed (i.e., abdomen)** is documented for reference purposes in the photograph.
6. At each photograph timepoint take 3 photographs with the camera looking down at the abdomen so that the abdominal area fills the camera window, clearly showing the entire surgical abdominal incision. This is done to ensure that there will be at least one photograph taken that best represents the abdominal incision area.

Appendix H: DAY 60 FOLLOW-UP PHONE CALL

Subjects will receive a follow-up phone call from the site on Day 60 (±7 days). Sites will attempt to contact subjects at least twice to complete this assessment; attempts must be recorded, including the phone number called, in source documents.

During the Day 60 call, subjects will be asked the following questions. The results will be recorded in source documents.

1. Are you having any pain related to the operation?

   Yes/No

2. Thinking about the past 24 hours, on a scale of 0-10 with 0 being no pain and 10 being the worst possible pain, what is your pain related to the operation?

   0 – 10

3. Thinking about the past 24 hours, have you taken any medication(s) to treat pain related to the operation?

   Yes/No

4. If you answered Yes to Question 3, what medications (name, dose, and route) have you taken?

   _____

   _____

   _____

   Enter "N/A" if not applicable

Signature Manifest

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All dates and times are in Pacific Standard Time .

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Document Approval

Name/Signature	Title	Date	Meaning/Reason
Mary Rose Keller (MKELLER)	VP. Clinical Operations	14 Feb 2017, 10:14:32 AM	Approved

Final Approval

Name/Signature	Title	Date	Meaning/Reason
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