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Official Title:	A Phase 2 Open-Label Study of HTX-011 via Individualized Dosing Administration for Postoperative Analgesia Following Unilateral Simple Bunionectomy
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CLINICAL STUDY PROTOCOL: HTX-011-218

Protocol Title:	A Phase 2 Open-Label Study of HTX-011 via Individualized Dosing Administration for Postoperative Analgesia Following Unilateral Simple Bunionectomy
Brief Title:	Phase 2 Bunionectomy HTX-011 Administration Study
Investigational Products:	HTX-011 (bupivacaine and meloxicam) extended-release solution Aprepitant oral capsules
Phase of Development:	2
Sponsor:	Heron Therapeutics, Inc. 4242 Campus Point Court, Suite 200 San Diego, CA 92121 1-858-251-4400
Medical Monitors:	[redacted]
Medical Project Leader:	[redacted] Vice President, Clinical Research [redacted]
Protocol Version:	Version 4 14 January 2019 Version 3 12 December 2018 Version 2 27 November 2018 Version 1 27 September 2018

INVESTIGATOR AGREEMENT

CLINICAL STUDY PROTOCOL: HTX-011-218

TITLE: A Phase 2 Open-Label Study of HTX-011 via Individualized Dosing for Postoperative Analgesia Following Unilateral Simple Bunionectomy

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

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

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

Principal Investigator: _____

Address: _____

Signature: _____

Date: _____

PROTOCOL SYNOPSIS

Sponsor: Heron Therapeutics, Inc.	**Protocol Number:** HTX-011-218
Name of Investigational Products: HTX-011 (bupivacaine and meloxicam) extended-release solution Aprepitant capsules (Cohorts 2 and 4 only)	**Protocol Title:** A Phase 2 Open-Label Study of HTX-011 via Individualized Dosing Administration for Postoperative Analgesia Following Unilateral Simple Bunionectomy
Name of Active Ingredients: bupivacaine and meloxicam aprepitant (Cohorts 2 and 4 only)	**Phase of Development:** 2

Study Objectives:

Primary Objectives:

- To assess the efficacy and duration of analgesia, following a single individualized dose of HTX-011, during the first 72 hours after unilateral simple bunionectomy (Cohort 1).
- To assess the analgesic efficacy following a 3-day regimen of oral aprepitant and a single individualized dose of HTX-011 during the first 72 hours after unilateral simple bunionectomy (Cohort 2).
- To assess the analgesic efficacy following a single individualized dose of HTX-011 as part of a multimodal analgesic regimen during the first 72 hours after unilateral simple bunionectomy (Cohort 3).
- To assess the analgesic efficacy following a 3-day regimen of oral aprepitant and a single individualized dose of HTX-011 as part of a multimodal analgesic regimen during the first 72 hours after unilateral simple bunionectomy (optional Cohort 4).

Secondary Objectives:

- To assess the effect of study treatment on opioid load during the first 72 hours following surgery in this study population.
- To assess the proportion of subjects who are opioid-free after receiving HTX-011 as part of a multimodal analgesic regimen during the first 72 hours in this study population (Cohort 3 and optional Cohort 4).
- To assess the proportion of subjects who are opioid-free after receiving HTX-011 as part of a multimodal analgesic regimen during the first 72 hours with or without aprepitant and who remain opioid-free through Day 10 and Day 28 (Cohort 3 and optional Cohort 4).
- To assess the safety and tolerability of study treatment in this study population.
- To confirm the pharmacokinetic (PK) parameters of bupivacaine and meloxicam for a single individualized dose of HTX-011 in this study population.
- To analyze the PK parameters of aprepitant in the presence of HTX-011 in this study population (Cohort 2 and optional Cohort 4).

Methodology:

This is a Phase 2, open-label, multi-cohort study to evaluate the analgesic efficacy, safety, and PK of a single, individualized dose of HTX-011 administered into the surgical site as a monotherapy or with other medications to enhance analgesia in subjects undergoing unilateral simple bunionectomy. The study will include up to 4 cohorts, which will be conducted sequentially. Subjects in all cohorts will receive

HTX-011. Cohort 2 of the study will also include administration of oral aprepitant on Days 1 through 3. Cohort 3 and optional Cohort 4 will include a scheduled multimodal analgesic regimen during the 72-hour postoperative period. Optional Cohort 4 will also include oral aprepitant on Days 1 through 3.

	Cohort			
Treatment	**1**	**2**	**3**	**4[a]**
HTX-011	√	√	√	√
Oral aprepitant[b]		√		√
Multimodal analgesic regimen[c]			√	√

[a] Optional cohort.
[b] Days 1 through 3.
[c] During the 72-hour postoperative period.

Subjects will be screened within 28 days prior to surgery. Subjects who meet the Screening eligibility criteria will be included. Verification that subjects continue to meet the eligibility criteria will be assessed on the day of surgery (Day 1). Eligible subjects will undergo a unilateral simple bunionectomy under regional anesthesia with no more than 20 mL of 1% lidocaine without epinephrine administered as a Mayo block. Epidural or spinal anesthesia is not permitted. During surgery, the use of intravenous (IV) fentanyl up to 4 µg/kg will be permitted for intraoperative pain control. Intraoperative administration of other opioids or any other analgesics (including ketamine), local anesthetics, or anti-inflammatory agents (except as specified by the protocol) is prohibited, unless needed to treat an adverse event (AE) that occurs after signing the Informed Consent Form (ICF), for pretreatment prior to a IV needle placement, or to decrease venous irritation (eg, caused by propofol, in which case no more than a single administration of lidocaine plain 1% 20 mg IV may be administered).

Study Cohorts:

Cohorts 1 through 4

Near the completion of surgery and after irrigation and suction have been completed, a single dose of HTX-011 will be given intraoperatively via application into the surgical site. The dose is individualized for each subject, up to a maximum of 2.1 mL (up to 60 mg/1.8 mg [bupivacaine/meloxicam doses]). The exact amount of HTX-011 instilled will be determined by the Investigator at the time of surgery. Following surgery and immediate postoperative recovery, all subjects will be transferred to the post anesthesia care unit (PACU).

Cohorts 2 and Optional Cohort 4

Subjects will be administered a single oral dose of aprepitant 125 mg approximately 3 hours prior to the start of surgery. Subjects will also be administered a single oral dose of aprepitant 80 mg at approximately 24 hours (Day 2) and at approximately 48 hours (Day 3) after the presurgery dose of aprepitant.

Cohorts 3 and Optional Cohort 4

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

Postoperative Observation Period and Follow-Up:

All subjects will remain in the hospital/research facility for a minimum of 72 hours after the start of HTX-011 administration to undergo postoperative assessments. After the 72-hour assessments have been completed, subjects may be discharged. Subject should be instructed at the time of discharge to leave the

bandage clean, dry, and intact until the Day 7 visit. In addition, the subject should be provided with a cast guard to assist with keeping the bandage dry and instructed to contact the site if the bandage gets wet.

Subjects in Cohorts 3 and 4 (whether or not they were discharged with an opioid prescription) will receive a diary at discharge, which they will complete each day to record whether they take an opioid medication between 72 hours and Day 28.

All subjects will return to the study site on Days 7 and 28 to complete follow-up assessments. In addition, subjects will return for a Safety Follow-Up Visit on Day 42.

Postoperative Analgesic Medications:

Rescue Medication During Inpatient 72-Hour Postoperative Period

Subjects should only receive rescue medication upon request for pain control, as needed, during the 72-hour postoperative observation period. Rescue medication should not be given for pain prophylaxis, but only for treating postoperative pain. Prior to the administration of the first dose of rescue medication, if the subject has not already had at least 1 postoperative pain score assessed, then a Numeric Rating Scale (NRS) score at rest (NRS-R) followed by an NRS score with activity (NRS-A) must be obtained.

Cohorts 1 and 2: Postoperative rescue medication will consist of oral immediate-release oxycodone (no more than 10 mg within a 4-hour period as needed), IV morphine (no more than 10 mg within a 2-hour period as needed), and/or oral acetaminophen (no more than 1 gram [1000 mg] in a 6-hour window). For subjects administered any acetaminophen-containing product, the total combined daily dose must not exceed 4 grams (4000 mg). Combination products containing an opioid and non-opioid are not allowed. No other analgesic agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), are permitted during the 72-hour postoperative observation period.

Cohorts 3 and 4: Postoperative rescue medication will consist of oral immediate-release oxycodone (no more than 10 mg within a 4-hour period as needed) and/or IV morphine (no more than 10 mg within a 2-hour period as needed). Combination products containing an opioid and non-opioid are not allowed. With the exception of oral ibuprofen and oral acetaminophen, no other analgesic agents, including NSAIDs, are permitted during the 72-hour postoperative observation period.

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

Postoperative Analgesia After Discharge

Cohorts 1 and 2: For subjects who are medically ready for discharge at 72 hours, oral acetaminophen (no more than 1000 mg every 6 hours as needed) should be recommended for postoperative pain. If a subject received 10 mg or more of oxycodone in the 12 hours prior to discharge, the subject should be provided with a prescription for immediate-release oxycodone (up to 10 mg orally [PO] q4h as needed).

Cohorts 3 and 4: Upon discharge, subjects will be instructed to manage pain with the following regimen:

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

If a subject received 10 mg or more of oxycodone in the 12 hours prior to discharge, the subject should be provided with a prescription for immediate-release oxycodone (up to 10 mg PO q4h as needed). Pharmacists should be instructed that substitutions with any other opioid-containing product are not permitted, including combination opioid/non-opioid products. Sites must record if a subject is discharged with an opioid prescription (yes or no) for Cohorts 3 and 4.

Number of Planned Subjects: Up to approximately 90 subjects will be enrolled and dosed: 30 subjects in Cohort 1, 15 subjects in Cohort 2, 30 subjects in Cohort 3, and 15 subjects in optional Cohort 4.

Study Sites: Up to 2 sites.

Study Population:

Inclusion Criteria

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

1. Is able to provide written informed consent, adhere to the study visit schedule, and complete all study assessments.
2. Is male or female, and ≥18 years of age at screening.
3. Is scheduled to undergo a primary unilateral, distal, first metatarsal bunionectomy with osteotomy and internal fixation under regional anesthesia.
4. Has an American Society of Anesthesiologists Physical Status of I, II, or III.
5. 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. For Cohorts 1 and 3, is surgically sterile; or is at least 2 years post-menopausal; or is in a monogamous relationship with a partner who is surgically sterile; or is practicing abstinence or agrees to use double-barrier contraception in the event of sexual activity; or is using an insertable, injectable, transdermal, or combination oral contraceptive approved by applicable regulatory authorities for greater than 2 months prior to screening and commits to the use of an acceptable form of birth control for the duration of the study and for 30 days after study drug administration. Note: women in only a same-sex relationship do not need to meet this criterion.
    e. For Cohorts 2 and 4, is surgically sterile; or is at least 2 years post-menopausal; or is in a monogamous relationship with a partner who is surgically sterile; or is practicing abstinence or agrees to use double-barrier contraception or a non-hormonal intra-uterine device (eg, copper) in the event of sexual activity for greater than 2 months prior to screening, for the duration of the study and for 30 days after last study drug administration. Note: Women in only a same-sex relationship do not need to meet this criterion. Hormonal contraceptives are not an acceptable form of birth control since the efficacy of hormonal contraceptives may be reduced with aprepitant.

Exclusion Criteria

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

1. Has had a contralateral foot bunionectomy in the past 3 months prior to the scheduled surgery.
2. Has a planned concurrent surgical procedure (eg, bilateral bunionectomy or collateral procedures on the surgical foot).
3. Has a pre-existing concurrent acute or chronic painful physical/restrictive condition expected to require analgesic treatment in the postoperative period for pain that is not strictly related to the bunionectomy and which may confound the postoperative assessments.
4. Has a contraindication or a known or suspected history of hypersensitivity or clinically significant idiosyncratic reaction to bupivacaine (or other local anesthetics), meloxicam (or other NSAIDs), oxycodone, morphine, acetaminophen, aprepitant (Cohorts 2 and 4 only), or ibuprofen (Cohorts 3 and 4 only).
5. Has known or suspected daily use of opioids for 7 or more consecutive days within the previous 6 months prior to the scheduled surgery.
6. Has taken any NSAIDs (including meloxicam) within at least 10 days prior to the scheduled

surgery with the exception of subjects on low-dose (≤100 mg) daily acetylsalicylic acid for cardio protection.

7. Has taken long-acting opioids within 3 days prior to the scheduled surgery.
8. Has taken any opioids within 24 hours prior to the scheduled surgery.
9. Has been administered bupivacaine within 5 days prior to the scheduled surgery.
10. For Cohorts 2 and 4 only, has been administered aprepitant or another NK_1 receptor antagonist such as rolapitant, netupitant, or fosaprepitant within 5 days prior to the scheduled surgery.
11. Has been administered any local anesthetic within 72 hours prior to the scheduled surgery, other than for pretreatment prior to IV needle placement, to treat an AE that occurs after signing the ICF, or to decrease venous irritation (eg, caused by propofol, in which case no more than a single administration of lidocaine 1% plain 20 mg IV may be administered).
12. Has initiated treatment with any of the following medications within 1 month prior to study drug administration **or** is taking any of these medications to control pain: selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin, or cyclooxygenase-2 (COX-2) inhibitors. (Note: If a subject is taking one of these medications for a reason other than pain control, the subject must be on a stable scheduled dose [ie, not "as needed"] for at least 1 month prior to study drug administration.) Anxiolytics prior to surgery are permitted, if necessary.
13. Has been administered systemic steroids within 5 half-lives or 10 days prior to administration of study drug (whichever is longer).
14. Has a medical condition such that, in the opinion of the Investigator, participating in the study would pose a health risk to the subject or confound the postoperative assessments. Conditions may include, but are not limited to, any of the following:
    a. History of clinically significant cardiac abnormality such as myocardial infarction within 6 months prior to signing the ICF, New York Heart Association class III or IV, or clinically significant abnormalities in cardiac function or on electrocardiogram (ECG; including but not limited to a PR interval >200 msec, a QT corrected by Fridericia's formula [QTcF] >480 msec, or 3rd degree heart block).
    b. History of coronary artery bypass graft surgery within 12 months prior to signing the ICF.
    c. History of severe liver function impairment as defined by Child-Pugh Class C, having an aspartate aminotransferase >3 × the upper limit of normal (ULN), or having an alanine aminotransferase >3 × ULN.
    d. History of severe kidney function impairment as defined by creatinine clearance (Cockcroft-Gault) <30 mL/min, being on dialysis, and/or having a serum creatinine >2 × ULN.
    e. History of known or suspected coagulopathy or uncontrolled anticoagulation (platelet count <100,000/μL, hemoglobin <12 g/dL, or hematocrit <35%).
    f. Loss of sensation in extremities or significant peripheral neuropathy.
15. As per subject history and/or medical records, has active infection or is currently undergoing treatment for Hepatitis B, Hepatitis C, or human immunodeficiency virus (HIV).
16. Has uncontrolled anxiety, psychiatric, or neurological disorder that, in the opinion of the Investigator, might interfere with study assessments.
17. For Cohorts 2 and 4 only, is receiving 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).

18. Had a malignancy in the last year, with the exception of non-metastatic basal cell or squamous cell carcinoma of the skin or localized carcinoma in situ of the cervix.
19. Has a known or suspected history of drug abuse, a positive urine drug screen at the screening visit or on the day of surgery prior to surgery, or a recent history of alcohol abuse (ie, within 10 years). 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 with Medical Monitor approval. Subjects taking medical or recreational marijuana are not allowed to participate in the study.
20. Previously participated in an HTX-011 study.
21. Received an investigational product or device in a clinical trial within 30 days or within 5 elimination half-lives (whichever is longer) prior to surgery, or is planning to take part in another clinical trial while participating in this study.
22. Has undergone 3 or more surgeries within 12 months prior to signing the ICF, other than for diagnostic procedures (eg, colonoscopy).
23. Has a body mass index (BMI) >39 kg/m^2.

Investigational Products, Doses, and Modes of Administration:

HTX-011 (All cohorts)

HTX-011 is a novel, extended-release, fixed-dose combination product that contains bupivacaine and low-dose meloxicam. Bupivacaine is an amide-type local anesthetic and meloxicam is a nonsteroidal anti-inflammatory drug (NSAID). HTX-011 is a solution that is formulated in a proprietary tri(ethylene glycol)-based poly(orthoester) polymer (TEG-POE), termed Biochronomer®. HTX-011 will be supplied by the Sponsor as a sterile, viscous liquid in 20 mL clear glass vials.

A single dose of no more than 2.1 mL HTX-011 [up to 60 mg/1.8 mg (bupivacaine/meloxicam doses)] will be applied without a needle into the surgical site using a Luer lock applicator to coat the tissues within the surgical site that could result in pain generation. Application of HTX-011 should follow final irrigation and suction and prior to suturing. A sufficient amount should be used to coat the tissues, ensuring there is not an excess that could be expressed from the site during closure. When using monofilament sutures, 3 or more knots are recommended because contact with HTX-011 may cause a single knot to loosen or untie. HTX-011 should be applied only to the tissue layers below the skin incision and not directly onto the skin. The syringe and Luer lock applicator will also be supplied by the Sponsor.

After preparing the syringe and before administration, the amount of HTX-011 withdrawn into the syringe (to the nearest tenth of 1 mL) and the weight of the syringe (to the nearest gram) will be recorded in the eCRF. After administering HTX-011, the amount of HTX-011 remaining in the syringe and the weight of the syringe will also be recorded in the eCRF.

Aprepitant (Cohorts 2 and 4)

Aprepitant is a substance P neurokinin-1 (NK-1) receptor antagonist. Aprepitant was initially approved by the US FDA in 2003 for the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV) and in 2006 for postoperative nausea and vomiting (PONV). Its use has also been investigated for the management of pain. Aprepitant capsules will be supplied by the Sponsor as a pack containing one 125 mg capsule and two 80 mg capsules.

Subjects in Cohorts 2 and 4 will take 3 single oral doses of aprepitant: approximately 3 hours presurgery on Day 1 (125 mg) and at approximately 24 hours (Day 2) and approximately 48 hours (Day 3) after the presurgery dose (80 mg at each of the 2 timepoints).

Required Concomitant Medications

Study sites will supply other required concomitant medications (eg, ibuprofen and acetaminophen for

Cohorts 3 and 4) as well as rescue medications during the 72-hour postoperative period (all cohorts, as needed).

Reference Therapy, Dose, and Mode of Administration:

None.

Duration of Treatment:

All subjects will receive a single dose of HTX-011. Subjects in Cohorts 2 and 4 will also receive 3 single doses of aprepitant. Subjects in Cohort 3 and 4 will also receive scheduled multimodal analgesia through 72 hours. The total duration of study participation for each subject (from Screening through the Safety Follow-Up on Day 42) will be up to 77 days. The overall duration of the study is anticipated to be approximately 7 months.

Criteria for Evaluation:

Efficacy, safety, and PK assessments will be performed. For Cohorts 1 and 3, the start of HTX-011 administration will be considered as Time 0 for all efficacy, safety, and PK timepoints. For Cohorts 2 and 4, the start of aprepitant administration will be considered Time 0 for aprepitant alone safety and PK assessments. The start of HTX-011 administration will be considered as Time 0 for all efficacy, safety, and PK assessments for HTX-011 with aprepitant.

Efficacy Assessments:

- Pain intensity scores using NRS-R and NRS-A at 1, 2, 4, 8, 12, 24, 36, 48, 60, 72 hours, and on Day 7 and Day 28.
  - 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).
- Date, time of administration, and amount of all opioid rescue medication taken through 72 hours.
- Subject daily diary to record whether any opioids were taken from 72 hours through Day 28 (Cohorts 3 and 4 only).

Safety Assessments:

- AEs from the time the subject signs the ICF through the Safety Follow-Up on Day 42.
- Clinical safety laboratory tests (hematology and serum chemistry) at the Screening Visit and at 72 hours.
- Physical examination at Screening Visit that also includes height, weight, and BMI calculation.
- Wound healing assessment on Day 7, Day 28, and at the Safety Follow-Up on Day 42.
- Vital signs (resting heart rate, blood pressure, respiration rate, and body temperature) at the Screening Visit, on Day 1 before surgery, and post-treatment at 30, 60, and 90 minutes and at 2, 4, 8, 12, 18, 24, 36, 48, 60, and 72 hours.
- ECG at the Screening Visit.

PK Assessments:

A presurgery blood sample for bupivacaine and meloxicam PK analysis will be collected from subjects in Cohort 3. Presurgery blood samples for bupivacaine, meloxicam, and aprepitant PK analysis will be collected from subjects in Cohorts 2 and 4 at approximately 2, 2.5, and 3 hours following the presurgery dose of aprepitant 125 mg. Blood samples for bupivacaine and meloxicam PK analysis (all subjects) and for aprepitant PK analysis (Cohorts 2 and 4 only) will be collected at 0.5, 1, 2, 4, 8, 12, 18, 24, 36, 48,

60, and 72 hours following the start of HTX-011 administration. (Note: when PK and NRS pain intensity assessments coincide, the NRS pain intensity assessments should be conducted before the blood draw.)

Study Endpoints:

Primary Efficacy Endpoint:

- Area under the curve (AUC) of the Numeric Rating Scale of pain intensity scores with activity (NRS-A) through 72 hours (AUC_{0-72}).

Secondary Efficacy Endpoints:

- Total postoperative opioid consumption (in morphine equivalents) through 72 hours.
- Proportion of subjects who are opioid-free through 72 hours.
- Proportion of subjects who are opioid-free through 72 hours who remain opioid-free through Day 10 and Day 28 (Cohorts 3 and 4 only).
- AUC_{0-72} of the NRS-R pain intensity scores.

Safety Endpoints

- Incidence of treatment-emergent AEs (TEAEs), serious TEAEs (SAEs), and opioid-related AEs (ORAEs) through the Safety Follow-Up on Day 42.
- Change from baseline in clinical laboratory results.
- Change from baseline in vital signs.
- Wound healing assessment on Day 7 and Day 28, and at the Safety Follow-Up on Day 42.

PK Endpoints

- The area under the plasma concentration-time curve from time zero to time t of the last measured concentration above the limit of quantification (AUC_{0-last}) (for bupivacaine and meloxicam only).
- The area under the plasma concentration-time curve from zero to infinity (AUC_{0-inf}) (for bupivacaine and meloxicam only).
- The maximum plasma concentration (C_{max}).
- Apparent total body clearance over bioavailability (Cl/F).
- Apparent total volume of distribution over bioavailability (V_Z/F).
- The time to reach maximum plasma concentration (T_{max}).
- The terminal elimination rate constant (λ_Z) with the respective half-life ($t_{½}$).

Statistical Methods:

Efficacy Analyses

All efficacy data will be summarized by cohort. AUCs of the NRS pain intensity scores will be adjusted for opioid use via windowed worst observation carried forward (wWOCF) method. In this method, pain intensity scores observed during the analgesic window (duration of effect) of any opioid rescue medication will be replaced with the worst (highest) postdose nonmissing NRS pain intensity score observed prior to the rescue medication window, with the following exception: if the NRS pain intensity score for a windowed observation is higher than the worst prewindow score, then it will not be replaced. Sensitivity analyses for endpoints involving NRS pain intensity scores will summarize the data without adjustment for the effect of opioid rescue medications.

Handling of Missing Data

Due to the required 72-hour inpatient postoperative observation period, the amount of missing data is expected to be very low. For any missing data observed through 72 hours in subjects who complete the 72-hour postoperative observation period, NRS pain intensity scores will be imputed via last observation carried forward (LOCF), in which the most recent post-dose value is used for a subsequent missing value.

For subjects who do not have a post-dose value prior to their first missing value, the median of the post-dose values at the relevant timepoint from subjects with observed data in the same treatment group will be used. Pre-dose values will not be carried forward to post-dose timepoints. In subjects who withdraw from the study prior to 72 hours, missing NRS pain intensity scores through 72 hours that were to be collected following withdrawal will be imputed via WOCF, in which the worst (highest) NRS pain intensity score observed prior to withdrawal will be used for post-withdrawal values through 72 hours. Analyses that adjust for the effect of opioid rescue medication will perform wWOCF following LOCF/WOCF (ie, perform LOCF/WOCF first, then apply wWOCF). The number and percentage of missing NRS pain intensity scores will be summarized.

Pharmacokinetic Analysis:

The PK parameters for bupivacaine and meloxicam (all subjects) and for aprepitant (Cohorts 2 and 4) will be calculated using noncompartmental analysis.

Safety Analyses

All safety data will be listed and summarized by cohort. All TEAEs will be coded and tabulated by System Organ Class and Preferred Term. Incidence of TEAEs, SAEs, and ORAEs will be summarized and presented in descending order of frequency. Associated laboratory parameters such as hepatic profile, renal function, and hematology values will be grouped and presented together in summary tables. Individual subject values will be listed and values outside of the standard reference range will be flagged. Changes in vital sign parameters will be summarized. Wound healing assessment results will be summarized.

Determination of Sample Size

The sample size was selected empirically without formal statistical assumptions.

SCHEDULE OF EVENTS

Assessments	Time Window	Screening	Preop	OR	Time After HTX-011 Administration*																
		≤28 days	D1										D2		D3		D7	D28	F/Up D42	ET[a]
					30 min	60 min	90 min	2h	4h	8h	12h	18h	24h	36h	48h	60h	72h				
					±5 min	±5 min	±10 min	±15 min	±15 min	±30 min	±30 min	±30 min	±1h	±2h	±2h	±4h	±4h	±3d	±4d	±7d	
Obtain informed consent		X																			
Urine drug screen[b]		X	X																		
Urine pregnancy test (WOCBP only)[b]		X	X																		
Assess/confirm eligibility		X	X																		
Medical history		X																			
Demographics		X																			
Physical examination		X[c]																			
Vital signs		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X				X[d]
12-lead ECG (triplicate)		X																			
Subject training for pain assessments		X	X																		
Hematology and serum chemistry tests		X															X				X[d]
Administer aprepitant (Cohorts 2 and 4)			X[e]										X[e]		X[e]						
Surgery[f]				X																	
Administer HTX-011				X																	
Administer scheduled multimodal analgesic regimen (Cohorts 3 and 4)[g]					←	-	-	-	-	-	-	-	-	-	-	-	→				
Pain intensity assessment (NRS-R)[h]						X[i]		X	X	X	X		X	X	X	X	X	X	X		X[j]
Pain intensity assessment (NRS-A)[k]						X[i]		X	X	X	X		X	X	X	X	X	X	X		X[j]
Record all pain medication					←	-	-	-	-	-	-	-	-	-	-	-	→				
Record if opioid prescription at discharge (Cohorts 3 and 4)[l]																	X				
Wound healing assessment																		X	X	X	X
PK blood sample			X[m]		X	X		X	X	X	X	X	X	X	X	X	X				
Record opioid use in daily diary (Cohorts 3 and 4)[n]																		←	-	→	X[j]
Concomitant medications[o]		←	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	→	X
Adverse events[p]		←	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	→	X

Abbreviations: D or d, day; ECG, electrocardiogram; ET, Early Termination; F/up, follow-up; h, hour; min, minutes; NRS-A, Numeric Rating Scale with activity; NRS-R, Numeric Rating Scale at rest; OR, operating room; PK, pharmacokinetic; Preop, preoperative assessments; WOCBP, women of childbearing potential.

* The start of HTX-011 administration will be considered as Time 0 for all efficacy, safety, and PK assessments for HTX-011 with or without aprepitant. For Cohorts 2 and 4, the start of aprepitant administration will be considered Time 0 for aprepitant alone safety and PK 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 Numeric Rating Scale (NRS) pain intensity assessments coincide, the NRS pain intensity assessments should be conducted before the blood draw. See Section 6 for more information on study procedures and assessments.

[a] Subjects who withdraw from the study will be asked to complete Early Termination procedures based on the timing of withdrawal (ie, prior to 72 hours, prior to the Day 28 Visit, or after the Day 28 Visit and prior to the Safety Follow-Up Visit on Day 42).

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

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

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

[e] Subjects in Cohorts 2 and 4 will be administered 3 single doses of aprepitant orally: approximately 3 hours presurgery on Day 1 (125 mg) and at approximately 24 hours (Day 2) and approximately 48 hours (Day 3) after the presurgery dose (80 mg at each of the 2 timepoints).

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

[g] Postoperatively and upon discharge, subjects in Cohort 3 and 4 will be administered the following scheduled analgesic regimen: 600 mg oral ibuprofen every 6 hours as needed (PRN) as first-line therapy before acetaminophen, and 1g oral acetaminophen ibuprofen every 6 hours PRN as second-line therapy through Day 28.

[h] NRS-R should be assessed while the subject is 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-R should be completed prior to the NRS-A.

[i] If a subject requires rescue medication before the 1-hour 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 1-hour NRS-R and NRS-A assessments.

[j] Only if subject withdraws prior to Day 28.

[k] The prescribed activity for NRS-A is sitting with the plantar surface of the ball of the surgically attended foot touching the floor (no weight-bearing). NRS-R should be completed prior to the NRS-A.

[l] Sites must record if a subject is discharged with an opioid prescription (yes or no) in Cohorts 3 and 4.

[m] A presurgery blood sample for bupivacaine and meloxicam PK analysis will be collected from subjects in Cohort 3. Presurgery blood samples for bupivacaine, meloxicam, and aprepitant PK analysis will be collected from subjects in Cohorts 2 and 4 at approximately 2, 2.5, and 3 hours following the presurgery dose of aprepitant 125 mg.

[n] Subjects in Cohorts 3 and 4 will complete a daily diary from 72 hours through Day 28 to record if they take any opioid medication. Subject diary results will be reviewed at the Day 7 and Day 28 Visits. If a subject recorded "yes" for taking an opioid, sites must record the medication on concomitant medication electronic Case Report Form (eCRF).

[o] At the Screening Visit, ensure subject is not taking any prohibited medications. Record all medications taken from the time the subject signs the Informed Consent Form (ICF) through the Safety Follow-Up on Day 42.

[p] Adverse events will be collected from the time the subject signs the ICF through the Safety Follow-Up Visit on Day 42.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
AUC	Area under the curve
BMI	Body mass index
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CINV	Chemotherapy induced nausea and vomiting
C_{max}	Maximum observed plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
COX-2	Cyclooxygenase-2
CV	Cardiovascular
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPP	Good Publication Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
h	Hour(s)
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous(ly)
LAST	Local Anesthetic Systemic Toxicity

LOCF	Last observation carried forward
min	Minute
NK_1	Neurokinin-1
NRS	Numeric Rating Scale
NRS-A	NRS scores with activity
NRS-R	NRS scores at rest
NSAID	Nonsteroidal anti-inflammatory drug
ORAE	Opioid-related adverse event
PACU	Postanesthesia care unit
PK	Pharmacokinetic(s)
PO	By mouth, orally
PONV	Postoperative nausea and vomiting
PRN	As needed
QTcF	QT correction Fridercia's formula
REB	Research Ethics Board
SAE	Serious adverse event
SAR	Serious adverse reaction
SD	Standard deviation
SE	Standard error
SNRI	Selective norepinephrine reuptake inhibitor
SOP	Standard operating procedure
SSRI	Selective serotonin reuptake inhibitor
TEAE	Treatment-emergent adverse event
TEG-POE	Tri(ethylene glycol) poly(orthoester)
T_{max}	Time to maximum plasma concentration
ULN	Upper limit of normal
US	United States
WOCF	Worst observation carried forward
wWOCF	Windowed worst observation carried forward

1. INTRODUCTION

1.1. Background Information and Study Rationale

Up to 70% of patients have moderate to severe pain after surgery, and the most severe pain occurs within the first 72 hours (Lynch 1997; Svensson 2000; Apfelbaum 2003; Gan 2014; Misiolek 2014; Singla 2014; Meissner 2015). Administering a local anesthetic (eg, bupivacaine, ropivacaine, or levobupivacaine) is a relatively simple and safe means of providing postoperative pain relief. A major limitation of current local anesthetics is their short duration of effect (6 to 12 hours following surgery) (Kehlet 2011). Consequently, many patients are given opioids for pain management. The requirement for opioids postoperatively is a serious manifestation of ineffective pain relief. Exposure to opioids can lead to opioid-related adverse events (ORAEs) resulting in worse patient outcomes and increased hospital costs (Coley 2002; Wheeler 2002; Stephens 2003; Cashman 2004; Shirakami 2005; Jarzyna 2011; Ramachandran 2011; Chan 2013; Kessler 2013; Oderda 2013; Lee 2015; Lee 2016). Furthermore, transition from acute opioid use to chronic use can occur quickly. A recent review of a random sample of records from patients who had at least 1 opioid prescription between 2006 and 2015 showed that the probability of chronic opioid use begins to increase after the third day supplied and rises rapidly thereafter (Shah 2017). The United States (US) is facing a national opioid crisis that has led to a public health epidemic with multiple national and state responses. In 2015, 2 million Americans had a substance use disorder involving prescription pain relievers, and over 20,000 accidental overdose deaths were related to prescription pain relievers (Bose 2016; Rudd 2016). Reduced exposure to opioids and better pain management is associated with improved patient outcomes and reduced risk for the development of persistent pain and consequent opioid abuse (Barnett 2017). Therefore, there is a medical need for clinical alternatives to prescription opioids to manage ambulatory nonmalignant pain. The development of an extended-release local anesthetic applicable for a broad range of surgeries that could significantly reduce both pain and opioid use after surgery and can be easily administered with a favorable safety profile would address an important public health need.

Heron Therapeutics, Inc. (Heron) is developing HTX-011 for application into the surgical site to reduce postoperative pain for up to 72 hours and the need for opioid analgesics. HTX-011 is a novel, extended-release (also referred to as prolonged-release), fixed-dose combination product that contains bupivacaine and low-dose meloxicam. Bupivacaine is the disease-active ingredient and meloxicam enhances the effectiveness of bupivacaine. HTX-011 is a solution that is formulated in a proprietary tri(ethylene glycol)-based poly(orthoester) polymer (TEG-POE), termed Biochronomer®. HTX-011 is administered as a single dose that is applied into the surgical site to coat the affected tissues that could result in pain generation. Unlike other local anesthetics, HTX-011 is not injected; it is applied without a needle using a syringe with an applicator attached. After administration, the polymer enables extended release of bupivacaine and meloxicam simultaneously for approximately 3 days.

Both bupivacaine and meloxicam are approved in the US, Europe, and other regions, and have a long history of clinical use. Bupivacaine is an amide-type local anesthetic and meloxicam is a nonsteroidal anti-inflammatory drug (NSAID). Inclusion of low-dose meloxicam in HTX-011 reduces local inflammation caused by surgery and normalizes the local pH. This is believed to

result in enhanced penetration of bupivacaine into the nerves, thereby potentiating its analgesic effect. Bupivacaine is commercially available as a solution for injection and is approved for surgical anesthesia and for acute pain management (nerve block) in adults and children (MARCAINE, SENSORCAINE®, and VIVACAINE™). Meloxicam is available as an oral tablet that is approved for the relief of signs and symptoms of osteoarthritis, relief of signs and symptoms of rheumatoid arthritis and relief of the signs and symptoms of pauciarticular or polyarticular course Juvenile Rheumatoid Arthritis in patients who weigh ≥60 kg.

This Phase 2 open-label study will evaluate the analgesic efficacy, safety, and pharmacokinetics (PK) of a single, individualized dose of HTX-011 administered into the surgical site as a monotherapy or with other medications to enhance analgesia in subjects undergoing a primary unilateral bunionectomy. The study will include up to 4 cohorts.

Cohort 1 will evaluate HTX-011 as a monotherapy. Cohort 2 will evaluate HTX-011 and a 3-day regimen of aprepitant. Aprepitant is approved in the US and many other countries in the world for chemotherapy induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV). In the US, it is commercially available as oral capsules, an oral solution, and an injectable emulsion for intravenous (IV) use. Aprepitant exerts its effects by blocking substance P activity on the neurokinin-1 (NK_1) receptor. Substance P is involved in a vast array of processes other than emesis including pain, anxiety, depression, and inflammation (Patel 2003). The use of aprepitant as an adjuvant to existing analgesics has shown some promising results (Kakuta 2011; Moon 2014).

Cohort 3 will evaluate HTX-011 as part of a multimodal analgesic regimen of ibuprofen and acetaminophen. The American Pain Society guidelines recommend the use of multimodal analgesia for the treatment of postoperative pain (Kehlet 1993; Kehlet 2006; Krenzel 2009; Garimella 2013; Chou 2016). Multimodal analgesia is defined as the use of a variety of analgesic medication and techniques that target different mechanisms of action in the peripheral and/or central nervous system. These medications and techniques can also be combined with nonpharmacological interventions and may have additive or synergistic effects and more effective pain relief compared with single modality interventions. The goal of this approach is to provide improved pain control while reducing or eliminating the need for opioids.

An optional Cohort 4 will evaluate HTX-011 as part of a multimodal analgesic regimen of ibuprofen and acetaminophen and with a 3-day regimen of aprepitant.

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

This study in subjects undergoing a simple unilateral bunionectomy is designed to evaluate the safety and effectiveness of HTX-011 using an individualized dose, as tested in the completed Human Factor Validation Study for HTX-011, rather than a fixed dose. Bunionectomy is a bony surgical model that has shown good assay sensitivity for approximately 72 hours after the surgical insult (Singla 2014), which allows for analysis of acute analgesia over an extended period of time.

The study includes 4 cohorts. In each cohort, a single dose of HTX-011 will be evaluated in this study of no more than 2.1 mL (up to 60 mg/1.8 mg [bupivacaine/meloxicam doses]) administered via instillation (ie, application into the surgical site). Subjects in Cohort 2 and optional Cohort 4 will also receive 3 single doses of aprepitant orally: approximately 3 hours

presurgery on Day 1 (125 mg) and at approximately 24 hours (Day 2) and 48 hours (Day 3) after the presurgery dose (80 mg at each timepoint). Subjects in Cohort 3 and optional Cohort 4 will receive a scheduled postoperative multimodal analgesic regimen consisting of ibuprofen and acetaminophen.

In a previous Phase 2, dose finding study in bunionectomy (Study 208) that evaluated doses ranging from 30 mg/0.9 mg to 200 mg/6 mg administered via different local administration techniques (injection, injection using a Mayo block, instillation), the 30 mg/0.9 mg dose administered via injection was determined to be the minimally effective dose; however, 60 mg/1.8 mg administered via instillation was selected for Phase 3 based on superior postoperative analgesia through 72 hours with a favorable safety profile. The incidence of local inflammatory treatment-emergent adverse events (TEAEs) appeared to be dose dependent with a higher incidence for HTX-011 120 mg/3.6 mg, and 200 mg/6 mg doses compared with bupivacaine HCl.

In Phase 3, HTX-011 60 mg/1.8 mg provided superior, sustained pain relief and less need for opioids, with fewer subjects experiencing severe pain, more subjects who were opioid-free, and fewer subjects who experienced ORAEs over 72 hours compared with bupivacaine HCl (standard of care) and saline placebo. The overall safety profile of HTX-011 was similar to the well-established safety profile of bupivacaine HCl. The proportion of subjects with any wound healing symptom was similar across all treatment groups; however, there was a small increase in the incidence of local inflammatory TEAEs in the HTX-011 group.

In both Phase 2 (Study 208) and Phase 3 (Study 301) studies, the full dose of HTX-011 of 60 mg/1.8 mg (2.1 mL) was required to be administered into the surgical site. Surgeons performing the surgeries noted that HTX-011 drug product was expressed from the surgical site at closure in some subjects. Despite some product being expressed from the surgical site with the HTX-011 60 mg/1.8 mg dose given by instillation, efficacy was demonstrated in both Phase 2 and Phase 3. Since the excess volume of HTX-011 expressed from the surgical site cannot contribute to efficacy and may cause some of the local irritation observed in patients, the volume of HTX-011 should be individualized up to 60 mg/1.8 mg (ie, no more than 2.1 mL) for each subject undergoing bunionectomy using a sufficient amount to coat the tissues without expressing excess from the surgical site during closure. This individualized approach to dosing was tested in a completed Human Factors Validation Study for HTX-011 and is also consistent with the planned package insert instructions for use of HTX-011 once commercially available.

Aprepitant is often used in the surgical setting to prevent PONV. Single oral doses of 40 mg and 125 mg of aprepitant were studied in 2 large Phase 3 multicenter, randomized, double-blind controlled trials in patients undergoing open abdominal surgery to support registration for PONV (Diemunsch 2007; Gan 2007). In these studies the 40 mg dose was more effective at preventing PONV and is the approved dose; however, the 125 mg dose that was administered to a total of 525 patients across the 2 studies was well-tolerated with a similar safety profile to the 40 mg dose. The most commonly reported AEs across the studies were consistent and typical of surgical patients and included bradycardia, pyrexia, constipation, headache, pruritus, and nausea.

The nociception system uses numerous transmitter substances in parallel and its sensitivity is adjusted in response to tissue injury; therefore, the use of an NK_1 receptor antagonist as an adjuvant to existing analgesics could provide more promising results (Hill 2000).The initial clinical studies investigating NK_1 receptor antagonists for pain management performed in

subjects undergoing molar extraction were encouraging, but subsequent studies in peripheral neuropathy, osteoarthritis, and migraine were less promising (Rupniak 1999). Two recent studies of aprepitant in PONV in subjects undergoing laparoscopic gynaecologic surgery evaluated pain intensity and analgesic use at single doses of 40 mg and 80 mg. In a double-blind, randomized clinical study, IV fentanyl administration using patient-controlled analgesia was significantly lower 24 hours after surgery in subjects who received a single oral 40 mg dose of aprepitant than in subjects who received a single IV dose of palonosetron, although there was no significant difference in pain intensity (Moon 2014). These results were similar to that of an earlier study in which the rescue analgesic requirement was lower for subjects who received a single oral 80 mg dose of aprepitant preoperatively compared with a no treatment control despite no effect on pain intensity (Kakuta 2011).

The approved dose regimen of oral aprepitant for CINV prevention is a 3-day regimen with 125 mg given on Day 1, followed by 80 mg on Days 2 and 3 (EMEND Oral USPI May 2017). Due to the inconsistent effects on pain reduction in prior studies that utilized a single dose of aprepitant at doses of 40 mg and 80 mg, this study will include the approved 3-day dosing regimen to examine the potential added benefit of aprepitant in the reduction in pain and use of opioids observed with HTX-011 alone.

Acetaminophen and ibuprofen (an NSAID) were selected for the scheduled multimodal regimen in this study using doses consistent with the prescribing information for each medication. Both are commonly used analgesics with a long history of use and relatively few side effects. These pain medications are frequently given as part of multimodal therapy for pain management following foot and ankle surgery (Halaszynski 2016; Kohring 2017), and a review of the literature showed that combining acetaminophen with NSAIDs reduced acute postoperative pain better than either medication alone (Ong 2010).

No control group is included in this study because the efficacy and safety of HTX-011 in bunionectomy was demonstrated in the prior Phase 2 and Phase 3 studies, Study 208 and Study 301, respectively. Local inflammatory TEAEs and wound healing assessments will be evaluated using the same methods as in Study 301. The main efficacy endpoints for this study are the same as included in Study 301 to permit cross-study comparisons. The primary endpoint is mean area under the curve (AUC) of the Numeric Rating Scale of pain intensity scores with activity (NRS-A) through 72 hours (AUC_{0-72}) for HTX-011. It was selected based on FDA and Committee for Medicinal Products for Human Use (CHMP) guidance as well as regulatory precedent. Draft FDA Guidance for Industry on *Analgesic Indications: Developing Drug and Biological Products* (February 2014) states that "pain intensity is the fundamental measure that defines the efficacy of an analgesic drug."

1.3. Potential Risks and Benefits

For more information on HTX-011, refer to the Investigator's Brochure (IB). For more information on the active ingredients, bupivacaine and meloxicam, refer to the US prescribing information for MARCAINE and MOBIC, respectively. For information on aprepitant, refer to the US prescribing information for aprepitant capsules. The Investigator should also refer to the respective US prescribing information for information on risks associated with the required concomitant medications or rescue medications.

1.3.1. HTX-011

As of July 2018, a total of 1077 subjects had received a single dose of the intended commercial formulation of HTX-011 in 8 clinical studies. The numbers of subjects exposed to HTX-011 by study phase include 10 in one Phase 1 study, 430 in three Phase 2a studies, 317 in two Phase 2b studies, and 320 in two Phase 3 studies.

The potential risks and benefits of the intended commercial formulation of HTX-011 are described for all clinical studies, including the 2 studies in which subjects underwent bunionectomy (Study 208 and Study 301).

Safety

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

Safety data from subjects who received HTX-011 via instillation into the surgical site in the two Phase 2b studies in total knee arthroplasty (TKA; Study 209) and augmentation mammoplasty (Study 211), and from the two Phase 3 studies in bunionectomy (Study 301) and herniorrhaphy (Study 302) were integrated for analysis. Results from these studies revealed that the safety profile of a single dose of HTX-011 was similar to the well-established safety profile of bupivacaine HCl, but without the risk of injection-related high plasma concentrations and resulting toxicities. Specifically, the incidences of any TEAE and of any study drug-related TEAE were similar for the total HTX-011 group (60 mg/1.8 mg to 400 mg/12 mg doses combined) compared with active and placebo controls (ie, the total bupivacaine HCl group [50 mg to 125 mg doses combined] and the saline placebo group, respectively), and there were no dose-dependent trends in the individual HTX-011 dose groups. The most common TEAEs were nausea, constipation, dizziness, vomiting, and headache. The incidences were generally similar for HTX-011 compared with the controls, and there was no apparent dose-dependent trend in the HTX-011 dose groups. The majority of TEAEs were mild or moderate in severity. The incidence of severe TEAEs was low and similar across all treatment groups, as well as the individual HTX-011 dose groups. The incidences of SAEs were low (1.8% to 2.2%) for the integrated treatment groups, with the highest incidences reported in the HTX-011 400 mg/12 mg (3.7%) and bupivacaine HCl 125 mg group (4.6%). No deaths were reported for subjects who received HTX-011.

The incidences of ORAEs were similar for the total HTX-011 and control groups (50.5% to 55.5%), and there was no apparent dose-dependent trend in the HTX-011 dose groups. However, the incidences were higher for HTX-011 200 mg/6 mg and 400 mg/12 mg and bupivacaine HCl 125 mg. All except for 5 subjects administered these doses received at least 1 opioid rescue medication during the 72-hour postoperative period.

There were no clinically meaningful differences in laboratory results, vital sign measurements, physical examination findings, or electrocardiogram (ECG) findings.

There was no evidence of Local Anesthetic System Toxicity (LAST) based on a review of potential LAST-related TEAEs, vital signs, ECGs, and bupivacaine plasma concentrations. The incidence of local inflammatory TEAEs was similar for the total HTX-011 group and comparators; however, the incidences were higher for the HTX-011 60 mg/1.8 mg and bupivacaine HCl 50 mg groups, which were the doses used in the Phase 3 bunionectomy study (Study 301). Finally, there were no clinically meaningful differences among treatment groups in assessments of wound healing or bone healing (Study 301).

Serious Adverse Reactions

As of 30 May 2018, a total of 3 SARs (SAEs considered related to study drug by the Investigator and/or the Sponsor) have been reported in 3 subjects who received the intended commercial formulation of HTX-011. One SAR of severe impaired healing was reported in a subject who received HTX-011 200 mg/6 mg via injection using a Mayo block in the bunionectomy study (Study 208), 1 SAR of mild wound dehiscence was reported in a subject who received HTX-011 300 mg/9 mg via combination (injection and instillation) administration technique in the abdominoplasty study (Study 203), and 1 SAR of moderate post procedural cellulitis was reported in a subject who received HTX-011 400 mg/12 mg instillation + 50 mg ropivacaine in the TKA study (Study 209). All 3 SARs resolved; the 1 SAR of impaired healing resolved with sequelae.

Efficacy

A precedent Phase 2a formulation-, dose-, and administration technique-finding study was conducted in bunionectomy (Study 208). The study evaluated 4 HTX-011 doses (30 mg/0.9 mg, 60 mg/1.8 mg, 120 mg/3.6 mg, and 200 mg/6 mg) administered into the surgical site via different administration techniques (injection, injection using a Mayo block, or instillation [with or without a Luer lock applicator]). All subjects also received a 1% lidocaine Mayo block just prior to the start of surgery for intraoperative pain control. HTX-011 60 mg/1.8 mg (the Phase 3 dose) administered via instillation significantly reduced the mean area under the curve from Time 0 through 72 hours (AUC_{0-72}) of Numeric Rating Scale (NRS) pain intensity scores compared with saline placebo and bupivacaine HCl controls (p=0.0128 and p=0.0083, respectively) and significantly reduced the mean total opioid consumption through 72 hours compared with both controls (p=0.0392 and p=0.0267, respectively). In addition, a higher proportion of HTX-011-treated subjects were opioid-free for 72 hours compared with both controls (17.6% vs 5.6% and 10.0%, respectively), but the differences were not statistically significant.

In the adequate and well-controlled Cohort 2 of the Phase 2b TKA study (Study 209), a bony surgical model, HTX-011 400 mg/12 mg administered with or without low-dose ropivacaine significantly reduced pain over 48 and 72 hours compared with saline placebo. In addition, HTX-011 + low-dose ropivacaine significantly reduced pain over 48 and 72 hours compared

with bupivacaine HCl. Furthermore, fewer subjects in the HTX-011 alone group and significantly fewer subjects in the HTX-011 + low-dose ropivacaine group experienced severe pain (NRS of pain intensity score at rest [NRS-R] score ≥7) at any timepoint through 72 hours compared with saline placebo and bupivacaine HCl. Finally, total opioid consumption was lower for HTX-011 and significantly lower for HTX-011 + low dose ropivacaine compared with saline placebo and bupivacaine HCl over 48 and 72 hours.

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

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

Risks

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

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

Potential risks for meloxicam include CV adverse reactions, gastrointestinal bleeding, and liver tests elevations (MOBIC Tablets USPI 2016). NSAIDs may cause an increased risk of serious CV thrombotic events, myocardial infarction, and stroke, which can be fatal, and this risk may increase with duration of use. Patients with known CV disease or risk factors for CV disease may be at greater risk. NSAIDs may also cause an increased risk of serious gastrointestinal adverse events (AEs) including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach or intestines, which can be fatal. Elderly patients are at greater risk for serious gastrointestinal events. Borderline elevations of 1 or more liver tests may occur in patients taking NSAIDs, including meloxicam, which may worsen. It is unclear how applicable these potential risks are for meloxicam when given as single dose via application into the surgical site (a novel administration method for meloxicam) for postoperative pain as part of a fixed-ratio combination

(eg, HTX-011). Any subject in this study with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction.

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

1.3.2. Aprepitant

Potential benefits of aprepitant for postoperative pain based on the published literature are described in Section 1.2.

Potential risks for aprepitant include clinically significant CYP3A4 drug interactions, a decrease in International Normalized Ratio (INR) with concomitant warfarin, risk of reduced efficacy of hormonal contraceptives, and hypersensitivity including anaphylactic reactions have been reported (EMEND Oral USPI May 2017). Aprepitant is contraindicated in patients with hypersensitivity to aprepitant or any component of the capsules and in patients taking pimozide due to inhibition of CYP3A4 by aprepitant that could result in elevated plasma concentrations potentially causing serious or life-threatening reactions, such as QT prolongation (a known adverse reaction of pimozide). INR must be monitored in patients on chronic warfarin therapy for 2 weeks following initiation of the 3-day regimen of aprepitant. Upon coadministration with aprepitant, the efficacy of hormonal contraceptives may be reduced during administration of and for 30 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. Although very rare, Stevens-Johnson syndrome has been reported in a patient receiving the aprepitant regimen with cancer chemotherapy (EMEND Oral USPI May 2017). The most common adverse reactions reported for aprepitant given as a 3-day regimen (125 mg on day 1 and 80 mg on days 2 and 3) in patients receiving emetogenic chemotherapy included fatigue, diarrhea, asthenia, dyspepsia, abdominal pain, hiccups, white blood cell count decreased, dehydration, and alanine aminotransferase increased (EMEND Oral USPI May 2017).

2. STUDY OBJECTIVES

2.1. Primary Objectives

The primary objectives are as follows:

- To assess the efficacy and duration of analgesia, following a single individualized dose of HTX-011, during the first 72 hours after unilateral simple bunionectomy.
- To assess the analgesic efficacy following a 3-day regimen of oral aprepitant and a single individualized dose of HTX-011 during the first 72 hours after unilateral simple bunionectomy (Cohort 2).
- To assess the analgesic efficacy following a single individualized dose of HTX-011 as part of a multimodal analgesic regimen during the first 72 hours after unilateral simple bunionectomy (Cohort 3).
- To assess the analgesic efficacy following a 3-day regimen of oral aprepitant and a single individualized dose of HTX-011 as part of a multimodal analgesic regimen during the first 72 hours after unilateral simple bunionectomy (optional Cohort 4).

2.2. Secondary Objectives

The secondary objectives are as follows:

- To assess the effect of study treatment on opioid load during the first 72 hours following surgery in this study population.
- To assess the proportion of subjects who are opioid-free after receiving HTX-011 as part of a multimodal analgesic regimen during the first 72 hours in this study population (Cohort 3 and optional Cohort 4).
- To assess the proportion of subjects who are opioid-free after receiving HTX-011 as part of a multimodal analgesic regimen during the first 72 hours with or without aprepitant and who remain opioid-free through Day 10 and Day 28 (Cohort 3 and optional Cohort 4).
- To assess the safety and tolerability of study treatment in this study population.
- To confirm the PK parameters of bupivacaine and meloxicam for a single individualized dose of HTX-011 in this study population.
- To analyze the PK parameters of aprepitant in the presence of HTX-011 in this study population (Cohort 2 and optional Cohort 4).

3. INVESTIGATIONAL PLAN AND ENDPOINTS

3.1. Description of the Study Design

3.1.1. Overall Study Design

This is a Phase 2 open-label, multi-cohort study to evaluate the analgesic efficacy, safety, and PK of a single, individualized dose of HTX-011 administered into the surgical site as a monotherapy or with other medications to enhance analgesia in subjects undergoing unilateral simple bunionectomy. The study will include up to 4 cohorts, which will be conducted sequentially (Table 1). Subjects in all cohorts will receive HTX-011. Cohort 2 will also include administration of oral aprepitant on Days 1 through 3. Cohort 3 and optional Cohort 4 will include a scheduled multimodal analgesic regimen during the 72-hour postoperative period. Optional Cohort 4 will also include oral aprepitant on Days 1 through 3.

Table 1: Overview of Treatment by Study Cohort

Treatment	Cohort			
	1	2	3	4[a]
HTX-011	√	√	√	√
Oral aprepitant[b]		√		√
Multimodal analgesic regimen[c]			√	√

[a] Optional cohort.
[b] Days 1 through 3.
[c] During the 72-hour postoperative period.

All subjects will be screened within 28 days prior to surgery. Subjects who meet the Screening eligibility criteria will be included. Verification that subjects continue to meet the eligibility criteria will be assessed on the day of surgery (Day 1). Eligible subjects will undergo a unilateral simple bunionectomy under regional anesthesia with no more than 20 mL of 1% lidocaine without epinephrine administered as a Mayo block. Epidural or spinal anesthesia is not permitted. During surgery, the use of IV fentanyl up to 4 µg/kg will be permitted for intraoperative pain control. Intraoperative administration of other opioids or other analgesics (including ketamine), local anesthetics, or anti-inflammatory agents (except as specified by the protocol) is prohibited, unless needed to treat an AE that occurs after signing the Informed Consent Form (ICF), for pretreatment prior to a needle placement, or to decrease venous irritation (eg, caused by propofol, in which case no more than a single administration of lidocaine 1% plain 20 mg IV may be administered).

3.1.1.1. Study Cohorts

3.1.1.1.1. Cohort 1

Approximately 30 subjects will be enrolled in Cohort 1. Near the completion of surgery and after irrigation and suction have been completed, a single individualized dose of HTX-011 of no more than 2.1 mL HTX-011 [up to 60 mg/1.8 mg (bupivacaine/meloxicam doses)] will be given

intraoperatively via application into the surgical site, as described in Section 5.5. The exact amount of HTX-011 instilled will be determined by the Investigator at the time of surgery.

Following surgery and immediate postoperative recovery, all subjects will be transferred to the postanesthesia care unit (PACU).

3.1.1.1.2. Cohort 2

Approximately 15 subjects will be enrolled in Cohort 2. Subjects will receive a single oral dose of aprepitant 125 mg approximately 3 hours prior to the start of surgery. Near the completion of surgery and after irrigation and suction have been completed, a single individualized dose of HTX-011 of no more than 2.1 mL HTX-011 [up to 60 mg/1.8 mg (bupivacaine/meloxicam doses)] will be given intraoperatively via application into the surgical site, as described in Section 5.5. The exact amount of HTX-011 instilled will be determined by the Investigator at the time of surgery.

Following surgery and immediate postoperative recovery, all subjects will be transferred to the PACU. Subjects will be administered a single oral dose of aprepitant 80 mg at approximately 24 hours (Day 2) and at approximately 48 hours (Day 3) after the presurgery dose of aprepitant.

3.1.1.1.3. Cohort 3

Approximately 30 subjects will be enrolled in Cohort 3. Near the completion of surgery and after irrigation and suction have been completed, a single dose of HTX-011 will be given intraoperatively via application into the surgical site. The dose is individualized for each subject, up to a maximum of 2.1 mL [up to 60 mg/1.8 mg (bupivacaine/meloxicam doses)]. The exact amount of HTX-011 instilled will be determined by the Investigator at the time of surgery.

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

3.1.1.1.4. Cohort 4 (Optional)

At the Sponsor's discretion upon completion of Cohort 3, Cohort 4 may be initiated. If initiated, approximately 15 subjects will be enrolled in Cohort 4. Subjects will receive a single oral dose of aprepitant 125 mg approximately 3 hours prior to the start of surgery. Near the completion of surgery and after irrigation and suction have been completed, a single dose of HTX-011 will be given intraoperatively via application into the surgical site. The dose is individualized for each subject, up to a maximum of 2.1 mL [up to 60 mg/1.8 mg (bupivacaine/meloxicam doses)]. The exact amount of HTX-011 instilled will be determined by the Investigator at the time of surgery.

Following surgery and immediate postoperative recovery, all subjects will be transferred to the PACU. Subjects will receive a scheduled postoperative analgesic regimen as follows: start with

600 mg oral ibuprofen once they are able to tolerate oral intake in the PACU, then 3 hours after the ibuprofen dose administer the first postoperative dose of 1 g oral acetaminophen, then alternate these 2 medications so a dose is delivered every 3 hours. (In other words, 3 hours after their first 600 mg oral ibuprofen dose, subjects will receive a 1 g oral acetaminophen dose, then after 3 more hours another 600 mg oral ibuprofen dose, and so on until the 72-hour postoperative period is complete.) In addition, subjects will be administered a single oral dose of aprepitant 80 mg at approximately 24 hours (Day 2) and at approximately 48 hours (Day 3) after the presurgery dose of aprepitant.

3.1.2. Postoperative Observation Period and Follow-Up

All subjects will remain in the hospital/research facility for a minimum of 72 hours after the start of study drug administration to undergo postoperative assessments. After the 72-hour assessments have been completed, subjects may be discharged. Subjects should be instructed at the time of discharge to leave the bandage clean, dry, and intact until the Day 7 visit. In addition, the subject should be provided with a cast guard to assist with keeping the bandage dry and instructed to contact the site if the bandage gets wet.

Subjects in Cohorts 3 and 4 (whether or not they were discharged with an opioid prescription) will receive a diary at discharge, which they will complete each day to record whether they take an opioid medication between 72 hours and Day 28.

All subjects will return to the study site on Days 7 and 28 to complete follow-up assessments. In addition, subjects will return for a Safety Follow-Up Visit on Day 42.

3.1.3. Postoperative Analgesic Medications

3.1.3.1. Rescue Medication During Inpatient 72-Hour Postoperative Period

Subjects should only receive rescue medication upon request for pain control, as needed, during the 72-hour postoperative observation period. Rescue medication should not be given for pain prophylaxis, but only for treating postoperative pain. Prior to the administration of the first dose of rescue medication, if the subject has not already had at least 1 postoperative pain score assessed, then a Numeric Rating Scale (NRS) score at rest (NRS-R) followed by a Numeric Rating Scale score with activity (NRS-A) pain score must be obtained.

Cohorts 1 and 2: Postoperative rescue medication will consist of oral immediate-release oxycodone (no more than 10 mg within a 4-hour period as needed), IV morphine (no more than 10 mg within a 2-hour period as needed), and/or oral acetaminophen (no more than 1 gram [1000 mg] in a 6-hour window). For subjects administered any acetaminophen-containing product, the total combined daily dose must not exceed 4 grams (4000 mg) as severe liver damage may occur. Combination products containing an opioid and non-opioid are not allowed. No other analgesic agents, including NSAIDs, are permitted during the 72-hour postoperative observation period.

Cohorts 3 and 4: Postoperative rescue medication will consist of oral immediate-release oxycodone (no more than 10 mg within a 4-hour period as needed) and/or IV morphine (no more than 10 mg within a 2-hour period as needed). Combination products containing an opioid and non-opioid are not allowed. With the exception of oral ibuprofen and oral acetaminophen, no

other analgesic agents, including NSAIDs, are permitted during the 72-hour postoperative observation period.

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

3.1.3.2. Postoperative Analgesia After Discharge

Cohorts 1 and 2: For subjects who are medically ready for discharge at 72 hours, oral acetaminophen (no more than 1000 mg every 6 hours as needed) should be recommended for postoperative pain. If a subject received 10 mg or more of oxycodone in the 12 hours prior to discharge, the subject should be provided with a prescription for immediate-release oxycodone (up to 10 mg orally [PO] q4h as needed).

Cohorts 3 and 4: Upon discharge, subjects will be instructed to manage pain with the following regimen:

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

If a subject received 10 mg or more of oxycodone in the 12 hours prior to discharge, the subject should be provided with a prescription for immediate-release oxycodone (up to 10 mg PO q4h as needed). Pharmacists should be instructed that substitutions with any other opioid-containing product are not permitted, including combination opioid/non-opioid products. Sites must record if a subject is discharged with an opioid prescription (yes or no) in Cohorts 3 and 4.

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

3.1.4. Pharmacokinetic Assessments

PK assessments will include the collection of blood samples for bupivacaine, meloxicam, and aprepitant PK analysis.

3.1.5. Efficacy and Safety Assessments

Efficacy assessments will include pain intensity scores using NRS-R and NRS-A, and use of opioid medication.

Safety assessments will include AE recording, physical examinations, vital signs, hematology and serum chemistry, and wound healing assessments.

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

3.2. Study Endpoints

3.2.1. Efficacy Endpoints

3.2.1.1. Primary Efficacy Endpoint

- Area under the curve (AUC) of the Numeric Rating Scale of pain intensity scores with activity (NRS-A) through 72 hours (AUC_{0-72}).

3.2.1.2. Secondary Efficacy Endpoints

- Total postoperative opioid consumption (in morphine equivalents) through 72 hours.
- Proportion of subjects who are opioid-free through 72 hours.
- AUC_{0-72} of the NRS-R pain intensity scores.
- Proportion of subjects who are opioid-free through 72 hours who remain opioid-free through Day 10 and Day 28 (Cohorts 3 and 4 only).

3.2.2. Safety Endpoints

- Incidence of TEAEs, SAEs, and ORAEs through the Safety Follow-Up on Day 42.
- Change from baseline in clinical laboratory results.
- Change from baseline in vital signs.
- Wound healing assessment at 72 hours, on Day 7 and Day 28, and at the Safety Follow-Up on Day 42.

3.2.3. Pharmacokinetic Endpoints

- The area under the plasma concentration-time curve from time zero to time t of the last measured concentration above the limit of quantification (AUC_{0-last}) (for bupivacaine and meloxicam only).
- The area under the plasma concentration-time curve from zero to infinity (AUC_{0-inf}) (for bupivacaine and meloxicam only).
- The maximum plasma concentration (C_{max}).
- Apparent total body clearance over bioavailability (Cl/F).
- Apparent total volume of distribution over bioavailability (V_Z/F).
- The time to reach maximum plasma concentration (T_{max}).
- The terminal elimination rate constant (λ_Z) with the respective half-life ($t_{½}$).

3.3. Study Duration

The overall duration of the study is anticipated to be approximately 7 months. The total duration of study participation for each subject (from Screening through the Safety Follow-Up on Day 42) will be up to 77 days.

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

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1. Study Population

Approximately 90 subjects will be enrolled in this study at up to approximately 2 study sites.

4.1.1. Inclusion Criteria

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

1. Is able to provide written informed consent, adhere to the study visit schedule, and complete all study assessments.
2. Is male or female, and ≥18 years of age at screening.
3. Is scheduled to undergo a primary unilateral, distal, first metatarsal bunionectomy with osteotomy and internal fixation under regional anesthesia.
4. Has an American Society of Anesthesiologists Physical Status of I, II, or III.
5. 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. For Cohorts 1 and 3, is surgically sterile; or is at least 2 years post-menopausal; or is in a monogamous relationship with a partner who is surgically sterile; or is practicing abstinence or agrees to use double-barrier contraception in the event of sexual activity; or is using an insertable, injectable, transdermal, or combination oral contraceptive approved by applicable regulatory authorities for greater than 2 months prior to screening and commits to the use of an acceptable form of birth control for the duration of the study and for 30 days after study drug administration. Note: women in only a same-sex relationship do not need to meet this criterion.
    e. For Cohorts 2 and 4, is surgically sterile; or is at least 2 years post-menopausal; or is in a monogamous relationship with a partner who is surgically sterile; or is practicing abstinence or agrees to use double-barrier contraception or a non-hormonal intra-uterine device (eg, copper) in the event of sexual activity for greater than 2 months prior to screening, for the duration of the study and for 30 days after last study drug administration. Notes: Women in only a same-sex relationship do not need to meet this criterion. Hormonal contraceptives are not an acceptable form of birth control since the efficacy of hormonal contraceptives may be reduced with aprepitant.

4.1.2. Exclusion Criteria

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

1. Has 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).

3. Has a pre-existing concurrent acute or chronic painful physical/restrictive condition expected to require analgesic treatment in the postoperative period for pain that is not strictly related to the bunionectomy and which may confound the postoperative assessments.
4. Has a contraindication or a known or suspected history of hypersensitivity or clinically significant idiosyncratic reaction to bupivacaine (or other local anesthetics), meloxicam (or other NSAIDs), oxycodone, morphine, acetaminophen, aprepitant (Cohorts 2 and 4 only), or ibuprofen (Cohorts 3 and 4 only).
5. Has known or suspected daily use of opioids for 7 or more consecutive days within the previous 6 months.
6. Has taken any NSAIDs (including meloxicam) within at least 10 days prior to the scheduled surgery with the exception of subjects on low dose (≤100 mg) daily acetylsalicylic acid for cardioprotection.
7. Has taken long-acting opioids within 3 days prior to the scheduled surgery.
8. Has taken any opioids within 24 hours prior to the scheduled surgery.
9. Has been administered bupivacaine within 5 days prior to the scheduled surgery.
10. For Cohorts 2 and 4 only, has been administered aprepitant or another NK_1 receptor antagonist such as rolapitant, netupitant, or fosaprepitant within 5 days prior to the scheduled surgery.
11. Has been administered any local anesthetic within 72 hours prior to the scheduled surgery, other than for pretreatment prior to a needle placement, to treat an AE that occurs after signing the ICF, or to decrease venous irritation (eg, caused by propofol, in which case no more than a single administration of lidocaine 1% plain 20 mg IV may be administered).
12. Has initiated treatment with any of the following medications within 1 month prior to study drug administration **or** is taking any of these medications to control pain: selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin, or cyclooxygenase-2 (COX-2) inhibitors. (Note: If a subject is taking one of these medications for a reason other than pain control, the subject must be on a stable scheduled dose [ie, not "as needed"] for at least 1 month prior to study drug administration.) Anxiolytics prior to surgery are permitted, if necessary.
13. Has been administered systemic steroids within 5 half-lives or 10 days prior to administration of study drug (whichever is longer).
14. Has a medical condition such that, in the opinion of the Investigator, participating in the study would pose a health risk to the subject or confound the postoperative assessments. Conditions may include, but are not limited to, any of the following:
    a. History of clinically significant cardiac abnormality such as myocardial infarction within 6 months prior to signing the ICF, New York Heart Association class III or IV, or clinically significant abnormalities in cardiac function or on ECG (including but not limited to a PR interval >200 msec, a QT corrected by Fridericia's formula [QTcF] >480 msec, or 3rd degree heart block).

b. History of coronary artery bypass graft surgery within 12 months prior to signing the ICF.
c. History of severe liver function impairment as defined by Child-Pugh Class C, having an aspartate aminotransferase >3 × the upper limit of normal (ULN), or having an alanine aminotransferase >3 × ULN.
d. History of severe kidney function impairment as defined by creatinine clearance (Cockcroft-Gault) <30 mL/min, being on dialysis, and/or having a serum creatinine >2 × ULN.
e. History of known or suspected coagulopathy or uncontrolled anticoagulation (platelet count <100,000/μL, hemoglobin <12 g/dL, or hematocrit <35%).
f. Loss of sensation in extremities or significant peripheral neuropathy.

15. As per subject history and/or medical records, has active infection or is currently undergoing treatment for Hepatitis B, Hepatitis C, or human immunodeficiency virus (HIV).
16. Has uncontrolled anxiety, psychiatric, or neurological disorder that, in the opinion of the Investigator, might interfere with study assessments.
17. For Cohorts 2 and 4 only, is receiving 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).
18. 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.
19. Has a known or suspected history of drug abuse, a positive urine drug screen on the day of surgery, or a recent history of alcohol abuse (ie, within 10 years). 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 taking medical or recreational marijuana are not allowed to participate in the study.
20. Previously participated in an HTX-011 study.
21. Received an investigational product or device in a clinical trial within 30 days or within 5 elimination half-lives (whichever is longer) prior to surgery, or is planning to take part in another clinical trial while participating in this study.
22. Has undergone 3 or more surgeries within 12 months prior to signing the ICF, other than for diagnostic procedures (eg, colonoscopy).
23. Has a body mass index (BMI) >39 kg/m^2.

4.2. Method of Assigning Subjects to Treatment Groups

The study is not randomized. All eligible subjects will be enrolled into 1 of 4 cohorts. Cohorts 1 through 4 will be conducted sequentially.

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: HTX-011 (all subjects) or aprepitant (Cohorts 2 and 4).

Subjects who meet the Screening eligibility criteria, but who do not meet the eligibility criteria on Day 1 will be withdrawn from the study without receiving study drug. In the event a subject does not meet the eligibility criteria, but receives study drug, HTX-011 (all subjects) or aprepitant (Cohorts 2 and 4), 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. Subject Withdrawal and Replacement

4.3.1. Subject Withdrawal

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

Possible reasons for early withdrawal include the following:

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

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

4.3.2. Subject Replacement

Subjects who withdraw from study will not be replaced. To account for withdrawal of subjects who are ineligible at Day 1, enrollment will continue until at least 30 subjects have been dosed in Cohort 1, 15 subjects in Cohort 2, 30 subjects in Cohort 3, and 15 subjects in optional Cohort 4.

5. STUDY TREATMENT

Study drug is defined as HTX-011 (investigational product) and aprepitant capsules (investigational use of a marketed product). HTX-011 and aprepitant capsules will be supplied by the Sponsor.

Study sites will supply other required concomitant medications (eg, ibuprofen and acetaminophen for Cohorts 3 and 4) as well as rescue medications during the 72-hour postoperative period (all cohorts, as needed [Section 3.1.3.1]).

5.1. Description of Investigational Products

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

Aprepitant capsules for oral administration contain either 80 mg or 125 mg of aprepitant and the following inactive ingredients: sucrose, microcrystalline cellulose, hydroxypropyl cellulose and sodium lauryl sulfate. The capsule shell excipients are gelatin, titanium dioxide, and may contain sodium lauryl sulfate and silicon dioxide. The 125-mg capsule also contains red ferric oxide and yellow ferric oxide.

5.2. Manufacturing, Packaging, and Labeling

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

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

Aprepitant capsules will be provided as a commercial pack containing one 125 mg capsule and two 80 mg capsules and labeled for investigational use in compliance with all applicable national and local laws and regulations.

5.3. Storage

At the study site, HTX-011 should be stored at a controlled room temperature of 20 to 25°C (with excursions permitted from 15 to 30°C). The room should be locked with restricted access. A temperature log must be maintained to monitor the room's temperature.

Aprepitant capsules should be stored according to the US prescribing information.

5.4. Preparation

Study drug will be prepared at the study site. HTX-011 will be prepared in a group of syringes without a needle. Refer to the Instructions for Use (IFU) and the Pharmacy Manual for details on HTX-011 preparation. Refer to the US prescribing information for aprepitant capsules.

5.5. Study Drug Administration

HTX-011 will be given via application into the surgical wound prior to wound closure, after final irrigation and suction of each layer are complete. Refer to the IFU for details on HTX-011 administration.

HTX-011 will be administered via instillation (ie, application into the surgical site) using a syringe and a Luer lock applicator supplied by the Sponsor. A single dose of no more than 2.1 mL HTX-011 [up to 60 mg/1.8 mg (bupivacaine/meloxicam doses)] will be applied without a needle into the surgical site using a Luer lock applicator to coat the tissues within the surgical site that could result in pain generation. Application of HTX-011 should follow final irrigation and suction prior to suturing. A sufficient amount should be used to coat the tissues, ensuring there is not an excess that could be expressed from the site during closure. HTX-011 should be applied only to the tissue layers below the skin incision and not directly onto the skin.

Thereafter, skin closure will commence to complete the surgical procedure (ie, there should be no betadine wash until after skin closure at the end of the case). When using monofilament sutures, 3 or more knots are recommended as contact with HTX-011 may cause a single knot to loosen or untie.

In Cohorts 2 and 4 only, subjects should be administered 3 single oral doses of aprepitant: approximately 3 hours presurgery on Day 1 (125 mg) and at approximately 24 hours (Day 2) and 48 hours (Day 3) after the presurgery dose (80 mg at each timepoint).

5.6. Study Drug Compliance

Because HTX-011 is being administered as a component of the surgical procedure, a lack of treatment compliance is not expected. Aprepitant capsules are being administered when the subjects are inpatient; therefore, a lack of treatment compliance is also not expected for aprepitant.

For HTX-011, after preparing the syringe and before administration, the amount of HTX-011 withdrawn into the syringe (to the nearest tenth of 1 mL) and the weight of the syringe (to the nearest tenth of a gram) will be recorded in the CRF. After administering HTX-011, the amount remaining in the syringe and the weight of the syringe will also be recorded in the eCRF.

5.7. Study Drug Accountability

The study drugs provided for this study (HTX-011 and aprepitant capsules) will be used only as directed in the study protocol. In accordance with Good Clinical Practice (GCP), Investigators are required to maintain accurate and up-to-date records of all study drug to permit reconciliation. The Investigator or designee must maintain adequate records of distribution, including the date received, number and units received, lot numbers, dispensing, and return or destruction of all study drug (ie, accountability or dispensing logs).

All study drug records must be readily available for inspection by the site's clinical monitor and/or auditor. No study drug can be returned to the Sponsor or designee or disposed of at the study site until the clinical monitor has verified the accuracy of the study drug records at the study site. All returns, disposal, or destruction must be approved by the Sponsor in writing.

6. STUDY PROCEDURES AND ASSESSMENTS

The following sections describe the study procedures and assessments that will be performed during the study. Additional information about the timing of assessments is provided in Section 7 and the Schedule of Events table.

6.1. Medical History and Demographics

6.1.1. Medical History

A complete medical history will be obtained to ensure subjects qualify for the study. Medical history will be obtained through subject interview. A review of the subject's medical records from their primary care physician is recommended. Data collected will include medical and surgical history.

6.1.2. Demographics

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

6.2. Prior and Concomitant Therapy

All medications taken by subjects between signing the ICF and the Safety Follow-Up Visit on Day 42 will be recorded in the subject's eCRF. The dosing regimen of "prn" should not be recorded on the eCRF for medications taken during the 72-hour postoperative period.

During the 72-hour postoperative period, the name, dose, and route, as well as the start date and time, of concomitant medications must be recorded. Medications include prescription and over-the-counter medications (including herbal products and vitamins). For subjects entering on a stable dose of permitted medication, any change in dose should also be recorded. Note: All medications received during this period must have a start time recorded, except for IV fluids and oxygen during surgery, which do not need to be recorded unless being used to treat an AE.

After the 72-hour period until the Safety Follow-Up on Day 42, at least the start date of each concomitant medication should be recorded and stop date if the medication was discontinued prior to Day 42.

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's in keeping with the standard of medical care.

In Cohorts 1 and 3, antiemetic medications may be given to treat nausea and/or vomiting, but should not be administered prophylactically (ie, as a routine preventative in the absence of signs or symptoms of nausea or vomiting). In Cohorts 2 and 4, granisetron, palonosetron, or ondansetron are permitted to treat nausea and/or vomiting following surgery, but should not be administered prophylactically. Another NK_1 receptor antagonist such as rolapitant (VARUBI®), netupitant (AKYNZEO®), or fosaprepitant (EMEND® IV) should not be given.

During surgery, the use of IV fentanyl up to 4 µg/kg is permitted for intraoperative pain control. As the prescribing information for fentanyl citrate (Fentanyl Citrate USPI 2012) specifies that for

intraoperative use a "moderate dose" of 2 to 20 µg/kg IV is necessary in order to allow the anesthesiologist to respond to any signal that the surgical stress is increasing or anesthesia lightening, this dose was chosen to be in the lowermost portion of that range and therefore not interfere with assessment of postoperative opioid load. As clinically appropriate, the minimum possible fentanyl dose should be used.

See Section 3.1.3 for information on rescue medications permitted.

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

6.2.2. Prohibited Medications

6.2.2.1. Medications Prohibited Prior to Surgery

Refer to exclusion criteria 5 through 9, 11, 12, and 19 (all subjects) and exclusion criteria 10 and 16 (Cohorts 2 and 4 only) for medications that are prohibited prior to the scheduled surgery (Section 4.1.2). Of note, for exclusion criterion 13, oral, parenteral, and topical steroids are considered systemic steroids, but inhaled and ophthalmic steroids are not considered systemic steroids.

6.2.2.2. Medications Prohibited During Surgery

Epidural or spinal anesthesia is not permitted.

Intraoperative administration of opioids or any other analgesics (including ketamine), local anesthetics, or anti-inflammatory agents except as specified by the protocol (ie, HTX-011, and fentanyl) is prohibited, unless needed to treat an AE that occurs after signing the ICF, for pretreatment prior to a needle placement, or to decrease venous irritation (eg, caused by propofol, in which case no more than a single administration of lidocaine 1% plain 20 mg IV may be administered).

6.2.2.3. Medications Prohibited From Time 0 Through 72 Hours

With the exception of study treatment specified in Section 3.1.1.1 and rescue medications specified in Section 3.1.3, no other analgesic agents, including NSAIDs, are permitted during the 72-hour postoperative observation period.

Refer to exclusion criterion 16 (Cohorts 2 and 4 only) for medications that are prohibited during the study with aprepitant (Section 4.1.2).

In Cohorts 1 and 3, subjects should not receive an antiemetic prophylactically. In Cohorts 2 and 4, subjects should not receive an antiemetic prophylactically or another NK_1 receptor antagonist as an antiemetic to treat nausea and/or vomiting (Section 6.2.1).

6.3. Efficacy Assessments

6.3.1. Pain Intensity Assessment

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

Pain intensity scores will be assessed using an 11-point NRS (0–10) where 0 represents "no pain" and 10 represents "worst pain imaginable" (Breivik 2008). NRS scores will be recorded first at rest (NRS-R) and then with activity (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; see photo below).

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

6.3.2. Use of Opioid Medications

6.3.2.1. Opioid Rescue Medication Through 72 Hours

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

6.3.2.2. Subject Daily Diary of Opioid Use From 72 Hours Through Day 28 (Cohorts 3 and 4 Only)

At discharge, subjects in Cohorts 3 and 4 will be provided a daily diary to record if they take any opioid medication from 72 hours through the Day 28 Visit (yes or no). If a subject records "yes" for taking an opioid, sites must record the medication on concomitant medication eCRF.

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 Safety Follow-Up on Day 42. Additional safety information is provided in Section 8. Clinically significant post-treatment findings for laboratory results, vital signs, should

be recorded as AEs. Abnormal physical examination findings and wound healing abnormalities should also be recorded as AEs.

6.4.2. Physical Examinations

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

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

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

6.4.3. Vital Signs

Vital signs will include systolic and diastolic blood pressure, resting heart rate, respiration rate, and body temperature. Subjects should be in a supine position or semi-supine position (eg, sitting in a recliner chair) for at least 5 minutes before taking vital signs.

6.4.4. 12-Lead Electrocardiograms

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

6.4.5. Wound Healing Assessment

A wound healing assessment questionnaire is provided (see 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. Any abnormality of wound healing should be followed to resolution.

6.4.6. Clinical Laboratory Tests

Blood and urine samples will be collected for diagnostic screening tests and for safety laboratory tests (hematology and serum chemistry). A list of clinical laboratory tests and parameters is provided in Table 2. Urine samples will be tested by local laboratories. Blood samples will be tested by a central laboratory.

Laboratory results will be reviewed by the Investigator. Any laboratory values outside of the normal reference range will be evaluated for clinical significance.

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

Table 2: Clinical Laboratory Tests

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

6.5. Pharmacokinetic Assessments

Blood samples for bupivacaine and meloxicam PK analysis (all subjects) and aprepitant (Cohorts 2 and 4 only) will be collected from subjects prior to surgery and at specified times following surgery through 72 hours after study medication administration. Blood samples may be drawn using a properly maintained indwelling cannula. Samples will be sent to a central laboratory for analysis. Refer to the Laboratory Manual for detailed instructions on sample collection, processing, storage, and shipping procedures.

7. TIMING OF PROCEDURES AND ASSESSMENTS

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

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

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

- NRS-R pain intensity 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).
- Vital signs.
- 12-lead ECG (Screening only).
- NRS-A pain intensity assessment (subjects should be seated with the plantar surface of the ball of the surgically attended foot touching the floor [no weight bearing]).
- Blood sample collection.
- Physical examination.
- Wound healing assessment.

7.1. Screening Period

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

Screening procedures and assessments will include the following:

- Urine drug screen.
- Urine pregnancy test (female subjects of child-bearing potential only).
- Medical history.
- Demographic recording.
- Physical examination (including weight, height, and BMI calculation).
- Vital signs measurements.
- 12-lead ECG (in triplicate).

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

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

7.2. Treatment and Postoperative Observation Period

7.2.1. Day of Surgery (Day 1)

7.2.1.1. Prior to Surgery

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

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

- Blood sample collection for bupivacaine and meloxicam PK (Cohort 3).
- Vital signs measurements.
- Subject training for pain intensity assessments (refresher training).
- AE recording.
- Prior and concomitant medication assessment.

Subjects in Cohorts 2 and 4 only will receive a single oral dose of aprepitant 125 mg approximately 3 hours prior to the start of surgery and have the following study procedures and assessments prior to surgery:

- **Blood sample collection for bupivacaine, meloxicam, and aprepitant PK**: 2 hours (±15 min), 2.5 hours (±15 min), and 3 hours (±15 min) post aprepitant study drug administration.
- **AE recording:** (Note: the start date and time of all AEs during this timeframe must be recorded).

Note: The start of aprepitant administration will be considered as Time 0 for aprepitant alone safety and PK assessments.

7.2.1.2. Surgery and HTX-011 Administration

Subjects will undergo a unilateral simple bunionectomy under regional anesthesia (no more than 20 mL of 1% lidocaine without epinephrine administered as a Mayo block; epidural or spinal anesthesia is not permitted). Sites should follow intraoperative safety monitoring in accordance with ASA Standards for Basic Anesthetic Monitoring (American Society of Anesthesiologists 2015), which is consistent with the European Board of Anesthesiology (EBA) recommendations for minimal monitoring during Anesthesia and Recovery (for review in 2018) (EBA UEMS 2016). The start and stop time of surgery and additional surgical details (including the length of the surgical incision) should be recorded in the eCRF.

Subjects will be administered HTX-011 unless they experience a clinically significant event during surgery (eg, excessive bleeding, hemodynamic instability) that would render the subject medically unstable or complicate their postoperative course. Study drug will be administered via application into the surgical site at the end of the surgical procedure, but prior to wound closure. Complete details on the study drug administration technique are provided in Section 5.5.

The start and stop times of study drug dosing will be recorded in the eCRF. Details of administration will be recorded on a worksheet, which will be used in the dictation of the surgical notes and will become part of the source document. **Note: The start of HTX-011 administration will be considered as Time 0 for all efficacy, safety, and PK assessments for HTX-011 with and without aprepitant.** Placement of the last suture will be considered the end of surgery.

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

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

7.2.2. Postoperative Assessment Period (Up to 72 Hours)

Subjects in Cohorts 2 and 4 will receive single doses of aprepitant 80 mg at approximately 24 hours (Day 2) and approximately 48 hours (Day 3) after the presurgery aprepitant dose.

Subjects in Cohorts 3 and 4 will be started on a scheduled multimodal analgesic regimen once they are able to tolerate oral intake in the PACU. The regimen will consist of 600 mg oral ibuprofen alternating with 1 g oral acetaminophen every 6 hours and will be administered as follows: 3 hours after the first 600 mg oral ibuprofen dose, subjects will receive a 1 g oral acetaminophen dose, then after 3 more hours another 600 mg oral ibuprofen dose, and so on until the 72-hour postoperative period is complete. These medications will be administered on a round-the-clock, scheduled basis through the 72-hour postoperative period.

Subjects will remain in the hospital/research facility for 72 hours after HTX-011 administration. Study procedures and assessments that will be performed are listed below.

All postoperative timepoints are referenced to the start of HTX-011 administration. Actual times will be recorded for all events, and any deviation outside the specified ranges must be clearly documented in the subject's study records.

- **NRS-R and NRS-A pain intensity assessments:** at 1 hour (±5 min), 2 and 4 hours (±15 min), 8 and 12 hours (±30 min), 24 hours (±1 h), 36 and 48 hours (±2 h), 60 and 72 hours (±4 h).

  - Note: **NRS-R should be collected prior to the NRS-A.** If a subject requires rescue medication before the 1-hour 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 1-hour NRS-R and NRS-A assessments.

- **Vital signs measurements:** 30 minutes (±5 min), 60 minutes (±5 min), 90 minutes (±10 min), 2 hours (±15 min), 4 hours (±15 min), 8 hours (±30 min), 12 hours (±30 min), 18 hours (±30 min), 24 hours (±1 h), 36 hours (±2 h), 48 hours (±2 h), 60 hours (±4 h), and 72 hours (±4 h).
- **Blood sample for hematology and serum chemistry tests:** 72 hours (±4 h; hematology and serum chemistry).
- **Blood sample collection for PK**: 30 minutes (±5 min), 1 hour (±5 min), 2 hours (±15 min), 4 hours (±15 min), 8 hours (±30 min), 12 hours (±30 min), 18 hours (±30 min), 24 hours (±1 h), 36 hours (±2 h), 48 hours (±2 h), 60 hours (±4 h), and 72 hours (±4 h) post HTX-011 administration.
- **AE recording:** (Note: the start date and time of all AEs during this timeframe must be recorded).
- **Concomitant medication recording:** (Note: the start date and time of all concomitant medications during this timeframe must be recorded).
- **Use of pain medication (rescue and scheduled) recording:** Any time between HTX-011 administration and 72 hours (Note: the start date and time of all medications during this timeframe must be recorded).

7.2.3. End of the Postoperative Assessment Period

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

Subjects who are not medically ready for discharge at 72 hours may receive the same rescue medication as outlined in Section 3.1.3.1 to treat postoperative pain until discharge. Postoperative analgesia after discharge is outlined in Section 3.1.3.2. In Cohorts 3 and 4, sites must record if a subject is discharged with an opioid prescription (yes or no).

Subject should be instructed at the time of discharge to leave the bandage clean, dry, and intact until the Day 7 visit. In addition, the subject should be provided with a cast guard to keep the bandage dry and instructed to contact the site if the bandage gets wet.

All subjects in Cohort 3 and 4 will be given a diary at discharge to complete daily and record whether they take any opioid medication from 72 hours through Day 28.

7.3. Follow-Up Period

7.3.1.1. Day 7 Visit (+3 Days)

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

- NRS-R pain intensity assessment. (NRS-R should be collected prior to the NRS-A.)
- NRS-A pain intensity assessment.
- Wound healing assessment.
- New dry dressing applied. Instruct subjects that they may remove bandage after Day 21.
- Review subject diary results (Cohorts 3 and 4). If a subject recorded "yes" for taking an opioid, sites must record the medication on concomitant medication eCRF.
- AE recording.
- Concomitant medication recording.

7.3.1.2. Day 28 Visit (±4 Days)

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

- NRS-R pain intensity assessment. (NRS-R should be collected prior to the NRS-A.)
- NRS-A pain intensity assessment.
- Wound healing assessment.
- Review subject diary results (Cohorts 3 and 4). If a subject recorded "yes" for taking an opioid, sites must record the medication on concomitant medication eCRF.
- AE recording.
- Concomitant medication recording.

7.3.1.3. Safety Follow-Up (Day 42 ±7 Days)

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

- Wound healing assessment.
- Review and record subject diary results in the eCRF (if after the 72-hour discharge but before Day 28). If a subject recorded "yes" for taking an opioid, sites must record the medication on concomitant medication eCRF.
- AE recording.
- Concomitant medication recording.

7.4. Early Termination Visit

Subjects who withdraw from the study before their Day 28 Visit will be asked to complete Early Termination procedures, which will include the items listed in Section 7.4.1. Subjects who

withdraw from the study after the Day 28 Visit but prior to the Safety Follow-Up on Day 42 will be asked to complete Early Termination procedures, which will include the items listed in Section 7.4.2.

7.4.1. Withdrawal Prior to the Day 28 Visit

- NRS-R pain intensity assessment. (NRS-R should be collected prior to the NRS-A.)
- NRS-A pain intensity assessment.
- Vital signs (if withdrew prior to 72 hours).
- Blood sample collection for hematology and serum chemistry (if withdrew prior to 72 hours).
- Wound healing assessment.
- AE recording.
- Concomitant medication recording.

7.4.2. Withdrawal After the Day 28 Visit and Prior to the Safety Follow-Up on Day 42

- AE recording.
- Concomitant medication recording.
- Wound healing assessment.

7.5. Unscheduled Visits and Assessments

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

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

8. SAFETY MONITORING AND REPORTING

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

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

8.1. Definition of Safety Parameters

8.1.1. Definition of an Adverse Event

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

An AE may be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not considered causally associated with the use of the study drug. Any abnormal laboratory value or vital sign result deemed clinically significant by the Investigator, regardless of causal relationship, must be reported as an AE. Clinically significant wound healing abnormalities should also be recorded as AEs. When appropriate, a clinical diagnosis, rather than the changes in laboratory analyte or other assessment, should be recorded (eg, anemia rather than low hemoglobin value).

Examples of AEs include the following:

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

- Any laboratory abnormality that required additional monitoring and follow-up visits.
- Any laboratory abnormality requiring further diagnostic investigation.

The following examples are not considered AEs:

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

8.1.2. Definition of a Serious Adverse Event

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

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

The following events do not meet the definition of an SAE: hospitalization for elective treatment of a pre-existing condition that does not worsen from baseline, hospitalizations for a standard procedure for study drug administration and routine monitoring of the studied indication not associated with any deterioration in condition, social or convenience admission to a hospital, prolongation of a hospitalization for social or convenience reasons not associated with the

occurrence of an AE, or hospitalization or an emergency room visit that lasts less than 24 hours that does not meet the criteria of an important medical or a life-threatening event.

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

8.1.3. Definition of a Suspected Adverse Reaction

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

8.1.4. Definition of a Serious Suspected Adverse Reaction

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

8.1.5. Definition of Unanticipated Problems

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

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

An unanticipated adverse device effect is defined in Section 8.1.2.

8.2. Classification of Adverse Events

8.2.1. Severity of Adverse Events

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

- **Mild:** Event is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.

- **Moderate:** Event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe:** Event interrupts a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2. Relationship to Study Drug

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

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

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

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

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

8.3.1. Adverse Event and Serious Adverse Event Monitoring

All AEs regardless of causality or seriousness will be recorded from the time the subject signs the ICF through the Safety Follow-Up on Day 42. Note: the AE start time, as well as the date, must be recorded during the 72-hour postoperative period. After this period, only the start and stop dates must be recorded.

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

8.3.2. Follow-Up of Events

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

Non-serious 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 non-serious) 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/resolved:** At the end of the study, a nonserious event either has not changed in intensity or may not have recovered to baseline values, and the outcome is unknown. Examples include headache, low-grade fever, or nausea.
- **Unknown:** The subject has withdrawn from the study prematurely or is lost to follow-up, and the status of the event is unknown.
- **Fatal**

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

8.4. Reporting Procedures

8.4.1. Reporting Serious Adverse Events to the Sponsor

If the Investigator determines that an event meets the protocol definition of an SAE due to any cause that occurs during the course of this study, regardless of relationship to study drug, he/she

must notify the Sponsor by entering the SAE information into the eCRF **within 24 hours of the Investigator becoming aware of the SAE**.

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

Email Address: Heron_PV@ubc.com

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

- AE record
- Medical history
- Prior and concomitant medications

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

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

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

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

8.4.2. Reporting Unanticipated Problems to the Sponsor

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

Email Address: Heron_PV@ubc.com

The following information will be included with unanticipated problem reporting:

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

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

8.4.3. Regulatory Reporting Requirements

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

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

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

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

8.4.4. Pregnancy Reporting

Pregnancy is not considered to be an adverse event; 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

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

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

9. OTHER STUDY RESTRICTIONS

9.1. Contraception

Female subjects of child-bearing potential must use an acceptable form of contraception in the event of sexual activity during the study and for 30 days after study drug administration. Note: This does not apply to women in only a same-sex relationship or women in a monogamous relationship with a surgically sterile partner.

For Cohorts 1 and 3, acceptable forms of contraception include double-barrier contraception or an insertable, injectable, transdermal, or combination oral contraceptive approved by applicable regulatory authorities.

For Cohorts 2 and 4, hormonal contraceptives are not an acceptable form of birth control since the efficacy of hormonal contraceptives may be reduced with aprepitant. Therefore, female subjects in Cohorts 2 and 4 must agree to use double-barrier contraception or a non-hormonal intra-uterine device (eg, copper) in the event of sexual activity for greater than 2 months prior to screening, for the duration of the study and for 30 days after last study drug administration.

10. STATISTICAL CONSIDERATIONS

10.1. General Considerations

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

10.2. Determination of Sample Size

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

10.3. Analysis Populations

Intent-to-Treat (ITT) Population: All subjects who receive HTX-011 will be included in the ITT Population. This population will be used as the analysis population for all efficacy and safety endpoints.

10.4. Statistical Analysis Methods

10.4.1. Disposition and Demographics

Subject disposition, including the number of subjects screened, dosed, completing the 72-hour postoperative observation period, completing Day 28, completing the Safety Follow-up Visit on Day 42, and not completing the Safety Follow-up Visit on Day 42 by reason for withdrawal will be summarized by cohort. Subject demographics and baseline characteristics will also be summarized and will include age, age category, sex, race, ethnicity, height, weight, and BMI.

10.4.2. Efficacy Analysis

All efficacy data will be summarized by cohort. AUCs of the NRS pain intensity scores will be adjusted for opioid use via windowed worst observation carried forward (wWOCF) method. In this method, pain intensity scores observed during the analgesic window (duration of effect) of any opioid rescue medication will be replaced with the worst (highest) postdose nonmissing NRS pain intensity score observed prior to the rescue medication window, with the following exception: if the NRS pain intensity score for a windowed observation is higher than the worst prewindow score, then it will not be replaced. Sensitivity analyses for endpoints involving NRS pain intensity scores will summarize the data without adjustment for the effect of opioid rescue medications.

10.4.2.1. Handling of Missing Data

Due to the required 72-hour inpatient postoperative observation period, the amount of missing data is expected to be very low. For any missing data observed through 72 hours in subjects who complete the 72-hour postoperative observation period, NRS pain intensity scores will be

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

10.4.3. Safety Analysis

All safety data will be listed and summarized by cohort.

AEs that occur between the time the subject signs the ICF and the start of study drug (HTX-011 for Cohorts 1 and 3 or aprepitant for Cohorts 2 and 4) administration will be considered pretreatment AEs. AEs that start during or after study drug administration, or AEs with an onset prior to study drug administration that worsen after study drug administration will be considered TEAEs. All TEAEs will be coded and tabulated by System Organ Class and Preferred Term. Incidence of TEAEs and SAEs will be summarized and presented in descending order of frequency. AEs leading to study withdrawal, if any, will be listed separately.

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

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

Wound healing assessment results will be summarized at each timepoint.

10.4.4. Pharmacokinetic Analysis

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

10.5. Interim Analysis

No formal interim analyses are planned; however, preliminary analyses of data by cohort may be conducted to plan future studies or for regulatory reporting purposes.

11. QUALITY ASSURANCE AND QUALITY CONTROL

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

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

12. REGULATORY AND ETHICAL CONSIDERATIONS

12.1. Regulatory Authority Approval

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

12.2. Ethical Conduct of the Study

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

12.3. Ethics Committee Approval

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

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

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

12.4. Informed Consent Process

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

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

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

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

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

12.5. Confidentiality

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

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

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

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

13. STUDY ADMINISTRATION

13.1. Clinical Monitoring

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

13.2. Source Documents and Record Retention

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

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

13.3. Management of Protocol Amendments and Deviations

13.3.1. Protocol Modification

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

13.3.2. Protocol Violations and Deviations

Protocol deviations are a change, divergence, or departure from the study design or procedures defined in this protocol. An Important Protocol Deviation is a deviation that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. The Investigator will notify the EC of any protocol deviations as required by EC guidelines and site requirements. Protocol deviations will be

documented at the site and in the Sponsor files. In the event of an Important Protocol Deviation, the site will notify the Sponsor or designee. The Sponsor is responsible for notifying the regulatory authorities of any protocol deviations, if required.

13.4. Financial Disclosure

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

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

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

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

13.5.1. Suspension of Study

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

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

13.5.2. Termination of Study or Investigational Site

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

- If there is a suspension of the study and further investigation shows that any death or 3 non-fatal SAEs are determined by the Sponsor to be related to study drug and pose an unacceptable risk to the study subjects, the study will be terminated.
- Discovery of an unexpected, significant, or unacceptable risk to the subjects.
- Failure of the Investigator to comply with the protocol, GCP regulations and guidelines, or local requirements.

- Insufficient adherence to protocol requirements or an unacceptably high rate of missing, erroneous, or improperly collected data.
- Data are not sufficiently complete and/or evaluable.
- Inadequate recruitment of subjects by the Investigator.
- Sponsor decision.

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

13.6. Publication and Information Disclosure Policy

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

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

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

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

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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. BMI CALCULATION

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

Meters = inches × 0.0254

Kilograms = pounds × 0.45

Example:

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

165 lbs. × 0.45 = 74.25 kg

71 in. × 0.0254 = 1.8 m

74.25 / (1.8 × 1.8) = 22.92 kg/m^2

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

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

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

The response must be one of the following:

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

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

Appendix D. WOUND HEALING ASSESSMENT

Record "Present" or "Absent" for each of the following symptoms in relationship to the wound. Signs and symptoms that are present should be entered on the electronic case report form (eCRF) as adverse events (AEs). Note that if an event qualifies as a serious adverse event (SAE; see Section 8.4.1), the Sponsor must be notified within 24 hours of when the Investigator is first aware of the event.

Bruising	Present ☐	Absent ☐
Erythema	Present ☐	Absent ☐
Edema	Present ☐	Absent ☐
Heat	Present ☐	Absent ☐
Drainage	Present ☐	Absent ☐
Cellulitis	Present ☐	Absent ☐
Delayed healing	Present ☐	Absent ☐
Dehiscence	Present ☐	Absent ☐

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

Cohorts 1 and 2

The following text should be read by the Investigator or designee to subjects in Cohorts 1 and 2 at the time of discharge:

You have completed the initial part of the study which required you to stay at the facility. You are now being discharged to go home. You will come back here again for check-up visits on Day 7 (approximately 1 week from now), Day 28 (approximately 3½ weeks from now), and for a Safety Follow-Up on Day 42 (approximately 5½ weeks from now).

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

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

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

Cohorts 3 and 4

The following text should be read by the Investigator or designee to subjects in Cohorts 3 and 4 at the time of discharge:

You have completed the initial part of the study, which required you to stay at the facility. You are now being discharged to go home. You will come back here again for check-up visits on Day 7 (approximately 1 week from now), Day 28 (approximately 3½ weeks from now), and for a Safety Follow-Up on Day 42 (approximately 5½ weeks from now).

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

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

NOTE: If a subject required 10 mg or more of oxycodone in the 12 hours prior to discharge, the subject should be provided with a prescription for oxycodone up to 10 mg PO q4h #15, as needed. Pharmacists should be instructed that substitutions for any other opioid-containing product are not permitted. Sites must record if a subject is discharged with an opioid prescription (yes or no).

Signature Page for VV-CLIN-003792 v1.0

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