Document Type:	Study Protocol
Official Title:	A Phase 1b/2, Randomized, Blinded, Active-Controlled Study of Escalating Doses of HTX-034 for Postoperative Analgesia in Subjects Undergoing Unilateral, First Metatarsal Bunionectomy With Osteotomy and Internal Fixation
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CLINICAL STUDY PROTOCOL: HTX-034-101

Protocol Title:	A Phase 1b/2, Randomized, Blinded, Active-Controlled Study of Escalating Doses of HTX-034 for Postoperative Analgesia in Subjects Undergoing Unilateral, First Metatarsal Bunionectomy With Osteotomy and Internal Fixation
Brief Title:	Dose-Escalation Study of HTX-034 Following Bunionectomy
Test Product:	HTX-034 (bupivacaine, aprepitant, and meloxicam) extended-release solution
Phase of Development:	1b/2
Sponsor:	Heron Therapeutics, Inc. 4242 Campus Point Court, Suite 200 San Diego, CA 92121 1-858-251-4400
Medical Monitor:	[redacted]
Medical Project Leader:	[redacted] Vice President, Clinical Research and Medical Affairs [redacted]

Protocol Version:		
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	Version 7	05 February 2021
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	Version 4	21 April 2020
	Version 3	08 April 2020
	Version 2	02 April 2020
	Version 1	05 March 2020

SPONSOR SIGNATURE

Protocol Title:	A Phase 1b/2, Randomized, Blinded, Active-Controlled Study of Escalating Doses of HTX-034 for Postoperative Analgesia in Subjects Undergoing Unilateral, First Metatarsal Bunionectomy With Osteotomy and Internal Fixation
Protocol Number:	HTX-034-101

This protocol Version 8 has been reviewed and approved by the Sponsor.

The electronic signature is appended.

[redacted]
Chief Medical Officer
Heron Therapeutics, Inc.

INVESTIGATOR AGREEMENT

CLINICAL STUDY PROTOCOL: HTX-034-101

TITLE: A Phase 1b/2, Randomized, Blinded, Active-Controlled Study of Escalating Doses of HTX-034 for Postoperative Analgesia in Subjects Undergoing Unilateral, First Metatarsal Bunionectomy With Osteotomy and Internal Fixation

I have read the protocol and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. I will conduct the study as outlined herein.

I will provide copies of the protocol, the Investigator's Brochure, and all other information on the study drugs and study devices that are furnished to me by the Sponsor to all physicians and other study personnel responsible to me who participate in this study, and will discuss this material with them to ensure that they are fully informed regarding the test product and the conduct of the study.

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

Principal Investigator: _____

Address: _____

Signature: _____

Date (DD-Month-YYYY): _____

PROTOCOL SYNOPSIS

NAME OF SPONSOR:	Heron Therapeutics, Inc.
NAME OF TEST PRODUCT:	HTX-034 (bupivacaine, aprepitant, and meloxicam) extended-release solution
NAME OF ACTIVE INGREDIENTS:	bupivacaine, aprepitant, and meloxicam
PROTOCOL NUMBER:	HTX-034-101
PHASE OF DEVELOPMENT:	1b/2

PROTOCOL TITLE: A Phase 1b/2, Randomized, Blinded, Active-Controlled Study of Escalating Doses of HTX-034 for Postoperative Analgesia in Subjects Undergoing Unilateral, First Metatarsal Bunionectomy With Osteotomy and Internal Fixation

STUDY SITES: Up to 6 sites in the United States (US)

STUDY OBJECTIVES:

Primary

- To evaluate the safety and tolerability of single-dose administration of escalating doses of HTX-034 in subjects undergoing bunionectomy (Phase 1b).
- To evaluate the efficacy of HTX-034 in subjects undergoing bunionectomy (Phase 2).

Secondary

- To evaluate the efficacy of escalating doses of HTX-034 in this study population (Phase 1b).
- To evaluate the safety and tolerability of HTX-034 in this study population (Phase 2).
- To characterize the pharmacokinetic (PK) profile of HTX-034 in this study population (Phase 1b and Phase 2).

BACKGROUND AND RATIONALE FOR THE STUDY: Up to 70% of patients have moderate to severe pain after surgery and as a result many receive opioids. Poorly managed pain and opioid-related adverse reactions result in worse patient outcomes and increased hospital costs.

This study is designed to evaluate the safety, PK, and analgesic efficacy of escalating doses of HTX-034 administered as a single dose into the surgical site compared with bupivacaine HCl (standard of care) in subjects undergoing bunionectomy.

HTX-034 is a novel, non-opioid, fixed-dose combination, extended-release solution of bupivacaine, aprepitant, and low-dose meloxicam formulated in a proprietary polymer that enables extended release of the 3 active ingredients. A related product, HTX-011, contains the same fixed doses of bupivacaine and meloxicam in the proprietary polymer, but without aprepitant. In Phase 3 studies in bunionectomy, a single dose of HTX-011 (60 mg/1.8 mg [bupivacaine/meloxicam doses]) significantly reduced pain and opioid consumption through 72 hours compared with both bupivacaine HCl and saline placebo, and was well tolerated. A follow-on study evaluated single individualized doses of HTX-011 up to 60 mg/1.8 mg (mean dose of 46.25 mg/1.39 mg) in bunionectomy and demonstrated similar efficacy.

Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK_1) receptors that is approved for use as an antiemetic. Substance P is involved in pain perception and transmits pain signals from the sensory nerves to the central nervous system. It is also believed to play a role in neurogenic inflammation. Studies of HTX-034 in a nonclinical model of postoperative pain have demonstrated that administration of HTX-034 produced prolonged analgesia.

Preliminary results from Part 1b of this study demonstrated that both HTX-034 dose cohorts were well tolerated and reduced pain and opioid use compared with pooled bupivacaine HCl. Phase 2 will further assess the efficacy, safety, and PK of HTX-034.

METHODOLOGY: This is a Phase 1b/2, randomized, blinded, active-controlled study. Phase 1b will evaluate escalating doses of HTX-034 compared with bupivacaine HCl (without epinephrine). Phase 2 will be a dose-expansion phase to evaluate additional subjects treated with the HTX-034 doses selected based on Phase 1b compared with bupivacaine HCl (without epinephrine).

Subjects and site personnel performing all postoperative assessments will be blinded to treatment assignments. Sponsor staff directly interacting with blinded site personnel will maintain the blind. The data for Cohorts 1 and 2 may be unblinded after Phase 1b is complete.

Study Overview

Subjects will be screened within 28 days prior to the planned surgery date. Subjects who meet the screening eligibility criteria will be randomized to receive HTX-034 or bupivacaine HCl. On the day of surgery (Day 1), subjects who continue to meet the eligibility criteria will undergo a bunionectomy under regional anesthesia with no more than 20 mL of 1% lidocaine without epinephrine administered as a Mayo block. During surgery, the use of intravenous (IV) fentanyl up to 4 μg/kg will be permitted for intraoperative pain control per site practice. Near the completion of surgery, a single dose of study drug (HTX-034 or bupivacaine HCl) will be administered into the surgical site.

Subjects will remain in the hospital/research facility for 7 days (Phase 1b) or 3 days (Phase 2) from the start of study drug administration to undergo postoperative safety, PK, and efficacy assessments. All subjects will perform self-assessments of pain intensity during the inpatient period and will record the use of postoperative rescue medication through the Day 15 Visit. Subjects in the Phase 2 will also perform self-assessments of pain intensity during the outpatient period (Day 4 through Day 8). After discharge, follow-up PK samples will be collected at home visits by a healthcare professional on Days 9, 10, 11, and 22 in Phase 1b or at the study site on Days 8, 15, and 29 in Phase 2 to characterize the PK profile of HTX-034. Subjects will return to the study site on Day 8 (subjects in Phase 2 only) and on Days 15, 29, and 43 (all subjects) for follow-up assessments. A serum drug test for opioids will be performed at the Day 8 Visit (subjects in Phase 2 only) and at the Day 15 Visit (all subjects).

Phase 1b (Dose Escalation)

There are 2 planned sequential dose cohorts (Table 1). Cohort 1 will evaluate a single dose level of HTX-034. Cohort 2 will evaluate individualized doses of HTX-034; the amount administered will be determined for each subject by the surgeon at the time of surgery and will be based on the volume sufficient to coat the pain-generating tissues, while ensuring there is not an excess that could be expressed from the site during closure.

Each cohort will include a total of approximately 16 subjects (with a minimum of 10 subjects per cohort evaluable for PK). Within each cohort, subjects will be randomized in a 3:1 ratio to receive either HTX-034 (n=12) or bupivacaine HCl (n=4).

Table 1: Summary of Dose Cohorts in Phase 1b

Cohort	HTX-034				Bupivacaine HCl 0.5% Dose (Volume)
	Syringe Volume to Withdraw	Syringe Volume to Expel[a]	Actual Volume Administered[b]	Dose to Administer[c]	
Cohort 1	1 mL	1 mL	0.73 mL	21.7 mg/4.3 mg/0.6 mg	50 mg (10 mL)
Cohort 2	2 mL	1.3 mL to 2 mL	1.03 mL to 1.73 mL	30.6 mg/6.1 mg/0.9 mg to 51.5 mg/10.3 mg/1.5 mg	50 mg (10 mL)

[a] Syringe volume to expel in Cohort 2 will be determined by the Investigator at the time of administration based on the volume sufficient to coat the pain-generating tissues, while ensuring there is not an excess that could be expressed from the site during closure. The volume to expel will range between 1.3 mL and 2 mL.
[b] Actual volume administered takes into account the volume retained in syringe and Luer lock applicator (0.27 mL) after study drug administration.
[c] Dose to administer is based on actual volume administered, which will be determined by weighing syringes before and after study drug administration. HTX-034 doses list the bupivacaine dose first followed by the aprepitant dose and then the meloxicam dose.

Dose escalation to Cohort 2 will be guided by safety data from Cohort 1. After all subjects in Cohort 1 have completed the Day 29 Visit, an internal Interim Review Committee (IRC) will review the data. If the IRC deems it appropriate, the next dose cohort may begin to enroll.

Dose escalation will not take place if any of the following occur:

- ≥2 subjects in a dose cohort experience a serious adverse event (SAE) reported by the Investigator and confirmed by Sponsor to be possibly related to HTX-034.
- ≥2 subjects experience a moderate or severe treatment-emergent adverse event (TEAE) compatible with local anesthetic systemic toxicity (LAST) reported by the Investigator and confirmed by the Sponsor to be possibly related to HTX-034.
- ≥2 subjects treated with HTX-034 who have a wound healing complication of Grade IV or V using the Southampton Wound Scoring System.

Phase 2 (Dose Expansion)

Following a review of the Phase 1b data, up to approximately 40 additional subjects will be randomized to 1 of 2 HTX-034 dose levels or to bupivacaine HCl in a 2:1:1 ratio at the same doses assessed in Phase 1b.

- HTX-034 high dose: 30.6 mg/6.1 mg/0.9 mg to 51.5 mg/10.3 mg/1.5 mg (20 subjects).
- HTX-034 low dose: 21.7 mg/4.3 mg/0.6 mg (10 subjects).
- Bupivacaine HCl 0.5%: 50 mg (10 subjects).

All subjects in Phase 2 will be inpatient for 3 days.

Postoperative Rescue Medication

Subjects must only receive rescue medication upon request for pain control, as needed. Rescue medication must not be given for pain prophylaxis, but only for treating postoperative pain. Prior to the administration of the first dose of rescue medication, if the subject has not already had at least 1 postoperative pain score assessed, then a numeric rating scale of pain intensity at rest (NRS-R) score followed by a numeric rating scale of pain intensity with activity (NRS-A) score must be obtained.

After Surgery Through 72 Hours

Postoperative rescue medication through the first 72 hours after surgery will consist of 1 or more of the following 3 medications: oral (PO) acetaminophen (1,000 mg no more frequently than every 6 hours, as needed; not to exceed 4,000 mg in a 24-hour period), PO immediate-release oxycodone (≤10 mg

within a 4-hour period), and/or IV morphine (≤10 mg within a 2-hour period). The choice of rescue medication will be at the site's discretion. Combination products containing an opioid and a non-opioid are not allowed. Nonsteroidal anti-inflammatory drugs (NSAIDs) are not permitted; no other analgesic agents are permitted.

After 72 hours Through Day 15 Visit

After 72 hours through the Day 15 Visit, the following medications are recommended to treat pain when necessary in a step-wise fashion:

1. PO acetaminophen as needed (1,000 mg no more frequently than every 6 hours; not to exceed 4,000 mg in a 24-hour period).
2. PO immediate-release oxycodone (≤10 mg within a 4-hour period) only if acetaminophen fails to adequately manage pain.

Morphine is not permitted after 72 hours. NSAIDs are not permitted; no other analgesic agents are permitted.

After Day 15 Through End of Study

After the Day 15 Visit through the end of the study, postoperative pain should be managed per institutional standard of care.

Recording Rescue Medications

Postoperative rescue medication will be recorded through the Day 15 Visit. Subjects will record PO oxycodone and acetaminophen in an electronic patient-reported outcome (ePRO) device; IV morphine will be recorded on an electronic case report form (eCRF). Notes: morphine is not permitted after 72 hours. Pain medication taken after Day 15 is not considered rescue medication and will be recorded on the concomitant medication eCRF.

Opioid Prescriptions At and After Discharge

If a subject did not receive any opioids or received <5 IV morphine milligram equivalents (MME; eg, <10 mg PO oxycodone) within 12 hours prior to discharge, the subject should not receive an opioid prescription at discharge.

If a subject received ≥5 IV MME (eg, ≥10 mg PO oxycodone) in the 12 hours prior to discharge, the subject may be provided at site discretion with a prescription for PO immediate-release oxycodone: no more than ten 5 mg immediate-release oxycodone pills, take 1 to 2 pills every 4 hours as needed. The prescription must indicate that substitutions with any other opioid-containing product are not permitted, including combination opioid/non-opioid products.

Sites will record if subjects are discharged with an opioid prescription and information about the opioid prescription. From discharge through the Day 15 Visit, if a subject contacts the site about postoperative pain related to the surgery, a prescription for PO immediate-release oxycodone (ten 5 mg pills; do not substitute) may be provided at the Investigator's discretion. Sites will record if any subjects are provided an opioid prescription after discharge through the Day 15 Visit and information about the prescription.

After the Day 15 Visit, postoperative pain should be managed per institutional standard of care.

NUMBER OF PLANNED SUBJECTS: Up to approximately 72 subjects will be dosed.

STUDY POPULATION:

Inclusion Criteria

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

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

4. Is medically fit to undergo an elective unilateral, first metatarsal bunionectomy with osteotomy and internal fixation under regional anesthesia; no neuraxial technique (eg, no spinal, epidural, or general anesthesia).
5. Has an American Society of Anesthesiologists Physical Status of I, II, or III.
6. Female subjects are eligible only if all of the following apply:
    a. Not pregnant (female subjects of child-bearing potential must have a negative urine pregnancy test at Screening and on Day 1 before surgery).
    b. Not lactating.
    c. Not planning to become pregnant during the study.
    d. Is surgically sterile; or is at least 2 years post-menopausal; or is practicing abstinence; or is in a monogamous relationship with a male partner who is surgically sterile; or agrees to use double-barrier contraception or an intra-uterine device (eg, copper) in the event of sexual activity from the Screening Visit through 30 days after study drug administration. Hormonal contraceptives are not an acceptable form of birth control because the efficacy of hormonal contraceptives may be reduced with aprepitant. The contraception requirement does not apply to women in only a same-sex relationship.

Exclusion Criteria

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

1. Had a contralateral foot bunionectomy in the past 3 months.
2. Has a planned concurrent surgical procedure (eg, bilateral bunionectomy or collateral procedures on the surgical foot) during the study.
3. Has a contraindication or a known or suspected history of hypersensitivity or clinically significant idiosyncratic reaction (including methemoglobinemia) to bupivacaine (or other local anesthetics), meloxicam, aprepitant, oxycodone, morphine, acetaminophen/paracetamol, or fentanyl.
4. Has a pre-existing concurrent acute or chronic painful physical/restrictive condition expected to require analgesic treatment in the postoperative period for pain that is not strictly related to the bunionectomy and which may confound the postoperative assessments.
5. Has received or is taking any of the following medications:
    a. Long-acting opioids within 3 days prior to the scheduled surgery.
    b. Any opioids within 48 hours prior to the scheduled surgery.
    c. Daily use (known or suspected) of opioids for 7 or more consecutive days within the previous 6 months.
    d. Bupivacaine within 5 days prior to the scheduled surgery.
    e. Any local anesthetic within 72 hours prior to the scheduled surgery, other than for pretreatment prior to a needle placement, to treat an adverse event (AE) that occurs after signing the informed consent form (ICF), or to decrease venous irritation (eg, caused by propofol, in which case a single administration of lidocaine 1% up to 20 mg IV may be administered).
    f. Meloxicam or any other NSAID within 10 days prior to the scheduled surgery with the exception of subjects on low-dose (≤100 mg) daily acetylsalicylic acid for cardioprotection.
    g. Aprepitant or other NK_1 receptor antagonists such as fosaprepitant or netupitant within 28 days or rolapitant within 6 weeks prior to the scheduled surgery.
    h. Selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), gabapentin, or pregabalin to control pain within 1 month prior to the scheduled surgery. (Note: If a subject is taking one of these medications for a reason other

than pain control, the subject must be on a stable scheduled dose [ie, not "as needed"] for at least 1 month prior to study drug administration.) Anxiolytics prior to surgery are permitted, if necessary.

i. Systemic steroids within 5 half-lives or 10 days prior to the scheduled surgery (whichever is longer). Note that for purposes of this exclusion criterion, inhaled, ophthalmic, and topical steroids are not considered systemic.
j. Pimozide, a strong or moderate CYP3A4 inhibitor (eg, diltiazem, ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir), or a strong CYP3A4 inducer (eg, rifampin, carbamazepine, phenytoin) within 28 days prior to the scheduled surgery.
k. Warfarin or another anticoagulant, other than low-dose acetylsalicylic acid, within 7 days prior to the scheduled surgery.
l. An investigational product or device in a clinical trial within 30 days or within 5 elimination half-lives (whichever is longer) prior to the scheduled surgery, or is planning to take part in another clinical trial while participating in this study.

6. Has a known or suspected history of drug abuse or alcohol abuse (within 10 years) or a positive drug screen on the day of surgery. Note: Subjects with a positive drug screen who are taking an allowed, prescribed medication that is known to result in a positive drug test (eg, amphetamine and dextroamphetamine for attention-deficit/hyperactivity disorder, benzodiazepine for anxiety disorder) may be eligible for participation in the study. Subjects with a positive drug screen for cannabinoids on the day of surgery will not be allowed to participate in the study.
7. Has a history of clinically significant cardiac abnormality such as myocardial infarction within 6 months prior to signing the ICF, New York Heart Association class III or IV, or clinically significant abnormalities of electrocardiogram (ECG) or cardiac function.
8. Has a history of coronary artery bypass graft surgery within 12 months prior to signing the ICF.
9. Has a history of known or suspected coagulopathy.
10. As per subject history and/or medical records, has active infection with or is currently undergoing treatment for hepatitis B, hepatitis C, or HIV.
11. Has uncontrolled anxiety, psychiatric, or neurological disorder that, in the opinion of the Investigator, might interfere with study assessments.
12. Had a malignancy in the last year, with the exception of nonmetastatic basal cell or squamous cell carcinoma of the skin or localized carcinoma in situ of the cervix.
13. Has undergone 3 or more surgeries within 12 months prior to signing the ICF.
14. Has a known history of glucose-6-phosphate dehydrogenase deficiency.
15. Has any of the following laboratory abnormalities during Screening (1 retest permitted):
    a. Severe liver function impairment as defined by Child-Pugh Class C, having an aspartate aminotransferase >3 × the upper limit of normal (ULN), or having an alanine aminotransferase >3 × ULN.
    b. Severe kidney function impairment as defined by calculated creatinine clearance (Cockcroft-Gault) <30 mL/min or on dialysis.
    c. Platelet count <100,000/μL, hemoglobin <12 g/dL, or hematocrit <35%.
16. Has a body mass index (BMI) >39 kg/m^2.
17. Has a medical condition such that, in the opinion of the Investigator, participating in the study would pose a health risk to the subject or confound the postoperative assessments.

STUDY DRUG: Study drug is defined as HTX-034 (test product) and bupivacaine HCl (control product).

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION: HTX-034 is a non-opioid, fixed-dose combination, extended-release solution of bupivacaine (a long-acting, immediate-release, local anesthetic), aprepitant (a substance P/NK_1 receptor antagonist), and low-dose meloxicam (an NSAID), formulated in a proprietary polymer (referred to as tri(ethylene glycol) poly(orthoester) [TEG-POE] and termed Biochronomer®). HTX-034 will be supplied by the Sponsor in 10 mL glass vials as a homogenous solution containing 29.75 mg/mL bupivacaine, 5.95 mg/mL aprepitant, and 0.89 mg/mL meloxicam.

Subjects randomized to HTX-034 will receive a single dose of study drug. The dose will range from 21.7 mg/4.3 mg/0.6 mg to 51.5 mg/10.3 mg/1.5 mg. Syringes will be weighed before and after HTX-034 administration to determine the dose of HTX-034 administered.

HTX-034 will be administered intraoperatively at the end of the surgical procedure, but prior to wound closure. After irrigation and suction of each fascial layer, HTX-034 will be applied evenly so that the pain-generating tissues including the proximal and distal aspects of the metatarsal receive adequate coverage.

CONTROL PRODUCT, DOSE, AND MODE OF ADMINISTRATION: Bupivacaine HCl without epinephrine 0.5% (50 mg) will be administered by injection into the surgical site. Bupivacaine HCl will be supplied by the Sponsor in Phase 1b and by study sites in Phase 2.

PROTOCOL-SPECIFIED MEDICATIONS: Additional protocol-specified medications include fentanyl and postoperative rescue medication.

Fentanyl: The use of IV fentanyl (≤4 μg/kg) will be permitted during surgery.

Rescue medication: Rescue medication permitted to treat pain during the 72-hour postoperative period will consist of 1 or more of the following 3 medications: PO acetaminophen, PO immediate-release oxycodone, and/or IV morphine. After 72-hours through the Day 15 Visit, permitted postoperative rescue medications include PO acetaminophen and PO immediate-release oxycodone. Additional administration details are provided in the Postoperative Rescue Medication section of the Synopsis.

PROTOCOL-SPECIFIED DEVICE: The custom Luer lock applicator is an investigational device used for administration of HTX-034 without a needle into the surgical site. The Luer lock applicator will be supplied by the Sponsor.

DURATION OF TREATMENT: Subjects will receive a single dose of study drug (HTX-034 or bupivacaine HCl). The total duration of study participation for each subject (from Screening through the Day 43 Visit) will be up to 75 days. The overall duration of the study is anticipated to be approximately 18 months.

STUDY ASSESSMENTS: Safety, PK, and efficacy assessments will be performed. The start of HTX-034 or bupivacaine HCl administration will be considered Time 0 for all assessments.

Safety Assessments

- AEs from the time the subject signs the ICF through the Day 43 Visit.
- LAST questionnaire.
- 12-lead ECGs (in triplicate).
- Physical examinations.
- Vital signs, including blood pressure, resting heart rate, respiratory rate, and body temperature.
- Wound healing assessments using the Southampton Wound Scoring System (Phase 1b and Phase 2) and a wound healing questionnaire (Phase 2 only).

- Clinical laboratory tests (hematology and serum chemistry).
- Bone healing assessment (X-ray of surgical site).

PK Assessments

Blood samples will be collected to measure the plasma concentrations of bupivacaine, aprepitant, and meloxicam.

Efficacy Assessments

- Pain intensity assessments using NRS-R and NRS-A.
  - *NRS-R*: Subjects should be seated/recumbent with the surgically attended leg elevated or lying supine. Measurements should be obtained after the subject is in the resting position for at least 5 minutes.
  - *NRS-A*: Subjects should be seated with the plantar surface of the ball of the surgically attended foot touching the floor (no weight-bearing).
  - Subjects will record their pain intensity scores in an ePRO device after surgery through Day 8.
- Use of postoperative rescue medication through the Day 15 Visit: Date, time of administration, amount, and type of all rescue medication taken will be recorded.
- Opioid prescription at discharge.
- Opioid prescription after discharge through the Day 15 Visit.
- Patient Global Assessment (PGA) of pain control.
- Overall benefit of analgesia score (OBAS).
- Opioid-Related Symptom Distress Scale (OR-SDS) questionnaire.
- Modified Postanaesthetic Discharge Scoring System (MPADSS) assessment.

STUDY ENDPOINTS:

Primary Endpoints

- Incidence of TEAEs (Phase 1b).
- Mean area under the curve (AUC) of the NRS scores through 72 hours (AUC_{0-72}) for the pooled Phase 1b and Phase 2.

Secondary Endpoints

Safety

- Incidence of SAEs.
- Change from baseline in clinical laboratory results.
- Change from baseline in vital signs.
- Change from baseline in ECGs.
- Incidence of TEAEs (Phase 2).

Pharmacokinetics

PK parameters will be determined for HTX-034 as follows:

Phase 1b

- Maximum concentration (C_{max}).
- Time of occurrence of maximum concentration (T_{max}).
- Area under the concentration-time curve from Time 0 to the time of the last quantitative concentration (AUC_{last}).
- Area under the concentration-time curve from Time 0 extrapolated to infinity (AUC_{inf}).

- Apparent terminal half-life ($t_{½}$).

Phase 2

- C_{max}.
- T_{max}.
- AUC_{last}.

Efficacy

- Mean AUC of NRS scores through the Day 8 Visit.
- Total postoperative opioid consumption (in IV MME) through the Day 8 Visit.
- Proportion of subjects who are opioid-free through the Day 15 Visit.

Other Endpoints

- Incidence of potential opioid-related adverse events (ORAEs) and potential LAST-related TEAEs.
- Wound healing assessment results at each assessed timepoint.
- Bone healing X-ray results at each assessed timepoint.
- Proportion of subjects with an NRS score ≥7 at each timepoint and through the Day 8 Visit.
- Proportion of subjects who do not receive an opioid prescription through the Day 15 Visit.
- Proportion of subjects achieving a score of "good" or better (>1) pain control based on PGA at each timepoint.
- Mean OBAS at each timepoint.
- OR-SDS scores by symptom dimension.
- Proportion of subjects who first achieve an MPADSS score ≥9 at each timepoint.

STATISTICAL METHODS:

Determination of Sample Size

The sample size in Phase 1b was selected empirically without a formal statistical assumption and will be sufficient to characterize the PK profile for HTX-034.

Based on results from Phase 1b of this study and a Phase 3 bunionectomy study of HTX-011 (Study HTX-011-301), a sample size of 40 subjects in Phase 2 (2:1:1 ratio of HTX-034 high dose:HTX-034 low dose:bupivacaine HCl) when pooled with Phase 1b (Table 2) will provide 82% power to detect a statistical significant difference between the HTX-034 high dose and bupivacaine HCl for the primary endpoint, assuming mean (SD) AUC_{0-72} of NRS pain scores were 272 (122) for HTX-034 in Phase 1b and 394 (154) for bupivacaine HCl in Phase 3 using Satterthwaite's t-test with $\alpha = 0.05$, 2-sided.

Table 2: Sample Size per Phase

	HTX-034 High Dose	HTX-034 Low Dose	Bupivacaine HCl
Phase 1b Safety Population	13	11	9[a]
Planned Phase 2 Safety Population	20	10	10
Pooled Phase 1b and Phase 2	33	21	19

[a] Pooled across cohorts.

Safety Analyses

All safety data will be listed and summarized for each treatment group by phase and pooled across Phase 1b and Phase 2; no statistical hypothesis testing will be performed. All TEAEs will be coded and tabulated by System Organ Class and Preferred Term. Incidence of TEAEs, SAEs, potential ORAEs,

and potential LAST-related TEAEs will be summarized. Associated laboratory parameters, such as hepatic profile, renal function, and hematology values, will be grouped and presented together in summary tables. For each laboratory parameter, individual subject values will be listed and values outside of the standard reference range will be flagged. Changes from baseline in vital sign parameters and ECG results will be summarized. Wound healing and bone healing assessment results will be summarized.

Pharmacokinetic Analyses

Plasma bupivacaine, aprepitant, and meloxicam concentrations will be determined using validated liquid chromatography tandem-mass spectrometry assays. Concentrations will be calculated by interpolation from a calibration curve. PK parameters will be calculated using noncompartmental analysis.

Efficacy Analyses

All efficacy data will be listed and summarized for each treatment group by phase and pooled across Phase 1b and Phase 2.

For the primary efficacy endpoint, the comparison between pooled Phase 1b/2 HTX-034 high dose and pooled Phase 1b/2 bupivacaine HCl is considered the primary comparison and will be analyzed using an analysis of variance (ANOVA) model with treatment as the main effect. Results will be expressed as mean AUCs and SDs, least-squares mean differences and SEs with associated 95% CIs, and p-values. Other continuous efficacy endpoints will be analyzed similarly to the primary endpoint unless specified otherwise. Total opioid consumption in IV MME will be analyzed using the Wilcoxon rank sum test. Results will be expressed as median (range) and p-values. Categorical endpoints will be analyzed using Fisher's exact test. Results will be expressed as the number and percentage of subjects meeting the relevant endpoint, differences in proportions with 95% CIs, and p-values.

Interim Analyses

An interim analysis is planned to occur after all subjects in each cohort in Phase 1b have completed the Day 29 Visit. An internal IRC will review summary-level data from each cohort to make decisions on the next cohort. The internal IRC will be composed of 1 Sponsor representative from the Clinical Research, Biometrics, Pharmacovigilance, Regulatory, and Pharmaceutical and Translational Sciences functions. The IRC will operate under a written, detailed IRC Charter.

SCHEDULE OF EVENTS

Screening Period and Surgery for Phase 1b and Phase 2

	Screening		Surgery Day (Day 1)	
Assessments	**≤28 days**	**≤1 day**	**Preoperative**	**Operating Room**
Obtain informed consent	X			
Urine drug screen[a]	X		X	
Urine pregnancy test (WOCBP only)[a]	X		X	
Assess/confirm eligibility	X		X	
Medical history	X			
Demographics	X			
Physical examination[b]	X			
Vital signs	X		X	
12-lead ECG (triplicate)	X			
Subject training on ePRO device (including pain and rescue medication)	X		X	
Hematology and serum chemistry tests	X			
Subject randomization[c]		X		
Surgery[d]				X
Administer study drug (HTX-034 or bupivacaine HCl)				X
PK blood sample			X[e]	
Concomitant medications[f]	◄	- - - -	- - - -	- - - - ►
Adverse events[g]	◄	- - - -	- - - -	- - - - ►

Abbreviations: ECG, electrocardiogram; ePRO, electronic patient-reported outcome; ICF, informed consent form; PK, pharmacokinetic; WOCBP, women of childbearing potential.

[a] The urine drug screen and urine pregnancy test should be performed first. Results should be confirmed negative prior to performing any additional assessments and prior to initiation of surgery. Subjects with a positive drug screen who are taking an allowed, prescribed medication that is known to result in a positive drug test may be eligible for participation in the study. Subjects who fail the drug test may also be rescreened at the discretion of the Investigator.

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

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

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

[e] A presurgery blood sample will be collected for bupivacaine, aprepitant, and meloxicam PK analysis.

[f] Record all medications taken from the time the subject signs the ICF.

[g] Record all adverse events from the time the subject signs the ICF.

Schedule of Events for Phase 1b (7-Day Inpatient Period)

		7-Day Inpatient Period																	Outpatient[a]				Site Visit	Out patient[a]	Site Visits		
	Day	D1								D2		D3		D4	D4	D5	D6	D7	D8	D8	D9	D10	D11	D15	D22	D29	D43	ET[b]
	Time	30 min	60 min	90 min	2h	4h	8h	12h	18h	24h	36h	48h	60h	72h	8PM	8AM + 8PM	8AM + 8PM	8AM + 8PM	168 h	8PM								
Assessments	Window	±5 m	±5 m	±10 m	±15 m	±15 m	±30 m	±30 m	±30 m	±1h	±2h	±2h	±2h	±2h	±4h	±4h	±4h	±4h	±4h	±4h				±1d		±4d	±7d	
Pain intensity assessment (NRS-R)[c]			X[d]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X								X[f]
Pain intensity assessment (NRS-A)[c]			X[d]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X								X[f]
Record all rescue medication[g]	←	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	→				
PGA of pain control									X		X		X															
OBAS									X		X		X															
OR-SDS questionnaire									X		X		X															
Vital signs[h, i]	X	X	X	X	X		X	X	X	X	X	X	X						X									X[f]
12-lead ECG (triplicate)[h, i]									X		X		X						X									X[f]
Hematology and serum chemistry[h]													X						X				X		X			X[j]
PK blood sample	See table of PK blood sample collection for timepoints																											
Physical examination																									X			X[j]
Wound healing assessment (Southampton)																			X				X		X	X	X	
LAST questionnaire[i]	X	X			X		X		X		X		X															
MPADSS assessment[k]				X	X	X	X																					
Discharge subject																			X									
Record if opioid prescription at discharge																			X									
Record if opioid prescription after discharge[l]																				←	-	-	-	→				
Serum drug test for opioids																								X				

Bone healing assessment (X-ray)[m]																										X	X	X[n]
Concomitant medications[o]	←	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X
Adverse events[p]	←	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X

Abbreviations: D or d, day; ECG, electrocardiogram; eCRF, electronic Case Report Form; ePRO, electronic patient-reported outcome; ET, Early Termination; ICF, informed consent form; h, hour(s); IV, intravenous; LAST, local anesthetic systemic toxicity; m or min, minutes; MPADSS, Modified Postanaesthetic Discharge Scoring System; NRS-A, numeric rating scale of pain intensity with activity; NRS-R, numeric rating scale of pain intensity at rest; OBAS, overall benefit of analgesia score; OR-SDS, Opioid-Related Symptom Distress Scale; PGA, Patient Global Assessment; PK, pharmacokinetic; PO, oral.

Notes: The start of study drug administration will be considered as Time 0 for all safety, PK, and efficacy assessments. For assessments at timepoints when the subject is asleep, an attempt should be made to wake the subject. If there is no response, the assessments at these timepoints may be recorded as "Not Done." Assessments that can be done without waking the subject (eg, blood collection for PK) should be completed. When PK and pain intensity assessments coincide, the pain intensity assessments should be conducted before the blood draw. See Section 6 for more information on study assessments and procedures. See Section 7 for guidance on completing procedures and assessments, including the order of assessments scheduled at the same timepoint.

[a] A healthcare professional will visit the subject once a day on Days 9, 10, 11, and 22 to take blood samples for PK analysis. See table of PK blood sample collection for timepoints.

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

[c] Subjects will record their postoperative pain scores in an ePRO device. NRS-R should be completed prior to the NRS-A. For NRS-R assessment, subjects should be seated/recumbent with the surgically attended leg elevated or lying supine. Measurements should be obtained after the subject is in the resting position for at least 5 minutes. For NRS-A assessments, subjects should be seated with the plantar surface of the ball of the surgically attended foot touching the floor (no weight bearing).

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

[e] Subjects will record their pain scores at rest and then with activity at 8 AM ±4 hours.

[f] Only if subject withdraws prior to the Day 8 Visit.

[g] PO oxycodone and acetaminophen postoperative rescue medication will be recorded in an ePRO device through the Day 15 Visit. Postoperative morphine IV rescue medication will be recorded on an eCRF through 72 hours. Morphine is not permitted after 72 hours.

[h] If abnormal laboratory tests, vital signs, or ECG assessments are considered clinically significant, they should be reported as an adverse event and the result(s) of the abnormal assessment must be recorded on an eCRF (scheduled or unscheduled assessment eCRF, as applicable).

[i] If signs and symptoms potentially attributable to LAST are observed at a timepoint when vital signs, 12-lead ECG, and PK blood sample collection are not scheduled, unscheduled vital sign measurements, 12-lead ECG, and blood sample collection for PK must be performed.

[j] Only if subject withdraws before Day 29 Visit.

[k] This study instrument assesses a subject's potential readiness to be discharged and should be repeated at all scheduled timepoints. It is not meant to be used to decide whether or not to discharge a subject from the study.

[l] Sites will record if any subjects are provided an opioid prescription after discharge through the Day 15 Visit and information about the prescription.

[m] An X-ray finding of delayed healing must be followed with a repeat X-ray every 2 to 4 weeks until resolution (ie, signs of normal healing are evident).

[n] Only if the subject withdraws from the study after the Day 29 Visit but before the Day 43 Visit.

[o] Record all medications taken from the time the subject signs the ICF through the Day 43 Visit on the eCRF, except for PO oxycodone and acetaminophen rescue medication through the Day 15 Visit, which will be recorded in an ePRO device.

[p] Record all adverse events from the time the subject signs the ICF through the Day 43 Visit.

Schedule of Events for Phase 2 (3-Day Inpatient Period)

		3-Day Inpatient Period													Outpatient				Site Visits				
	Day	D1								D2		D3		D4	D4	D5	D6	D7	D8	D15	D29	D43	ET[a]
	Time	30 min	60 min	90 min	2h	4h	8h	12h	18h	24h	36h	48h	60h	72h	8PM	8AM + 8PM	8AM + 8PM	8AM + 8PM					
Assessments	Window	±5 min	±5 min	±10 min	±15 min	±15 min	±30 min	±30 min	±30 min	±1h	±2h	±2h	±2h	±2h	±4h	±4h	±4h	±4h	±1d	±1d	±4d	±7d	
Pain intensity assessment (NRS-R)[b]			X[c]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[d]				X[e]
Pain intensity assessment (NRS-A)[b]			X[c]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[d]				X[e]
Record all rescue medication[f]	◄	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	►		
PGA of pain control										X		X		X						►			
OBAS										X		X		X									
OR-SDS questionnaire										X		X		X									
Vital signs[g, h]	X	X	X	X	X	X		X	X	X	X	X	X	X					X				X[e]
12-lead ECG (triplicate)[g, h]										X		X		X					X				X[e]
Hematology and serum chemistry[g]														X					X	X	X		X[i]
PK blood sample	See table of PK blood sample collection for timepoints																						
Physical examination																					X		X[i]
Wound healing assessment (Southampton)																			X	X	X	X	X
Wound healing assessment (questionnaire)																			X	X	X	X	X
LAST questionnaire[h]	X	X			X		X		X		X		X										
MPADSS assessment[j]				X	X	X	X																
Discharge subject														X									
Record if opioid prescription at discharge														X									
Record if opioid prescription after discharge[k]															◄	-	-	-	-	►			
Serum drug test for opioids																			X	X			
Bone healing assessment (X-ray)[l]																					X	X	X[m]
Concomitant medications[n]	◄	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	►	X
Adverse events[o]	◄	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	►	X

Abbreviations: D or d, day; ECG, electrocardiogram; eCRF, electronic Case Report Form; ePRO, electronic patient-reported outcome; ET, Early Termination; ICF, informed consent form; IV, intravenous; h, hour(s); LAST, local anesthetic systemic toxicity; MPADSS, Modified Postanaesthetic Discharge Scoring System; NRS-A, numeric rating scale of pain intensity with activity; NRS-R, numeric rating scale of pain intensity at rest; OBAS, overall benefit of analgesia score; OR-SDS, Opioid-Related Symptom Distress Scale; PGA, Patient Global Assessment; PK, pharmacokinetic; PO, oral.

Notes: The start of study drug administration will be considered as Time 0 for all safety, PK, and efficacy assessments. For assessments at timepoints when the subject is asleep, an attempt should be made to wake the subject. If there is no response, the assessments at these timepoints may be recorded as "Not Done." Assessments that can be done without waking the subject (eg, blood collection for PK) should be completed. When PK and pain intensity assessments coincide, the pain intensity assessments should be conducted before the blood draw. See Section 6 for more information on study assessments and procedures. See Section 7 for guidance on completing procedures and assessments, including the order of assessments scheduled at the same timepoint.

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

[b] Subjects will record their postoperative pain scores in an ePRO device. NRS-R should be completed prior to the NRS-A. For NRS-R assessments, subjects should be seated/recumbent with the surgically attended leg elevated or lying supine. Measurements should be obtained after the subject is in the resting position for at least 5 minutes. For NRS-A assessments, subjects should be seated with the plantar surface of the ball of the surgically attended foot touching the floor (no weight bearing).

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

[d] Subjects will record their pain scores at rest and then with activity at 8 AM and 8 PM ±4 hours.

[e] Only if subject withdraws prior to the Day 8 Visit.

[f] PO oxycodone and acetaminophen postoperative rescue medication will be recorded in an ePRO device through the Day 15 Visit. Postoperative morphine IV rescue medication will be recorded on an eCRF through 72 hours. Morphine is not permitted after 72 hours.

[g] If abnormal laboratory tests, vital signs, or ECG assessments are considered clinically significant, they should be reported as an adverse event and the result(s) of the abnormal assessment must be recorded on an eCRF (scheduled or unscheduled assessment eCRF, as applicable).

[h] If signs and symptoms potentially attributable to LAST are observed at a timepoint when vital signs, 12-lead ECG, and PK blood sample collection are not scheduled, unscheduled vital sign measurements, 12-lead ECG, and blood sample collection for PK must be performed.

[i] Only if subject withdraws before Day 29 Visit.

[j] This study instrument assesses a subject's potential readiness to be discharged and should be repeated at all scheduled timepoints. It is not meant to be used to decide whether or not to discharge a subject from the study.

[k] Sites will record if any subjects are provided an opioid prescription after discharge through the Day 15 Visit and information about the prescription.

[l] An X-ray finding of delayed healing must be followed with a repeat X-ray every 2 to 4 weeks until resolution (ie, signs of normal healing are evident).

[m] Only if the subject withdraws from the study after the Day 29 Visit but before the Day 43 Visit.

[n] Record all medications taken from the time the subject signs the ICF through the Day 43 Visit on the eCRF, except for PO oxycodone and acetaminophen rescue medication through the Day 15 Visit, which will be recorded in an ePRO device.

[o] Record all adverse events from the time the subject signs the ICF through the Day 43 Visit.

PK Blood Sample Collection for Phase 1b and Phase 2

	Day	Inpatient (Phase 1b and Phase 2)												Inpatient/Site Visit				Home Visits			Site Visit	Home Visit	Site Visits		
		D1							D2		D3		D4	D5	D6	D7	D8	D9	D10	D11	D15	D22	D29	D43	ET
	Time	60 min	90 min	2h	4h	8h	12h	18h	24h	36h	48h	60h	72h	96h	120h	144h	168h								
	Window	±5 m	±10 m	±15 m	±15 m	±30 m	±30 m	±30 m	±1h	±2h	±2h	±2h	±2h	±4h	±4h	±4h	±4h				±1d		±4d	±7d	
PK blood sample collection: Phase 1b		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[a]	X[a]	X[a]	X	X[a]			X[b]
PK blood sample collection: Phase 2		X	X	X	X	X	X	X	X	X	X	X	X				X[c]				X		X		X[d]

Abbreviations: D or d, day; ET, Early Termination; h, hour(s); m or min, minutes; LAST, local anesthetic systemic toxicity; PK, pharmacokinetic.

Note: If signs and symptoms potentially attributable to LAST are observed at a timepoint when PK blood sample collection is not scheduled, unscheduled blood sample collection for PK must be performed.

[a] A healthcare professional will visit the subject once a day on Days 9, 10, 11, and 22 to take blood samples for PK analysis.

[b] Only if subject withdraws prior to the Day 22 Visit.

[c] The visit window for the Day 8 site visit for Phase 2 is ±1 day.

[d] Only if subject withdraws prior to Day 29.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AUC	Area under the curve
AUC_{0-72}	Area under the curve of the numeric rating scale of pain intensity scores through 72 hours
AUC_{last}	Area under the plasma concentration-time curve from Time 0 to the time of the last quantitative plasma concentration
BMI	Body mass index
CFR	Code of Federal Regulations
CINV	Chemotherapy-induced nausea and vomiting
C_{max}	Maximum concentration
CV	Cardiovascular
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ePRO	Electronic patient-reported outcome
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IRC	Interim Review Committee
IV	Intravenous(ly)
LAST	Local anesthetic systemic toxicity
LOCF	Last observation carried forward
MME	Morphine milligram equivalents
MPADSS	Modified Postanaesthetic Discharge Scoring System
NK_1	Neurokinin-1
NRS	Numeric rating scale of pain intensity
NRS-A	NRS score with activity

Abbreviation	Definition
NRS-R	NRS score at rest
NSAID	Nonsteroidal anti-inflammatory drug
OBAS	Overall benefit of analgesia score
ORAE	Opioid-related adverse event
OR-SDS	Opioid-Related Symptom Distress Scale
PACU	Postanesthesia care unit
PGA	Patient Global Assessment
PK	Pharmacokinetic(s)
PO	By mouth, orally
SAE	Serious adverse event
SJS	Stevens-Johnson Syndrome
TEAE	Treatment-emergent adverse event
T_{max}	Time of occurrence maximum concentration
ULN	Upper limit of normal
US	United States
WOCF	Worst observation carried forward
wWOCF	Windowed worst observation carried forward

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

1. INTRODUCTION

1.1. Background Information and Study Rationale

Up to 70% of patients have moderate to severe pain after surgery, and the most severe pain occurs within the first 72 hours (Apfelbaum 2003; Gan 2014; Lynch 1997; Meissner 2015; Misiolek 2014; Singla 2014; Svensson 2000). Administering a local anesthetic (eg, bupivacaine, ropivacaine, or levobupivacaine) perioperatively is a relatively simple and safe means of providing postoperative pain relief. A major limitation of most currently available local anesthetics is that their duration of effect is only 6 to 12 hours (Kehlet 2011). Consequently, many patients are given opioids to manage pain. The requirement for opioids postoperatively is a serious manifestation of ineffective pain control. Exposure to opioids can lead to opioid-related adverse reactions resulting in worse patient outcomes and increased hospital costs (Cashman 2004; Chan 2013; Coley 2002; Jarzyna 2011; Kessler 2013; Lee 2015; Lee 2016; Oderda 2013; Ramachandran 2011; Shirakami 2005; Stephens 2003; Wheeler 2002). Patients can quickly transition from acute opioid use to chronic use (Shah 2017). Reduced exposure to opioids and better pain management is associated with improved patient outcomes as well as reduced risk for the development of persistent pain and chronic opioid use and abuse (Barnett 2017). Therefore, there is a significant unmet need for a more effective non-opioid analgesic that provides sustained pain relief and reduces or eliminates the need for opioids, especially in the first 72 hours following surgery.

HTX-034 is a novel, non-opioid, fixed-dose combination, extended-release solution of bupivacaine, aprepitant, and low-dose meloxicam. HTX-034 is formulated in a proprietary polymer referred to as tri(ethylene glycol) poly(orthoester) (TEG-POE), termed Biochronomer®. HTX-034 is applied into the surgical site without a needle to coat the pain-generating tissues. After administration, the polymer enables extended release of the 3 active ingredients.

All active ingredients in HTX-034 have been approved by the United States (US) Food and Drug Administration (FDA). Bupivacaine, an amide-type local anesthetic, is available as a solution for injection and is approved for surgical anesthesia and for management of acute pain in adults and children (MARCAINE™, SENSORCAINE®).

Meloxicam, a nonsteroidal anti-inflammatory drug (NSAID), is available in tablets and capsules for oral (PO) use. The indications include relief of the signs and symptoms of osteoarthritis, rheumatoid arthritis, and pauciarticular or polyarticular course juvenile rheumatoid arthritis in patients who weigh ≥60 kg (MOBIC®); and management of osteoarthritis pain (VIVLODEX®).

Aprepitant exerts its effects by blocking activity of substance P on the neurokinin-1 (NK_1) receptor. Aprepitant is approved for the prevention of chemotherapy-induced nausea and vomiting (CINV). In the US, it is available as PO capsules and oral suspension (EMEND®) and an intravenous (IV) emulsion (CINVANTI® (aprepitant) injectable emulsion, for intravenous use).

A product related to HTX-034, HTX-011, contains the same fixed doses of bupivacaine and meloxicam in the proprietary polymer, but without aprepitant. In HTX-011, bupivacaine is the disease-active ingredient and meloxicam enhances the effectiveness of bupivacaine by reducing local inflammation caused by surgery and normalizing the local pH enhancing penetration of bupivacaine into the nerves, thereby potentiating bupivacaine's analgesic effect (Dasta 2018). In

Phase 3 studies in bunionectomy and herniorrhaphy, a single dose of HTX-011 (60 mg/1.8 mg and 300 mg/9 mg, respectively) significantly reduced pain and opioid consumption through 72 hours compared with both bupivacaine HCl and saline placebo, and was well tolerated. A follow-on study evaluated single individualized doses of HTX-011 up to 60 mg/1.8 mg (mean dose of 46.25 mg/1.39 mg) in bunionectomy and demonstrated similar efficacy. The safety and efficacy of HTX-011 have also been demonstrated in a Phase 3 study in herniorrhaphy and in Phase 2 studies in subjects undergoing total knee arthroplasty, augmentation mammoplasty, and abdominoplasty at HTX-011 doses up to 400 mg/12 mg.

The inclusion of aprepitant in HTX-034 is based on its ability to inhibit substance P. The nociceptive system uses several transmitter substances in parallel, including substance P (Patel 2003). Substance P mediates its effects through binding to the NK_1 receptor. Thus, the use of an NK_1 receptor antagonist as an adjuvant to existing analgesics could provide additional analgesic effect (Hill 2000). The initial clinical studies investigating NK_1 receptor antagonists for management of pain in subjects undergoing molar extraction were encouraging, but subsequent studies in peripheral neuropathy, osteoarthritis, and migraine were less promising (Rupniak 1999). It is anticipated that local administration of aprepitant in HTX-034 at the surgical site will be more effective compared with systemic administration. This is based on nonclinical studies with HTX-011 demonstrating that the synergistic analgesic effect of meloxicam with bupivacaine was only observed when meloxicam was administered locally at the site, not when administered systemically. Studies of HTX-034 in a nonclinical model of postoperative pain have demonstrated that administration of HTX-034 produced prolonged analgesia.

This study is designed to evaluate the safety, pharmacokinetics (PK), and analgesic efficacy of escalating doses of HTX-034 administered as a single dose into the surgical site compared with bupivacaine HCl (standard of care) in subjects undergoing bunionectomy.

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

Bunionectomy is an accepted model of postoperative pain. Bunionectomy produces generally reliable and persistent pain symptoms for a period typically lasting over 72 hours from the surgery, which allows for analysis of acute analgesia over an extended period of time.

Phase 1b of the study will evaluate escalating doses of HTX-034 compared with an active comparator, bupivacaine HCl without epinephrine. One dose level of HTX-034 will be evaluated in Cohort 1. Individualized dosing in Cohort 2 is based on prior experience with HTX-011 in bunionectomy, which demonstrated that analgesic efficacy was maintained with a decrease in local inflammatory adverse events (AEs) compared with a precedent Phase 3 study with a fixed dose of HTX-011. The Phase 2 will be a dose-expansion phase to evaluate additional subjects at HTX-034 doses selected based on Phase 1b and will be compared with bupivacaine HCl. Both phases will be randomized. To minimize potential bias, subjects and all site staff involved in safety and efficacy assessments will be blinded. Sponsor staff directly interacting with blinded site personnel will maintain the blind. The data for Cohorts 1 and 2 may be unblinded after Phase 1b is complete.

The dose of HTX-034 that subjects will be assigned to receive will range from 21.7 mg/4.3 mg/0.6 mg (bupivacaine/aprepitant/meloxicam doses) to 51.5 mg/10.3 mg/1.5 mg. HTX-034 is expected to be well tolerated at this range of doses based on prior clinical experience with HTX-011 and aprepitant. HTX-011 contains bupivacaine and meloxicam in the same

fixed-dose ratio formulated with the same polymer as HTX-034 and was well tolerated in Phase 2 and 3 studies at doses up to 400 mg/12 mg (bupivacaine/meloxicam). X-rays confirmed normal bone healing in 2 prior HTX-011 studies in bunionectomy: a Phase 2 dose-ranging study (doses of 30 mg/0.9 mg to 200 mg/6 mg) and a Phase 3 study (60 mg/1.8 mg). Additionally, the dose of aprepitant in HTX-034 that subjects may receive, 4.3 mg to 10.3 mg, is anticipated to be well tolerated given that aprepitant is approved for use as a single dose of 100 mg administered IV followed by 80 mg PO aprepitant given on Days 2 and 3 (CINVANTI USPI Oct 2019). Dose escalation to Cohort 2 will be guided by safety data from Cohort 1. A dose-expansion phase (Phase 2) will be conducted to collect additional data at the doses of HTX-034 selected based on Phase 1b.

The route of administration of HTX-034 in both phases, application into the surgical site with a Luer lock applicator, was selected because it is considered easier than injection and potentially safer, as it eliminates the need for multiple injections and the inherent risk of an inadvertent intravascular injection. Use of an applicator also allows for precise placement of HTX-034 into the surgical site. This route of administration has been extensively tested in the HTX-011 clinical program.

Bupivacaine HCl was selected as the active comparator because it is the widely accepted standard for local analgesia. The dose of bupivacaine solution selected for this study, 50 mg (10 mL of 0.5% solution), is within the range of dosing in bupivacaine labeling (MARCAINE USPI 2018) and is based on feedback from experts on standard doses used in clinical practice. This dose was used in a Phase 3 bunionectomy study where it was demonstrated to be superior to saline placebo through 24 hours, confirming the appropriateness of the dose. The route of administration for bupivacaine HCl, injection into the surgical site, is consistent with the prescribing information and clinical practice.

Subjects will remain in the hospital/research facility for 7 days (Phase 1b) or 3 days (Phase 2) from the start of study drug administration to undergo postoperative safety, PK, and efficacy assessments. The rationale for the 7-day inpatient period is to obtain intensive PK sampling and to record pain scores while subjects are under the supervision of site staff. A 3-day inpatient period for Phase 2 was selected to reduce the burden on subjects and to reflect the likely design of future studies.

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

Serial blood samples for PK analysis will be collected from subjects while inpatient to characterize systemic exposure of bupivacaine, aprepitant, and meloxicam. After discharge, follow-up PK samples will be collected at home visits by a healthcare professional on Days 9, 10, 11, and 22 in Phase 1b or at the study site on Days 8, 15, and 29 in Phase 2 to characterize the PK profile of HTX-034.

Pain intensity will be assessed using the numeric rating scale of pain intensity (NRS), a validated tool for assessing pain (Breivik 2008; Safikhani 2018). Pain will be assessed at rest and with activity. The prescribed activity (sitting with the plantar surface of the ball of the surgically attended foot touching the floor [no weight-bearing]) reflects a simple daily activity for patients. The efficacy endpoints for pain intensity are consistent with recommendations in the FDA Clinical Outcome Assessment Compendium (FDA 2019). Given the concern with postoperative opioid use on patient outcomes as well as the risk of long-term use and abuse, the study also includes endpoints to evaluate opioid use.

1.3. Potential Risks and Benefits

1.3.1. Preliminary Safety and Efficacy With HTX-034

Preliminary results from Part 1b of the study demonstrated that both HTX-034 dose groups were well tolerated. A total of 33 subjects were randomized and dosed: 11 in the HTX-034 low-dose cohort 1, 13 in the HTX-034 high-dose cohort 2, and 9 in the pooled bupivacaine HCl group. The most common treatment-emergent adverse events (TEAEs) in >2 subjects in either HTX-034 dose group included dizziness, headache, nausea, and vomiting. All TEAEs in the HTX-034 dose cohorts were mild or moderate in severity, and no serious adverse events (SAEs) or TEAEs leading to study withdrawal were reported.

HTX-034 reduced pain compared with bupivacaine HCl. The mean area under the curve (AUC) of the numeric rating scale of pain intensity scores with activity (NRS-A) were lower for the HTX-034 low-dose and high-dose cohorts compared with pooled bupivacaine HCl through 72 hours (282 and 271 vs 371, respectively) and through 168 hours (497 and 508 vs 551, respectively). A higher proportion of subjects receiving HTX-034 were opioid-free through Day 15 (45.5% opioid-free for low-dose HTX-034, 46.2% for high-dose HTX-034, and 22.2% for bupivacaine HCl).

1.3.2. Potential Risks Associated With HTX-034

The potential risks of HTX-034 are expected to be a subset of those associated with its active ingredients and are summarized in Section 1.3.2.1 through Section 1.3.2.3. HTX-034 is applied into the surgical site as a single dose. Therefore, it is unclear how applicable the known potential risks for aprepitant or for meloxicam are to HTX-034.

For more information on HTX-034, refer to the HTX-034 Investigator's Brochure (IB). For more information on the active ingredients, bupivacaine, aprepitant, and meloxicam, refer to the US prescribing information (CINVANTI USPI Oct 2019; EMEND USPI Nov 2019; MARCAINE USPI 2018; MOBIC USPI 2018).

1.3.2.1. Potential Risks Associated With Bupivacaine

Potential risks for bupivacaine include dose-related central nervous system and cardiovascular (CV) toxicity including, but not limited to, perioral tingling, metallic taste, visual and auditory disturbances, muscle twitching, seizure, acidosis, shortness of breath, bradycardia, hypotension, hypoxia, and cardiac arrest. Cases of methemoglobinemia have been reported in association with local anesthetic use (MARCAINE USPI 2018). Although all patients receiving a local anesthetic are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency,

congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. Patients with a known history of glucose-6-phosphate dehydrogenase deficiency or with congenital or idiopathic methemoglobinemia are excluded from this study. Close monitoring for symptoms and signs of methemoglobinemia is recommended.

1.3.2.2. Potential Risks Associated With Meloxicam

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

1.3.2.3. Potential Risks Associated With Aprepitant

Aprepitant is approved for the prevention of CINV, administered orally (EMEND USPI Nov 2019) and IV (CINVANTI USPI Oct 2019). Adverse reactions reported in at least 2% of adult healthy volunteers who received a single 130 mg dose of IV aprepitant (CINVANTI) as a 30-minute infusion were headache and fatigue. The most common adverse reactions (≥3%) reported for PO aprepitant in adult patients given a 3-day regimen (125 mg on Day 1 and 80 mg on Days 2 and 3) included fatigue, diarrhea, asthenia, dyspepsia, abdominal pain, hiccups, white blood cell count decreased, dehydration, and alanine aminotransferase (ALT) increased. Hypersensitivity including anaphylactic reactions have been reported with aprepitant. SJS has been reported in a patient receiving the PO aprepitant regimen with cancer chemotherapy. Serious adverse reactions reported in non-CINV studies of aprepitant (EMEND USPI Nov 2019) include single cases of each of the following: angioedema and urticaria, constipation, and subileus.

Aprepitant is a substrate, weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9. As such, potential risks for aprepitant include clinically significant drug interactions, such as an increase in pimozide concentrations, a decrease in International Normalized Ratio (INR) with concomitant warfarin (both excluded per protocol), and risk of reduced efficacy of hormonal contraceptives. The efficacy of hormonal contraceptives may be reduced during administration of and for 28 days following the last dose of aprepitant; therefore, effective alternative or back-up methods of contraception during treatment with aprepitant and for 1 month following the last dose of aprepitant is required. Use

of HTX-034 with strong or moderate CYP3A4 inhibitors is not anticipated to increase the risk of AEs related to aprepitant given the low dose and prolonged release profile of aprepitant in HTX-034. Concomitant use of HTX-034 with strong CYP3A4 inducers is not anticipated to impact the efficacy of aprepitant applied and released locally at the surgical site.

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

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

1.3.3.1. Bupivacaine HCl (Control Product)

The potential risks associated with bupivacaine HCl are addressed in Section 1.3.2.1. In addition, bupivacaine HCl is administered by injection. Cardiac arrest has occurred after convulsions resulting from systemic toxicity, presumably following unintentional intravascular injection, which must be avoided.

1.3.3.2. Other Protocol-Specified Medications

1.3.3.2.1. Opioid Medications

Opioids have the risk of addiction, abuse, and misuse, which can lead to overdose and death (Fentanyl Citrate USPI 2018; Morphine Sulfate Injection USPI 2019; OXAYDO USPI 2018). Taking an opioid with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, respiratory depression (including serious, life-threatening and fatal respiratory depression), coma, and death. Opioids can cause sleep-related breathing disorders including central sleep apnea and sleep-related hypoxemia. Additional possible side effects include nausea, vomiting, tiredness, sleepiness, headache, dizziness, constipation including severe constipation, and abdominal pain. Other risks include skeletal muscle rigidity, skeletal muscle movement, CV depression, CV instability, severe hypotension, and adrenal insufficiency and, in subjects with seizure disorder, an increase in seizure activity. Use of opioids may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Fentanyl citrate injection could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Use of an opioid in a subject already on a CYP3A4 inhibitor or inducer may impact plasma concentrations and opioid adverse reactions. Use is contraindicated in subjects with significant respiratory depression, with acute or severe bronchial asthma, or with known or suspected GI obstruction.

1.3.3.2.2. Acetaminophen

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

1.3.4. Potential Risks Associated With Protocol-Specified Device

The custom Luer lock applicator is an investigational device used for administration of HTX-034 without a needle into the surgical site. Although not observed in clinical studies when administering other drug products, there is a potential risk for the Luer lock applicator to detach from the syringe during HTX-034 application if not properly attached during preparation.

2. STUDY OBJECTIVES

2.1. Primary Objectives

The primary objectives are as follows:

- To evaluate the safety and tolerability of single-dose administration of escalating doses of HTX-034 in subjects undergoing bunionectomy (Phase 1b).
- To evaluate the efficacy of HTX-034 in subjects undergoing bunionectomy (Phase 2).

2.2. Secondary Objectives

The secondary objectives are as follows:

- To evaluate the efficacy of escalating doses of HTX-034 in this study population (Phase 1b).
- To evaluate the safety and tolerability of HTX-034 in this study population (Phase 2).
- To characterize the PK profile of HTX-034 in this study population (Phase 1b and Phase 2).

3. INVESTIGATIONAL PLAN AND ENDPOINTS

3.1. Description of the Study Design

3.1.1. Overall Study Design

This is a Phase 1b/2 study in subjects undergoing bunionectomy. Phase 1b will evaluate escalating doses of HTX-034 compared with bupivacaine HCl (without epinephrine). Phase 2 will be a dose-expansion phase to evaluate additional subjects treated with the HTX-034 doses selected based on Phase 1b compared with bupivacaine HCl (without epinephrine).

All subjects will be screened within 28 days prior to the planned surgery date. Subjects who meet the screening eligibility criteria will be randomized to receive HTX-034 or bupivacaine HCl. Randomization may be done within 1 business day prior to surgery. On the day of surgery (Day 1), subjects who continue to meet the eligibility criteria will undergo a bunionectomy under regional anesthesia with no more than 20 mL of 1% lidocaine without epinephrine administered as a Mayo block. Spinal, epidural, or general anesthesia is not allowed. During surgery, the use of IV fentanyl up to 4 µg/kg will be permitted for intraoperative pain control per site practice.

Near the completion of surgery, a single dose of study drug (HTX-034 or bupivacaine HCl) will be administered into the surgical site, as described in Section 5.5.

Subjects will remain in the hospital/research facility for 7 days (Phase 1b) or 3 days (Phase 2) from the start of study drug administration to undergo postoperative safety, PK, and efficacy assessments. All subjects will perform self-assessments of pain intensity during the inpatient period and will record the use of postoperative rescue medication through the Day 15 Visit. Subjects in the Phase 2 will also perform self-assessments of pain intensity during the outpatient period (Day 4 through Day 8). After discharge, follow-up PK samples will be collected at home visits by a healthcare professional on Days 9, 10, 11, and 22 in Phase 1b or at the study site on Days 8, 15, and 29 in Phase 2 to characterize the PK profile of HTX-034. Subjects will return to the study site on Day 8 (subjects in Phase 2 only) and on Days 15, 29, and 43 (all subjects) for follow-up assessments.

3.1.1.1. Phase 1b (Dose Escalation)

There are 2 planned sequential dose cohorts, as outlined in Table 3. Cohort 1 will evaluate a single dose level of HTX-034. Cohort 2 will evaluate individualized doses of HTX-034; the amount administered will be determined for each subject by the surgeon at the time of surgery and will be based on the volume sufficient to coat the pain-generating tissues, while ensuring there is not an excess that could be expressed from the site during closure.

Table 3: Summary of Dose Cohorts in Phase 1b

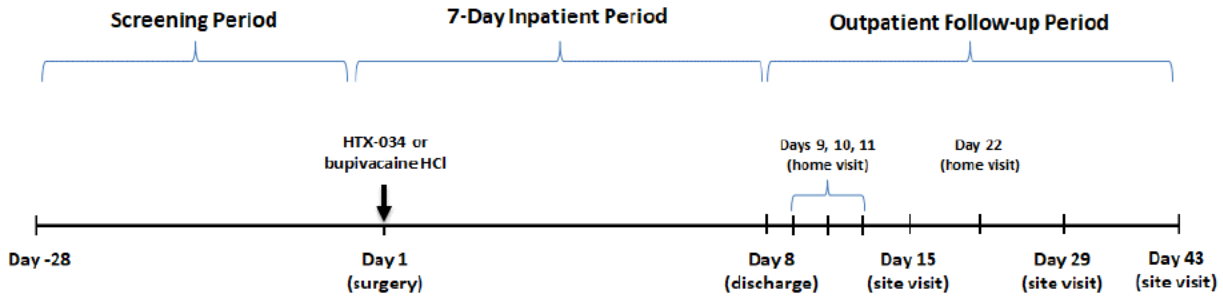
Cohort	HTX-034				Bupivacaine HCl 0.5% Dose (Volume)
	Syringe Volume to Withdraw	Syringe Volume to Expel[a]	Actual Volume Administered[b]	Dose to Administer[c]	
Cohort 1	1 mL	1 mL	0.73 mL	21.7 mg/4.3 mg/0.6 mg	50 mg (10 mL)
Cohort 2	2 mL	1.3 mL to 2 mL	1.03 mL to 1.73 mL	30.6 mg/6.1 mg/0.9 mg to 51.5 mg/10.3 mg/1.5 mg	50 mg (10 mL)

[a] Syringe volume to expel in Cohort 2 will be determined by the Investigator at the time of administration based on the volume sufficient to coat the pain-generating tissues, while ensuring there is not an excess that could be expressed from the site during closure. The volume to expel will range between 1.3 mL and 2 mL.
[b] Actual volume administered takes into account the volume retained in syringe and Luer lock applicator (0.27 mL) after study drug administration.
[c] Dose to administer is based on actual volume administered, which will be determined by weighing syringes before and after study drug administration. HTX-034 doses list the bupivacaine dose first followed by the aprepitant dose and then the meloxicam dose.

Each cohort will include a total of approximately 16 subjects (with a minimum of 10 subjects per cohort evaluable for PK). Within each cohort, subjects will be randomized in a 3:1 ratio to receive either HTX-034 (n=12) or bupivacaine HCl (n=4).

See Figure 1 for a study schematic for Phase 1b.

Figure 1: Study Design Schematic for Phase 1b (7-Day Inpatient Period)



Dose escalation to Cohort 2 will be guided by safety data from Cohort 1. After all subjects in Cohort 1 have completed the Day 29 Visit, an internal Interim Review Committee (IRC) will review the data. If the IRC deems it appropriate, the next dose cohort may begin to enroll.

Dose escalation will not take place if any of the following occur:

- ≥2 subjects in a dose cohort experience a SAE reported by the Investigator and confirmed by Sponsor to be possibly related to HTX-034.
- ≥2 subjects experience a moderate or severe TEAE compatible with LAST reported by the Investigator and confirmed by the Sponsor to be possibly related to HTX-034.
- ≥2 subjects treated with HTX-034 who have a wound healing complication of Grade IV or V using the Southampton Wound Scoring System.

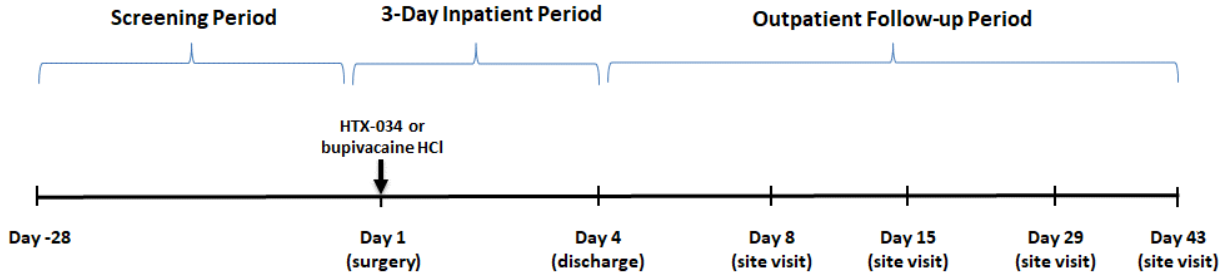
3.1.1.2. Phase 2 (Dose Expansion)

Following a review of the Phase 1b data, up to approximately 40 additional subjects will be randomized to 1 of 2 HTX-034 dose levels or to bupivacaine HCl in a 2:1:1 ratio at the same doses assessed in Phase 1b.

- HTX-034 high dose: 30.6 mg/6.1 mg/0.9 mg to 51.5 mg/10.3 mg/1.5 mg (20 subjects).
- HTX-034 low dose: 21.7 mg/4.3 mg/0.6 mg (10 subjects).
- Bupivacaine HCl 0.5%: 50 mg (10 subjects).

All subjects in Phase 2 will be inpatient for 3 days. See Figure 2 for a study schematic for Phase 2.

Figure 2: Study Design Schematic for Phase 2 (3-Day Inpatient Period)



3.1.2. Postoperative Rescue Medication

Subjects must only receive rescue medication upon request for pain control, as needed. Rescue medication must not be given for pain prophylaxis, but only for treating postoperative pain. Prior to the administration of the first dose of rescue medication, if the subject has not already had at least 1 postoperative pain score assessed, then a numeric rating scale of pain intensity at rest (NRS-R) score followed by NRS-A score must be obtained.

3.1.2.1. After Surgery Through 72 Hours

Postoperative rescue medication through the first 72 hours after surgery will consist of 1 or more of the following 3 medications: PO acetaminophen (1,000 mg no more frequently than every 6 hours as needed), PO immediate-release oxycodone (≤10 mg within a 4-hour period), and/or IV morphine (≤10 mg within a 2-hour period). The choice of rescue medication will be at the site's discretion. For subjects administered acetaminophen, the total combined daily dose must not exceed 4 grams (4,000 mg) as severe liver damage may occur. Combination products containing an opioid and a non-opioid are not allowed. NSAIDs are not permitted; no other analgesic agents are permitted.

3.1.2.2. After 72 Hours Through Day 15 Visit

After 72 hours through the Day 15 Visit, the following medications are recommended to treat pain when necessary in a step-wise fashion:

1. PO acetaminophen as needed (1,000 mg no more frequently than every 6 hours).
2. PO immediate-release oxycodone (≤10 mg within a 4-hour period) only if acetaminophen fails to adequately manage pain.

For subjects administered acetaminophen, the total combined daily dose must not exceed 4 grams (4,000 mg) as severe liver damage may occur.

Note: Morphine is not permitted after 72 hours. NSAIDs are not permitted; no other analgesic agents are permitted.

3.1.2.3. After Day 15 Through End of Study

After the Day 15 Visit through the end of the study, postoperative pain should be managed per institutional standard of care.

Pain medication taken after Day 15 is not considered rescue medication and will be recorded on the concomitant medication electronic case report form (eCRF).

3.1.3. Opioid Prescriptions At and After Discharge

If a subject did not receive any opioids or received <5 IV morphine milligram equivalents (MME) (eg, <10 mg PO oxycodone; see Table 4) within 12 hours prior to discharge, the subject should not receive an opioid prescription at discharge.

If a subject received ≥5 IV MME (eg, ≥10 mg PO oxycodone) in the 12 hours prior to discharge, the subject may be provided at site discretion with a prescription for immediate-release PO oxycodone: no more than ten 5 mg immediate-release oxycodone pills, take 1 to 2 pills every 4 hours as needed. The prescription must indicate that substitutions with any other opioid-containing product are not permitted, including combination opioid/non-opioid products.

Table 4: MME for Permitted Postoperative Opioid Rescue Medications Through 72 Hours

Medication	MME Factor	Sample Calculation
IV Morphine	1.00	5 mg × 1.00 = 5 MME
PO Oxycodone	0.50	5 mg × 0.50 = 2.5 MME

Abbreviations: IV, intravenous; MME, morphine milligram equivalents; PO, oral.

Sites will record if subjects are discharged with an opioid prescription and information about the opioid prescription. All subjects will record if they took any oxycodone and/or acetaminophen from discharge through the Day 15 Visit in an electronic patient-reported outcome (ePRO) device.

From discharge through the Day 15 Visit, if a subject contacts the site about postoperative pain related to the surgery, a prescription for PO immediate-release oxycodone (ten 5 mg pills; do not substitute) may be provided at the Investigator's discretion. Sites will record if any subjects are

provided an opioid prescription after discharge through the Day 15 Visit and information about the prescription.

After the Day 15 Visit, postoperative pain should be managed per institutional standard of care.

3.1.4. Postoperative Assessments

Safety assessments will include AE recording, physical examinations, vital signs, 12-lead ECGs, clinical safety laboratory tests (hematology and serum chemistry), LAST questionnaire, wound healing assessments, and bone healing assessments.

Blood samples will be for bupivacaine, aprepitant, and meloxicam PK analysis.

Efficacy assessments will include pain intensity assessments (using the NRS); the use of rescue medication; opioid prescriptions at and after discharge; subjects' assessment of pain (using Patient Global Assessment [PGA] of pain control), overall benefit of analgesia (using overall benefit of analgesia score [OBAS]), and opioid-related symptom distress (using the Opioid-Related Symptom Distress Scale [OR-SDS]); and Modified Postanaesthetic Discharge Scoring System (MPADSS) assessments.

More information on study procedures and assessments is provided in Section 6. The timing of procedures and assessments is provided in the SCHEDULE OF EVENTS section.

3.2. Study Endpoints

3.2.1. Primary Endpoint

- Incidence of TEAEs (Phase 1b).
- Mean AUC of the NRS scores through 72 hours (AUC_{0-72}) for the pooled Phase 1b and Phase 2.

3.2.2. Secondary Endpoints

Safety

- Incidence of SAEs.
- Change from baseline in clinical laboratory results.
- Change from baseline in vital signs.
- Change from baseline in ECGs.
- Incidence of TEAEs (Phase 2).

Pharmacokinetics

PK parameters will be determined for HTX-034 as follows:

Phase 1b

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

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

Phase 2

- C_{max}.
- T_{max}.
- AUC_{last}.

Efficacy

- Mean AUC of NRS scores through the Day 8 Visit.
- Total postoperative opioid consumption (in IV MME) through the Day 8 Visit.
- Proportion of subjects who are opioid-free through the Day 15 Visit.

3.2.3. Other Endpoints

- Incidence of potential opioid-related adverse events (ORAEs) and potential LAST-related TEAEs.
- Wound healing assessment results at each assessed timepoint.
- Bone healing X-ray results at each assessed timepoint.
- Proportion of subjects with an NRS score ≥7 at each timepoint and through the Day 8 Visit.
- Proportion of subjects who do not receive an opioid prescription through the Day 15 Visit.
- Proportion of subjects achieving a score of "good" or better (>1) pain control based on PGA at each timepoint.
- Mean OBAS at each timepoint.
- OR-SDS scores by symptom dimension.
- Proportion of subjects who first achieve an MPADSS score ≥9 at each timepoint.

3.3. Study Duration

The overall duration of the study is anticipated to be approximately 18 months. The total duration of study participation for each subject (from Screening through the Day 43 Visit) will be up to 75 days.

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

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1. Study Population

Up to approximately 72 subjects will be dosed at up to 6 study sites in the US.

4.1.1. Inclusion Criteria

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

1. Is able to provide written informed consent.
2. Is able to adhere to the study visit schedule and complete all study assessments.
3. Is male or female and ≥18 years of age at the time of the Screening Visit.
4. Is medically fit to undergo an elective unilateral, first metatarsal bunionectomy with osteotomy and internal fixation under regional anesthesia; no neuraxial technique (eg, no spinal, epidural, or general anesthesia).
5. Has an American Society of Anesthesiologists Physical Status of I, II, or III.
6. Female subjects are eligible only if all of the following apply:
    a. Not pregnant (female subjects of child-bearing potential must have a negative urine pregnancy test at Screening and on Day 1 before surgery).
    b. Not lactating.
    c. Not planning to become pregnant during the study.
    d. Is surgically sterile; or is at least 2 years post-menopausal; or is practicing abstinence; or is in a monogamous relationship with a male partner who is surgically sterile; or agrees to use double-barrier contraception or an intra-uterine device (eg, copper) in the event of sexual activity from the Screening Visit through 30 days after study drug administration. Hormonal contraceptives are not an acceptable form of birth control because the efficacy of hormonal contraceptives may be reduced with aprepitant. The contraception requirement does not apply to women in only a same-sex relationship.

4.1.2. Exclusion Criteria

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

1. Had contralateral foot bunionectomy in the past 3 months.
2. Has a planned concurrent surgical procedure (eg, bilateral bunionectomy or collateral procedures on the surgical foot) during the study.
3. Has a contraindication or a known or suspected history of hypersensitivity or clinically significant idiosyncratic reaction (including methemoglobinemia) to bupivacaine (or other local anesthetics), meloxicam, aprepitant, oxycodone, morphine, acetaminophen/paracetamol, or fentanyl.
4. Has a pre-existing concurrent acute or chronic painful physical/restrictive condition expected to require analgesic treatment in the postoperative period for pain that is not strictly related to the bunionectomy and which may confound the postoperative assessments.

5. Has received or is taking any of the following medications:
    a. Long-acting opioids within 3 days prior to the scheduled surgery.
    b. Any opioids within 48 hours prior to the scheduled surgery.
    c. Daily use (known or suspected) of opioids for 7 or more consecutive days within the previous 6 months.
    d. Bupivacaine within 5 days prior to the scheduled surgery.
    e. Any local anesthetic within 72 hours prior to the scheduled surgery, other than for pretreatment prior to a needle placement, to treat an AE that occurs after signing the informed consent form (ICF), or to decrease venous irritation (eg, caused by propofol, in which case a single administration of lidocaine 1% up to 20 mg IV may be administered).
    f. Meloxicam or any other NSAID within 10 days prior to the scheduled surgery with the exception of subjects on low-dose (≤100 mg) daily acetylsalicylic acid for cardioprotection.
    g. Aprepitant or other NK_1 receptor antagonists such as fosaprepitant or netupitant within 28 days or rolapitant within 6 weeks prior to the scheduled surgery.
    h. Selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), gabapentin, or pregabalin to control pain within 1 month prior to the scheduled surgery. (Note: If a subject is taking one of these medications for a reason other than pain control, the subject must be on a stable scheduled dose [ie, not "as needed"] for at least 1 month prior to study drug administration.) Anxiolytics prior to surgery are permitted, if necessary.
    i. Systemic steroids within 5 half-lives or 10 days prior to the scheduled surgery (whichever is longer). Note that for purposes of this exclusion criterion, inhaled, ophthalmic, and topical steroids are not considered systemic.
    j. Pimozide, a strong or moderate CYP3A4 inhibitor (eg, diltiazem, ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir), or a strong CYP3A4 inducer (eg, rifampin, carbamazepine, phenytoin) within 28 days prior to the scheduled surgery.
    k. Warfarin or another anticoagulant, other than low-dose acetylsalicylic acid, within 7 days prior to the scheduled surgery.
    l. An investigational product or device in a clinical trial within 30 days or within 5 elimination half-lives (whichever is longer) prior to the scheduled surgery, or is planning to take part in another clinical trial while participating in this study.
6. Has a known or suspected history of drug abuse or alcohol abuse (within 10 years) or a positive drug screen on the day of surgery. Note: Subjects with a positive drug screen who are taking an allowed, prescribed medication that is known to result in a positive drug test (eg, amphetamine and dextroamphetamine for attention-deficit/hyperactivity disorder, benzodiazepine for anxiety disorder) may be eligible for participation in the study. Subjects with a positive drug screen for cannabinoids on the day of surgery will not be allowed to participate in the study.

7. Has a history of clinically significant cardiac abnormality such as myocardial infarction within 6 months prior to signing the ICF, New York Heart Association class III or IV, or clinically significant abnormalities of ECG or cardiac function.
8. Has a history of coronary artery bypass graft surgery within 12 months prior to signing the ICF.
9. Has a history of known or suspected coagulopathy.
10. As per subject history and/or medical records, has active infection with or is currently undergoing treatment for hepatitis B, hepatitis C, or HIV.
11. Has uncontrolled anxiety, psychiatric, or neurological disorder that, in the opinion of the Investigator, might interfere with study assessments.
12. Had a malignancy in the last year, with the exception of nonmetastatic basal cell or squamous cell carcinoma of the skin or localized carcinoma in situ of the cervix.
13. Has undergone 3 or more surgeries within 12 months prior to signing the ICF.
14. Has a known history of glucose-6-phosphate dehydrogenase deficiency.
15. Has any of the following laboratory abnormalities during Screening (1 retest permitted):
    a. Severe liver function impairment as defined by Child-Pugh Class C, having an aspartate aminotransferase (AST) >3 × the upper limit of normal (ULN), or having an ALT >3 × ULN.
    b. Severe kidney function impairment as defined by calculated creatinine clearance (Cockcroft-Gault) <30 mL/min or on dialysis.
    c. Platelet count <100,000/µL, hemoglobin <12 g/dL, or hematocrit <35%.
16. Has a body mass index (BMI) >39 kg/m^2.
17. Has a medical condition such that, in the opinion of the Investigator, participating in the study would pose a health risk to the subject or confound the postoperative assessments.

4.2. Method of Assigning Subjects to Treatment Groups

The Investigator must evaluate the subject's medical history and the results of all Screening assessments to determine study eligibility. Subjects who meet the Screening eligibility criteria (Section 4.1) will be randomized to either HTX-034 or bupivacaine HCl within 1 business day prior to surgery, using a computer-generated randomization scheme. Subjects do not need to be present for randomization to occur. No subject may receive study drug prior to randomization.

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

Subjects who fail to meet the eligibility criteria should not, under any circumstances, receive study drug. In the event a subject does not meet the eligibility criteria, but receives study drug, the Investigator should inform the Sponsor immediately. The Sponsor's Medical Monitor and the Investigator will discuss whether to allow the subject to continue on study.

4.3. Blinding

The site's pharmacy and surgical staff will not be blinded to the treatment assignments because HTX-034 is a colored, viscous solution whereas bupivacaine HCl is a clear aqueous solution, and the volume and method of study drug administration are different between treatment groups. However, subjects will not be aware of the study drug they receive, and, once surgery is completed and the subject is transferred to the postanesthesia care unit (PACU), Investigators and all site staff involved in safety, efficacy, and PK assessments will be blinded to the treatment assignment. Sponsor staff directly interacting with blinded site personnel will maintain the blind. The data for Cohorts 1 and 2 may be unblinded after Phase 1b is complete.

4.3.1. Breaking the Blind

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

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

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

4.4. Subject Withdrawal and Replacement

4.4.1. Subject Withdrawal

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

Possible reasons for early withdrawal include the following:

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

The date and the primary reason for early withdrawal will be recorded on the eCRF. At the time of withdrawal from the study, every attempt should be made to complete the Early Termination Visit assessments.

4.4.2. Subject Replacement

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

5. STUDY TREATMENT AND PROTOCOL-SPECIFIED DEVICE

All subjects will receive a single dose of study drug intraoperatively while undergoing bunionectomy. Study drug is defined as HTX-034 (test product) and bupivacaine HCl (control product). HTX-034 and bupivacaine HCl will be supplied by the Sponsor.

HTX-034 will be administered using a custom Luer lock applicator, which will also be supplied by the Sponsor.

5.1. Description of Study Drug

5.1.1. Test Product

HTX-034 is a sterile, clear, yellow, homogenous solution containing 29.75 mg/mL bupivacaine, 5.95 mg/mL aprepitant, and 0.89 mg/mL meloxicam. HTX-034 is supplied in single-dose, 10 mL glass vials. The vials serve only as a closed container for the drug product. For administration of study drug, the formulation in the vials will be aseptically transferred to sterile syringes as described in the Pharmacy Manual.

5.1.2. Control Product

In Phase 1b, bupivacaine HCl 0.5% (without epinephrine) will be supplied in individually labeled cartons. Each carton contains one 10 mL single-dose vial.

In Phase 2, bupivacaine HCl will be supplied by study sites.

5.2. Packaging and Labeling

HTX-034 for Phase 1b and Phase 2, and bupivacaine HCl for Phase 1b, will be packaged and labeled by the Sponsor or designee and will be packed and dispatched to comply with shipping and storage conditions. Study drug labeling will comply with all applicable national and local laws and regulations.

In Phase 2, bupivacaine HCl will be supplied by study sites.

5.3. Storage

At the study site, HTX-034 should be stored at a refrigerated temperature of 2°C to 8°C. To protect from light, HTX-034 should be stored in the original packaging until time of use. The study drug storage area should be locked with restricted access. A temperature log must be maintained to monitor the storage area temperature.

Bupivacaine HCl will be stored as per the prescribing information.

5.4. Preparation

Study drug will be prepared at the study site. HTX-034 will be prepared in syringes without a needle. Bupivacaine HCl will be prepared in syringes with a needle. Refer to the Pharmacy Manual for details on study drug preparation.

5.5. Study Drug Administration

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

Study drug will be applied into the surgical site prior to wound closure. The start and stop times of study drug dosing will be recorded on the eCRF. Details of administration will be recorded on a worksheet, which will be used in the dictation of the surgical notes and will become part of the source document.

5.5.1. HTX-034 Administration

HTX-034 will be applied using a Luer lock applicator supplied by the Sponsor. Cohort 1 will evaluate a single dose level of HTX-034. Cohort 2 will evaluate individualized doses of HTX-034; the amount administered will be determined for each subject by the surgeon at the time of surgery and will be based on the volume sufficient to coat the pain-generating tissues, ensuring there is not an excess that could be expressed from the site during closure. Syringes will be weighed before and after HTX-034 administration to determine the actual dose of HTX-034 administered.

Following irrigation and suction of each fascial layer, HTX-034 will be applied evenly so that the pain-generating tissues receive adequate coverage. Care should be taken to ensure adequate exposure of the proximal and distal ends (ie, beyond the bony incision) of the wound to study drug. Study drug should form rings of anesthetic around both the proximal and distal aspects of the metatarsal. An appropriate way of doing this is as follows:

- If using a medial incision, it is helpful to have the medial aspect of the foot face the surgeon; if using a dorsal incision, keep the foot and leg in a supine position.
- It is suggested to apply study drug initially plantar lateral to the metatarsal head, then plantar central in relation to 1st metatarsal and finally medially and dorsally along the 1st metatarsal head.
- 2/3 of study drug should be placed around the osteotomy and underneath the capsule. The remaining HTX-034 may be placed circumferentially around the capsule.
- The superficial fascia may now be closed. Note that study drug should not be placed in the shallow subdermal layer. Thereafter, skin closure will commence to complete the surgical procedure.
- There should be no betadine wash until after skin closure at the end of the case.

5.5.2. Bupivacaine HCl Administration

Bupivacaine HCl will be administered via injection. Study drug should be administered throughout the tissue planes to ensure equal distribution across the surgical field. The medication should form rings of anesthetic around both the proximal and distal aspects of the metatarsal. An appropriate way of doing this is as follows:

- Start proximal to the bony incision and administer half the contents of the syringe distally past the bony incision.
- Repeat the procedure with the rest of the syringe but now start distally and inject proximally.
- Ensure adequate saturation of all exposed tissues in the surgical field.
- Thereafter, commence skin closure to complete the surgical procedure (ie, there should be no betadine wash until after skin closure at the end of the case).

5.6. Study Drug Compliance

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

5.7. Study Drug Accountability

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

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

5.8. Protocol-Specified Device

The custom Luer lock applicator is an investigational device used for administration of HTX-034 without a needle into the surgical site.

6. STUDY PROCEDURES AND ASSESSMENTS

The following sections describe the study procedures and assessments that will be performed during the study. The timing of procedures and assessments is provided in the SCHEDULE OF EVENTS section.

6.1. Medical History and Demographics

6.1.1. Medical History

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

6.1.2. Demographics

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

6.2. Prior and Concomitant Therapy

All medications taken by subjects between signing the ICF and the Day 43 Visit will be recorded. Prior and concomitant medication will be recorded on the eCRFs with the exception of PO oxycodone and acetaminophen rescue medication, which will be recorded in an ePRO device from surgery through the Day 15 Visit (see Section 6.6.2.1). For oxycodone and acetaminophen taken after the Day 15 Visit, the date of each dose should be recorded on the eCRF (ie, frequency should be once, not PRN).

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

After discharge until the Day 43 Visit, at least the start date, and stop date if applicable, of each concomitant medication should be recorded.

6.2.1. Allowed Concomitant Medications

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

Any antiemetic medications other than an NK_1 receptor antagonist may be given to treat nausea and/or vomiting, but should not be administered prophylactically (ie, as a routine preventative in the absence of signs or symptoms of nausea or vomiting).

During surgery, the use of fentanyl up to 4 µg/kg IV is permitted for intraoperative pain control.

Postoperative analgesia medications permitted to treat pain are outlined in Section 3.1.2.

6.2.2. Prohibited Medications

6.2.2.1. Medications Prohibited Prior to Surgery

Any drug formulation containing bupivacaine, aprepitant, or meloxicam is prohibited before surgery (within 5 days for bupivacaine and aprepitant and within 10 days for meloxicam). Refer to exclusion criterion 5 for a list of medications that are prohibited prior to the scheduled surgery (Section 4.1.2).

6.2.2.2. Medications Prohibited During Surgery

Intraoperative administration of opioids or any other analgesics (including ketamine), local anesthetics, or anti-inflammatory agents except as specified by the protocol (ie, HTX-034, bupivacaine HCl, fentanyl) is prohibited, unless needed to treat an AE that occurs after signing the ICF, for pretreatment prior to a needle placement, or to decrease venous irritation (eg, caused by propofol, in which case a single administration of lidocaine 1% up to 20 mg IV may be administered).

6.2.2.3. Medications Prohibited During the Postoperative Period

With the exception of the postoperative analgesia medications allowed by the protocol (Section 3.1.2), NSAIDs and other analgesics agents are not permitted through the Day 15 Visit. Morphine IV is permitted to treat pain during the 72-hour postoperative period but morphine is not permitted after 72 hours.

Medications containing bupivacaine or meloxicam are prohibited after surgery until the Day 15 Visit. Medications containing aprepitant are prohibited after surgery until study exit.

NK_1 receptor antagonists are not permitted to treat nausea and/or vomiting at any time during the study.

Pimozide, strong or moderate CYP3A4 inhibitors (eg, diltiazem, ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir), or strong CYP3A4 inducers (eg, rifampin, carbamazepine, phenytoin) are prohibited until the Day 15 Visit.

Systemic steroids are prohibited until the Day 15 Visit. (Note: inhaled, ophthalmic, and topical steroids are not considered systemic).

6.3. Surgery

Subjects will undergo a unilateral, first metatarsal bunionectomy with osteotomy and internal fixation under regional anesthesia. Spinal, epidural, and general anesthesia are not permitted. Sites should follow intraoperative safety monitoring in accordance with American Society of Anesthesiologists Standards for Basic Anesthetic Monitoring (American Society Anesthesiologists 2015). The start and stop time of surgery, length of the surgical incision, and additional surgical details should be recorded on the eCRF. The start time of the skin incision will be considered the start of surgery. Placement of the last suture will be considered the end of surgery. After immediate postoperative recovery, subjects will be transferred to the PACU.

6.4. Safety Assessments

6.4.1. Adverse Events

All AEs, regardless of causality or seriousness, will be recorded from the time the subject signs the ICF through the Day 43 Visit. Additional safety monitoring and reporting information is provided in Section 8.

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

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

6.4.2. Physical Examinations

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

Baseline height and weight measurements will be conducted and BMI calculated (Appendix B).

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

Any abnormal physical examination finding deemed clinically significant by the Investigator must be recorded as an AE.

6.4.3. Vital Signs

Vital sign measurements will include blood pressure, resting heart rate, respiration rate, and body temperature. Subjects should be in a supine position (includes sitting in a recliner chair) for at least 5 minutes before measuring vital signs.

Any abnormal vital sign result deemed clinically significant by the Investigator must be recorded as an AE and the abnormal vital sign result must be recorded on an eCRF (scheduled or unscheduled assessment eCRF, as applicable).

6.4.4. 12-Lead Electrocardiograms

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

Any abnormal ECG result deemed clinically significant by the Investigator must be recorded as an AE and the abnormal ECG result must be recorded on an eCRF (scheduled or unscheduled assessment eCRF, as applicable).

6.4.5. Wound Healing Assessments

Surgical wound healing will be assessed using the Southampton Wound Scoring System in Phase 1b and Phase 2 (Appendix C) and also using a wound healing assessment questionnaire in Phase 2 (Appendix D). Surgical wound healing will be evaluated by the Investigator or other medically qualified clinical site personnel; every attempt should be made by the site to use the same assessor for individual subject assessments. Only an abnormal wound healing finding deemed clinically significant by the Investigator should be recorded as an AE and should be followed to resolution.

6.4.6. Bone Healing Assessment

An X-ray of the surgical site will be obtained to evaluate the status of the bone healing process. X-rays should be evaluated by a physician with training and expertise in X-ray evaluations, including assessment of bone healing. The results should be reported as normal healing, delayed healing, or mal-union. The X-ray reports of anything other than normal healing will be provided to the Sponsor.

An X-ray finding of delayed healing must be followed with a repeat X-ray every 2 to 4 weeks until resolution (ie, signs of normal healing are evident).

Only abnormal X-ray findings that are considered clinically significant should be reported as AEs.

6.4.7. Local Anesthetic Systemic Toxicity Assessments

If a subject has clinically significant signs or symptoms at any time that the healthcare provider considers may be attributable to LAST, which include symptoms such as metallic/strange taste, perioral tingling, ringing in ears, visual disturbance, tremors, muscle twitching, dizziness/lightheadedness, convulsion/seizure, bradycardia, arrhythmia, hypotension (Vasques 2015), then vital sign measurements, 12-lead ECG (recorded in triplicate), and blood sample collection for PK must promptly be performed. In cases where those assessments are already scheduled within that time window, they do not need to be repeated. If symptoms are present at a timepoint when 1 of these assessments is not scheduled, an unscheduled assessment must be performed.

Subjects will also be assessed with a LAST questionnaire (Appendix E) to monitor for signs and symptoms potentially attributable to LAST. Signs and symptoms deemed clinically significant by the Investigator must be recorded as AEs and followed to resolution. If an AE potentially attributable to LAST is severe (Section 8.2.1), regardless of relationship to study drug, then the Investigator must notify the Sponsor **within 24 hours of becoming aware.** If a TEAE potentially attributable to LAST qualifies as an SAE (Section 8.1.2), the Investigator must notify the Sponsor **within 24 hours** of when the Investigator is first aware of the event.

6.4.8. Clinical Laboratory Tests

Blood and urine samples will be collected for diagnostic screening tests and for safety laboratory tests (hematology and serum chemistry). A list of clinical laboratory tests and parameters is provided in Table 5. In addition, a serum drug test for opioids will be performed at the Day 8 Visit (subjects in Phase 2 only) and at the Day 15 Visit (all subjects).

Scheduled hematology, serum chemistry tests, and serum drug tests for opioids will be performed by a central laboratory. Urine samples collected during the screening period for pregnancy and drug screening will be tested at the study site using kits provided by the central laboratory.

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

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

Table 5: Clinical Laboratory Tests

Diagnostic Screening Tests (Study Site):		
Urine Pregnancy test: Human chorionic gonadotropin test (female subjects of childbearing potential only) Drug screen: Amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates/opioids, and phencyclidine		
Follow-Up Drug Test (Central Laboratory):		
Serum: Opiates/opioids		
Safety Laboratory Tests (Central Laboratory):		
Hematology	**Serum Chemistry**	
Red blood cell count	Alanine aminotransferase	Gamma-glutamyltransferase
Hematocrit	Albumin	Glucose
Hemoglobin	Alkaline phosphatase	Lactate dehydrogenase
Mean corpuscular volume	Aspartate aminotransferase	Magnesium
Platelet count	Bicarbonate	Phosphorus
White blood cell count (with automated differential)	Blood urea nitrogen	Potassium
	Calcium	Sodium
	Chloride	Total bilirubin
	Creatinine	Total protein
	Direct bilirubin	Uric acid

6.5. Pharmacokinetic Assessments

Blood samples will be collected to measure plasma concentrations of bupivacaine, aprepitant, and meloxicam. Blood samples may be collected using a properly maintained indwelling cannula. Samples will be sent to a bioanalytical laboratory for analysis.

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

6.6. Efficacy Assessments

6.6.1. Pain Intensity Assessments

Subjects will evaluate their current pain level using an 11-point NRS (0 to 10) where 0 represents "no pain" and 10 represents "worst pain imaginable" (Appendix F). NRS scores will be recorded first at rest (NRS-R) and then with activity (NRS-A).

- *NRS-R assessments*: Subjects should be seated/recumbent with the surgically attended leg elevated or lying supine. Measurements should be obtained after the subject is in the resting position for at least 5 minutes.
- *NRS-A assessments*: Subjects should be seated with the plantar surface of the ball of the surgically attended foot touching the floor (no weight-bearing).

Subjects will record their pain levels in an ePRO device. Pain will be assessed at scheduled timepoints during the 72-hour postoperative period. At 8 PM (±4 hours) on Day 4, subjects will record their pain scores at rest and then with activity. Thereafter, subjects will record their pain scores at rest and then with activity every 12 hours through Day 8 (ie, at 8 AM and 8 PM ±4 hours each day).

Subjects will receive training by the site on how to provide pain intensity assessments.

6.6.2. Rescue Medication Use and Opioid Prescriptions

6.6.2.1. Rescue Medication Use

Postoperative rescue medication will be recorded through the Day 15 Visit. The name, dose, and route as well as the date and time of administration of any rescue medication must be recorded.

Subjects will record PO oxycodone and acetaminophen in an ePRO device. While inpatient, all PO rescue medication ePRO entries must be confirmed by site staff.

IV morphine will be recorded on an eCRF through 72 hours; morphine is not permitted after 72 hours.

Pain medication taken after Day 15 is not considered rescue medication and will be recorded on the concomitant medication eCRF.

6.6.2.2. Opioid Prescriptions

Guidance on opioid prescription at and after discharge is provided in Section 3.1.3. Sites will record if subjects are discharged with an opioid prescription and information about the opioid prescription.

Sites will also record if any subjects are provided an opioid prescription after discharge through the Day 15 Visit and information about the prescription.

6.6.3. Modified Postanaesthetic Discharge Scoring System Assessments

Discharge readiness will be assessed using the MPADSS, which considers a number of clinical variables: vital signs, ambulation, nausea/vomiting, pain, and surgical bleeding (Chung 1995). This study instrument assesses a subject's potential readiness to be discharged and should be

repeated at all scheduled timepoints. It is not meant to be used to decide whether or not to discharge a subject from the study. Subjects are required to remain in the hospital/research facility for 3 days or 7 days depending on to their treatment cohort.

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

See Appendix G for the MPADSS criteria.

6.6.4. Discharge Information

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

6.6.5. Patient Global Assessment of Pain Control

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

6.6.6. Overall Benefit of Analgesia Assessment

Subjects will be asked to evaluate their overall benefit of analgesia using a 7-item, multidimensional, quality assessment questionnaire (Lehmann 2010). The 7 items address pain, vomiting, itching, sweating, freezing, dizziness, and overall satisfaction with postoperative pain and make up the OBAS. See Appendix I for the OBAS scale.

6.6.7. Opioid-Related Symptom Distress Scale Questionnaire

Subjects will be asked about 10 opioid-related symptoms experienced over the preceding 24 hours: fatigue, drowsiness, inability to concentrate, nausea, dizziness, constipation, itching, difficulty with urination, confusion, and retching/vomiting. Each symptom will be assessed according to frequency, severity, and bothersomeness using categorical scales (Apfelbaum 2004). See Appendix J for the OR-SDS scale.

7. GUIDANCE FOR COMPLETING PROCEDURES AND ASSESSMENTS

Study procedures and assessments are described in Section 6. The timing of procedures and assessments is provided in the SCHEDULE OF EVENTS section. The start of study drug administration will be considered Time 0 for all safety, PK, and efficacy assessments.

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

During the Screening period, urine drug screen tests (all subjects) and urine pregnancy tests (female subjects of childbearing potential only) should be performed and confirmed as negative prior to performing any additional assessments. The definition of a woman of childbearing potential is provided in Section 9.1. Subjects with a positive drug screen who are taking an allowed, prescribed medication that is known to result in a positive drug test may be eligible for participation in the study. Subjects who fail the drug test may also be rescreened at the discretion of the Investigator.

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

- AE assessment.
- Pain intensity assessments (NRS-R followed by NRS-A).
- PGA of pain control assessment.
- OBAS assessment.
- OR-SDS assessment.
- Vital sign measurements.
- 12-lead ECG recording (in triplicate).
- Blood sample collection.
- Physical examination.
- Wound healing assessments.

For assessments at timepoints when the subject is asleep, an attempt should be made to wake the subject. If there is no response, the assessments at these timepoints may be recorded as “Not Done.” Assessments that can be done without waking the subject (eg, blood collection) should be completed.

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

8. SAFETY MONITORING AND REPORTING

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

Investigators must review the HTX-034 IB to be aware of the safety-related events that may be anticipated with its use.

8.1. Definition of Safety Parameters

8.1.1. Definition of an Adverse Event

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

An AE may be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not considered causally associated with the use of the study drug.

Any abnormal physical examination finding, laboratory value, vital sign result, ECG finding, wound healing assessment finding, bone healing assessment finding, or signs and symptoms of LAST or opioid-related symptom distress (per the LAST and OR-SDS study questionnaires, respectively) deemed clinically significant by the Investigator must be reported as an AE. A clinical diagnosis, rather than a change in a laboratory analyte or other assessment, should be recorded (eg, anemia rather than low hemoglobin value).

Examples of AEs include the following:

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

The following examples are not considered AEs:

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

8.1.2. Definition of a Serious Adverse Event

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

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

The following events do not meet the definition of an SAE:

- Hospitalization for the following:
  - Elective treatment of a pre-existing condition that does not worsen from baseline.
  - A standard procedure for study drug administration and routine monitoring of the studied indication not associated with any deterioration in condition.
- Social or convenience admission to a hospital.

- Prolongation of a hospitalization for social or convenience reasons not associated with the occurrence of an AE.
- Hospitalization or an emergency room visit that lasts less than 24 hours and does not meet the criteria of an important medical or a life-threatening event.

According to 21 Code of Federal Regulations (CFR) 812.3(s), an unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

8.1.3. Definition of Unanticipated Problems

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

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

An unanticipated adverse device effect is defined in Section 8.1.2.

8.2. Classification of Adverse Events

8.2.1. Severity of Adverse Events

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

- **Mild:** Event is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.
- **Moderate:** Event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe:** Event interrupts a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2. Relationship to Study Drug

The Investigator will assess the relationship of each AE to study drug (HTX-034 or bupivacaine HCl) based on his/her clinical judgment. The Investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

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

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

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

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

8.3.1. Adverse Event and Serious Adverse Event Monitoring

All AEs will be recorded from the time the subject signs the ICF through the Day 43 Visit. Note: the start time of all AEs during the inpatient postoperative period must also be recorded.

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

8.3.2. Follow-Up of Events

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

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

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

- **Recovered/Resolved:** The event resolved or the subject recovered without sequelae. An event (either serious or nonserious) occurred and had an endpoint, and the subject experienced no restrictions. Examples include stent placement for coronary artery disease (a device implanted is not a sequela), an appendectomy (a scar is not a sequela), a postoperative wound infection, or an upper respiratory tract infection.
- **Recovered/Resolved with sequelae:** The event has at least one secondary outcome that may result in permanent disability, functional limitation, or both. Such sequelae are usually limited to SAEs. Examples include hip replacement resulting in foot drop (foot drop is not the intended outcome but is a risk of surgery), stroke resulting in paralysis, or emboli formation after a bacterial infection resulting in a renal infarct and loss of renal function.
- **Recovering/Resolving**: The event is improving.
- **Not recovered/Not resolved:** At the end of the study, a nonserious event either has not changed in intensity or may not have recovered to baseline values, and the outcome is unknown. Examples include headache, low-grade fever, or nausea.
- **Unknown:** The subject has withdrawn from the study prematurely or is lost to follow-up, and the status of the event is unknown.
- **Fatal**

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

8.4. Reporting Procedures

8.4.1. Reporting Serious Adverse Events to the Sponsor

If the Investigator determines that an event that occurs during the course of this study meets the protocol definition of an SAE (see Section 8.1.2) due to any cause, regardless of relationship to study drug, he/she must notify the Sponsor by entering the SAE information into the eCRF **within 24 hours of the Investigator becoming aware of the SAE**.

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

Email Address: Heron_PV@ubc.com

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

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

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

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

8.4.2. Reporting Unanticipated Problems to the Sponsor

If the Investigator determines that an event meets the protocol definition of an unanticipated problem (see Section 8.1.3), he/she must notify the Sponsor by completing an Unanticipated Problem Form and emailing it to the Sponsor **within 24 hours of the Investigator becoming aware of the problem**.

Email Address: Heron_PV@ubc.com

The following information will be included with unanticipated problem reporting:

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

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

8.4.3. Regulatory Reporting Requirements

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

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

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

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

8.4.4. Pregnancy Reporting

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

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

Email Address: Heron_PV@ubc.com

8.5. Safety Oversight

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

The stopping criteria for suspending enrollment or terminating the study or closing a study site for safety issues are provided in Section 13.5.1 and Section 13.5.2, respectively.

9. OTHER STUDY RESTRICTIONS

9.1. Contraception

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

Female subjects of childbearing potential must use an acceptable form of contraception in the event of sexual activity from the Screening Visit through 30 days after study drug administration. Acceptable forms of contraception include double-barrier contraception or an intra-uterine device (eg, copper). Hormonal contraceptives are not an acceptable form of birth control because the efficacy of hormonal contraceptives may be reduced with aprepitant.

Note: This does not apply to women in only a same-sex relationship or women in a monogamous relationship with a surgically sterile partner.

10. STATISTICAL CONSIDERATIONS

10.1. General Considerations

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

10.2. Determination of Sample Size

The sample size in Phase 1b was selected empirically without a formal statistical assumption and will be sufficient to characterize the PK profile for HTX-034.

Based on results from Phase 1b of this study and a Phase 3 bunionectomy study of HTX-011 (Study HTX-011-301), a sample size of 40 subjects in Phase 2 (2:1:1 ratio of HTX-034 high dose:HTX-034 low dose:bupivacaine HCl) when pooled with Phase 1b (Table 6) will provide 82% power to detect a statistical significant difference between the HTX-034 high dose and bupivacaine HCl for the primary endpoint, assuming mean (SD) AUC_{0-72} of NRS pain scores were 272 (122) for HTX-034 in Phase 1b and 394 (154) for bupivacaine HCl in Phase 3 using Satterthwaite's t-test with $\alpha = 0.05$, 2-sided.

Table 6: Sample Size per Phase

	HTX-034 High Dose	HTX-034 Low Dose	Bupivacaine HCl
Phase 1b Safety Population	13	11	9[a]
Planned Phase 2 Safety Population	20	10	10
Pooled Phase 1b and Phase 2	33	21	19

[a] Pooled across cohorts.

10.3. Analysis Populations

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

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

10.4. Statistical Analysis Methods

10.4.1. Disposition and Demographics

The number and percentage of subjects in each analysis population will be summarized. Subject disposition, including the number of subjects screened, dosed, completing the 72-hour or 168-hour postoperative observation period, completing the study, and not completing the study by reason for withdrawal will be summarized for the Safety Population. Subject demographics and baseline characteristics will be summarized for the Safety Population and will include age, age category, sex, race, ethnicity, height, weight, and BMI.

10.4.2. Safety Analysis

All safety data will be listed and summarized for each treatment group by phase and pooled across Phase 1b and Phase 2; no statistical hypothesis testing will be performed.

AEs that occur between the time the subject signs the ICF and the start of study drug administration will be considered pretreatment AEs. AEs that start during or after study drug administration, or AEs with an onset prior to study drug administration that worsen after study drug administration will be considered TEAEs. All TEAEs will be coded and tabulated by System Organ Class and Preferred Term. The incidence of TEAEs, SAEs, potential ORAEs, and potential LAST-related TEAEs will be summarized. TEAEs leading to study withdrawal, if any, will be listed separately.

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

Changes from baseline in vital sign parameters and ECG results will be summarized. Wound healing and bone healing assessment results will be summarized at each timepoint and overall.

10.4.3. PK Analysis

Plasma bupivacaine, aprepitant, and meloxicam concentrations will be determined using validated liquid chromatography tandem-mass spectrometry assays. Concentrations will be calculated by interpolation from a calibration curve. PK parameters will be calculated using noncompartmental analysis.

10.4.4. Efficacy Analysis

All efficacy data will be listed and summarized for each treatment group by phase and pooled across Phase 1b and Phase 2.

For the primary efficacy endpoint, the comparison between pooled Phase 1b/2 HTX-034 high dose and pooled Phase 1b/2 bupivacaine HCl is considered the primary comparison and will be analyzed using an analysis of variance (ANOVA) model with treatment as the main effect. Results will be expressed as mean AUCs and SDs, least-squares mean differences and SEs with

associated 95% CIs, and p-values. Other continuous efficacy endpoints will be analyzed similarly to the primary endpoint unless specified otherwise.

All opiate dosages and formulations will have the MME calculated (Opioid Morphine Equivalent Conversion Factors, Centers for Disease Control and Prevention, Atlanta, GA, May 2014). Subjects who do not use an opioid during a period of interest will have their dose set to 0 for that period and will be characterized as "opioid-free" for that time interval. Total opioid consumption in IV MME will be analyzed using the Wilcoxon rank sum test. Results will be expressed as median (range) and p-values. Categorical endpoints will be analyzed using Fisher's exact test. Results will be expressed as the number and percentage of subjects meeting the relevant endpoint, differences in proportions with 95% CIs, and p-values.

10.4.4.1. Handling of Missing Data

For any missing pain scores observed in subjects who complete the 7-day (ie, 168-hour) observation period, NRS scores will be imputed via last observation carried forward (LOCF), in which the most recent postdose value is used for a subsequent missing value. For subjects who do not have a postdose value prior to their first missing value, the median of the postdose values at the relevant timepoint from subjects with observed data in the same treatment group will be used. In subjects who withdraw from the study prior to Day 8 (ie, before the end of 168-hour observation period), missing NRS scores through Day 8 that were to be collected following withdrawal will be imputed via worst observation carried forward (WOCF), in which the worst (highest) NRS score observed prior to withdrawal will be used for postwithdrawal values through Day 8. The number and percentage of missing NRS scores will be summarized.

Analyses that adjust for the effect of opioid rescue medication will perform windowed worst observation carried forward (wWOCF) following LOCF/WOCF (ie, perform LOCF/WOCF first, then apply wWOCF).

10.5. Interim Analyses

An interim analysis is planned to occur after all subjects in each cohort in Phase 1b have completed the Day 29 Visit. An internal IRC will review summary-level data from each cohort to make decisions on the next cohort. The internal IRC will be composed of 1 Sponsor representative from the Clinical Research, Biometrics, Pharmacovigilance, Regulatory, and Pharmaceutical and Translational Sciences functions. The IRC will operate under a written, detailed IRC Charter.

11. QUALITY ASSURANCE AND QUALITY CONTROL

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

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

12. REGULATORY AND ETHICAL CONSIDERATIONS

12.1. Regulatory Authority Approval

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

12.2. Ethical Conduct of the Study

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

12.3. Ethics Committee Approval

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

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

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

12.4. Informed Consent Process

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

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

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

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

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

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

12.5. Confidentiality

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

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

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

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

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

13. STUDY ADMINISTRATION

13.1. Clinical Monitoring

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

13.2. Source Documents and Record Retention

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

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

13.3. Management of Protocol Amendments and Deviations

13.3.1. Protocol Amendments

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

13.3.2. Protocol Deviations

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

13.4. Financial Disclosure

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

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

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

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

13.5. Stopping Criteria: Suspension or Termination of the Study or Closure of a Study Site

13.5.1. Suspension of the Study

If the Sponsor, Investigator, or officials from regulatory agencies discover conditions arising during the study that indicate that the study should be halted or that a study site should be closed, this action may be taken after appropriate consultation between the Sponsor and Investigator(s).

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

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

Following a review of the data by the Sponsor, a decision will be made to either resume, modify, or stop the study. If the study is terminated early by the Sponsor, written notification documenting the reason for study termination will be provided to the Investigator and regulatory authorities. The Investigator will promptly inform the EC and provide the reason(s) for study termination.

13.5.2. Closure of a Study Site

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

- Failure of the Principal Investigator to comply with the protocol, GCP regulations and guidelines, or local requirements.
- Insufficient adherence to protocol requirements or an unacceptably high rate of missing, erroneous, or improperly collected data.
- Insufficiently complete and/or evaluable data.
- Inadequate recruitment of subjects by the Investigator.
- Sponsor decision.

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

13.6. Publication and Information Disclosure Policy

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

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

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

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

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APPENDIX A. AMERICAN SOCIETY OF ANESTHESIOLOGISTS PHYSICAL STATUS CLASSIFICATION SYSTEM

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

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

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

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

APPENDIX B. BODY MASS INDEX CALCULATION

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

Weight in pounds × 0.453592 = weight in kg

Height in inches × 0.0254 = height in m

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

165 pounds × 0.453592 = 74.8 kg

71 inches × 0.0254 = 1.803 m

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

APPENDIX C. WOUND HEALING ASSESSMENT - SOUTHAMPTON WOUND SCORING SYSTEM

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

References:
Alam SI, Khan MY, Gul A, Jan QA. Surgical site infection. *Professional Med J.* 2014;21(2):377-381.
Bailey I. Community surveillance of complications after hernia surgery. *BMJ.* 1992;304:469-471.

APPENDIX D. WOUND HEALING ASSESSMENT QUESTIONNAIRE (PHASE 2 ONLY)

Bruising	Absent ☐	Present ☐	If present, is the bruising ☐ Expected ☐ Abnormal NCS ☐ Abnormal CS*
Erythema	Absent ☐	Present ☐	If present, is the erythema ☐ Expected ☐ Abnormal NCS ☐ Abnormal CS*
Edema	Absent ☐	Present ☐	If present, is the edema ☐ Expected ☐ Abnormal NCS ☐ Abnormal CS*
Heat	Absent ☐	Present ☐	If present, is the heat ☐ Expected ☐ Abnormal NCS ☐ Abnormal CS*
Drainage	Absent ☐	Present ☐	If present, is the drainage ☐ Abnormal NCS ☐ Abnormal CS* Type of drainage ☐ Serosanguinous ☐ Purulent*
Cellulitis	Absent ☐	Present ☐	If present, is the cellulitis ☐ Abnormal NCS ☐ Abnormal CS* Is there evidence of infection ☐ Yes* ☐ No
Delayed healing	Absent ☐	Present ☐	If present, is the delayed healing ☐ Abnormal NCS ☐ Abnormal CS*
Dehiscence	Absent ☐	Present ☐	If present, is the dehiscence ☐ Abnormal NCS ☐ Abnormal CS*

Abbreviations: CS, clinically significant; NCS, not clinically significant.
* Record as an adverse event.

APPENDIX E. LOCAL ANESTHETIC SYSTEMIC TOXICITY ASSESSMENT

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

If a subject has signs or symptoms that the healthcare provider considers clinical significant and may be attributable to LAST, then vital sign measurements, 12-lead ECG (recorded in triplicate), and blood sample collection for PK must be promptly performed. In cases where those assessments are already scheduled within that time window, they do not need to be repeated. If symptoms are present at a timepoint when 1 of these assessments is not scheduled, an unscheduled assessment must be performed.

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

LAST Questionnaire

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

Notes:

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

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

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

APPENDIX F. PAIN INTENSITY ASSESSMENT USING THE NUMERIC RATING SCALE

"On a scale of 0 to 10, please rate your pain by selecting the appropriate box that best describes your pain NOW."

The response must be one of the following:

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

Reference: Adapted from Breivik H, Borchgrevink PC, Allen SM, et al. Assessment of pain. *Br J Anaesth*. 2008;101(1):17-24.

APPENDIX G. MODIFIED POSTANAESTHETIC DISCHARGE SCORING SYSTEM CRITERIA

The Modified Postanaesthetic Discharge Scoring System (MPADSS) will be used to assess the subject's discharge readiness. This assessment will be used for data collection only and is not intended to interfere with the hospital's policy for determining when the subject should be discharged. Only subjects who achieve a score of 9 or higher will be considered ready for discharge.

Parameter	Score
Vital Signs	
Within 20% of preoperative value	2
20% to 40% of preoperative value	1
>40% of preoperative value	0
Ambulation	
Steady gait/no dizziness	2
With assistance	1
None/dizziness	0
Nausea/Vomiting	
Minimal	2
Moderate	1
Severe	0
Pain	
Minimal	2
Moderate	1
Severe	0
Surgical Bleeding	
Minimal	2
Moderate	1
Severe	0

Reference: Chung, F. Discharge criteria--a new trend. *Can J Anaesth*. 1995;42(11):1056-1058.

APPENDIX H. PATIENT GLOBAL ASSESSMENT OF PAIN CONTROL

"Overall, please rate how well your pain has been controlled during the last 24 hours?"

The response must be one of the following:

- Poor (0)
- Fair (1)
- Good (2)
- Excellent (3)

Reference: Adapted from Rothman M, Vallow S, Damaraju CV, Hewitt DJ. Using the patient global assessment of the method of pain control to assess new analgesic modalities in clinical trials. *Current Medical Research and Opinion*. 2009;25:1433-1443.

APPENDIX I. OVERALL BENEFIT OF ANALGESIA SCORE

		Rating
1	Please rate your current pain at rest on a scale between 0=minimal pain and 4=maximum imaginable pain	|__|
2	Please grade any distress and bother from vomiting in the past 24 h (0=not at all to 4=very much)	|__|
3	Please grade any distress and bother from itching in the past 24 h (0=not at all to 4=very much)	|__|
4	Please grade any distress and bother from sweating in the past 24 h (0=not at all to 4=very much)	|__|
5	Please grade any distress and bother from freezing in the past 24 h (0=not at all to 4=very much)	|__|
6	Please grade any distress and bother from dizziness in the past 24 h (0=not at all to 4=very much)	|__|
7	How satisfied are you with your pain treatment during the past 24 h (0=not at all to 4= very much)?	4 - |__| = |__|
	Overall Benefit of Analgesia Score:	|__|__|

To calculate the OBAS score, compute the sum of the scores in items 1 through 6 and add '4-score in item 7'

Example OBAS calculation: A patient with minimal pain (NRS=0), severe vomiting (NRS=4), and no itching, sweating, and freezing who is slightly dizzy (NRS=1), and is not very satisfied with his postoperative pain treatment (NRS=1) has an OBAS of 8.

Note that a low score indicates high benefit.

Reference: Adapted from Lehmann N, Joshi GP, Dirkmann D, et al. Development and longitudinal validation of the overall benefit of analgesia score: a simple multi-dimensional quality assessment instrument. *Br J Anaesth*. 2010;105(4):511-518.

APPENDIX J. OPIOID-RELATED SYMPTOM DISTRESS SCALE

We have listed 10 symptoms below. Read each one carefully. If you have had the symptom during the past 24 hours, let us know how OFTEN you had it, how SEVERE it was usually and how much it DISTRESSED OR BOTHERED you by placing an 'X' in the appropriate box. If you DID NOT HAVE the symptom, please place an 'X' in the box marked "Did not have".

For the symptom "retching/vomiting" below, you will indicate the actual **number** of episodes you experienced.

During the last 24 hours, did you have any of the following?

Symptoms	Did not have	(If yes), how often did you have it?				(If yes), how severe was it usually?				(If yes), how much did it distress or bother you?				
		Rarely	Occasionally	Frequently	Almost constantly	Slight	Moderate	Severe	Very severe	Not at all	A little bit	Somewhat	Quite a bit	Very much
Fatigue	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Drowsiness	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Inability to concentrate	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Nausea	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Dizziness	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Constipation	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Itching	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Difficultly with urination	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Confusion	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Retching/vomiting	☐	__ # of episodes				☐	☐	☐	☐	☐	☐	☐	☐	☐

Adapted with permission from the Memorial Symptom Assessment Scale by Portenoy, et al; OR-SDS© 2004 Pfizer Inc., Jeffrey L. Apfelbaum and Tong J. Gan.

Signature Page for VV-CLIN-004627 v1.0

Approval	[redacted] 11-Mar-2021 15:20:51 GMT+0000

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