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STATISTICAL ANALYSIS PLAN

HTX-011-218

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

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Upon review of this document, the undersigned approves the statistical analysis plan. The analysis methods are acceptable, and the table, listing, and figure shell production can begin.

Approved by: _____ Date: _____

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Director of Biostatistics
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Approved by: _____ Date: _____

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Abbreviation	Term
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Classification
AUC	Area under the curve
bpm	Beats per minute
BMI	Body mass index
BUN	Blood urea nitrogen
CRO	Contract research organization
CSR	Clinical Study Report
DBP	Diastolic blood pressure
DM	Data management
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDISH	Evaluation of drug-induced serious hepatotoxicity
GGT	Gamma-glutamyltransferase
HCl	Hydrochloride
IV	Intravenous(ly)
LAST	Local Anesthetic Systemic Toxicity
LOCF	Last observation carried forward
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MME	Morphine milligram equivalent
NRS	Numeric Rating Scale
NRS-A	Numeric Rating Scale with activity
NRS-R	Numeric Rating Scale at rest
NSAID	Nonsteroidal anti-inflammatory drug
ORAE	Opioid-related adverse event
PK	Pharmacokinetic(s)

Abbreviation	Term
PT	Preferred term
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SDA	Study drug administration
SDTM	Study Data Tabulation Model
SDTMIG	Study Data Tabulation Model Implementation Guide
SE	Standard error
SI	Standard international
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WBC	White blood cell
WHODDE	World Health Organization Drug Dictionary Enhanced
wWOCF	Windowed worst observation carried forward

1. ADMINISTRATIVE STRUCTURE

1.1. Sponsor and Oversight

This study is being conducted under the sponsorship of Heron Therapeutics, Inc. (Heron).

[redacted]

1.2. Data Quality Assurance

The DM and Biostatistics departments at the contract research organizations (CROs) will collaborate internally and with the Sponsor to ensure that the data collected and analyzed for this study are of the highest quality possible and meet the data standards set for the study. This will be accomplished in part through programmed edit checks which will be reviewed by the data managers, statisticians, programmers, and other team members on an ongoing basis to evaluate whether any checks need to be added or any existing checks need to be modified. In addition, periodic reviews of listings of accumulating data, assessment of data query trends, and resulting retraining of study site personnel will be performed to further ensure data quality.

2. INTRODUCTION

This statistical analysis plan (SAP) presents a detailed plan of the statistical methods to be used for the reporting of efficacy and safety data collected in this study. This SAP does not include the planned analysis and reporting of pharmacokinetics (PK) assessments in the study. Planned PK analysis will be presented in a separate PK analysis plan.

This SAP was prepared to provide full details of analyses to be presented in the clinical study report (CSR), including a detailed elaboration of the statistical analysis methods presented in the protocol. Revisions can be made to this SAP while the study is ongoing; however, it must be finalized prior to database lock. Any deviations from the analysis plan provided in the SAP will be fully documented in the final CSR.

This SAP should be read in conjunction with the study protocol and the electronic Case Report Forms (eCRFs).

3. OBJECTIVES

The primary objectives of the study 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 (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).

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 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).

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

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 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.

4.1.1. 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. 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).

4.1.2. 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. 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.

4.1.3. Cohort 3

Approximately 15 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.

4.1.4. 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.

4.2. Assessments

Efficacy assessments will include the following:

- Pain intensity scores using the NRS with activity (NRS-A) and using the NRS at rest (NRS-R).
- Use of opioid rescue medication.

Safety assessments will include the following:

- Adverse event (AE) recording.
- Concomitant medication recording.
- Clinical safety laboratory tests (hematology and serum chemistry).
- 12-lead electrocardiogram (ECG) at screening only.
- Physical examination at screening only.
- Wound healing assessment.
- Vital signs collections.

4.3. Endpoints

4.3.1. Efficacy Endpoints

The primary efficacy endpoint is the following:

- Mean area under the curve (AUC) of the NRS-A pain intensity scores through 72 hours ($AUC_{0\text{-}72}$).

The secondary efficacy endpoints are the following:

- Total postoperative opioid consumption (in morphine equivalents) through 72 hours.

- Proportion of subjects who are opioid-free through 72 hours.
- Mean 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).

4.3.2. Safety Endpoints

The safety endpoints are the following:

- 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 the Safety Follow-Up on Day 42.

5. GENERAL STATISTICAL CONSIDERATIONS

No statistical hypothesis testing will be performed. Continuous data will be presented using descriptive statistics: number of subjects (n), mean, standard deviation (SD), median, minimum and maximum. Descriptive statistics on efficacy measures will also include the standard error (SE). Categorical data will be summarized by the number and percent of subjects. Data will be displayed in all listings sorted by treatment group, subject number and visit/study day. When count data are presented, the percent will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where necessary to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in that treatment group within the population of interest, unless otherwise stated. Non-zero percentages will be rounded to 1 decimal place, except 100% will be displayed without any decimal places. Additional rounding rules are as follows:

- If the original value has 0 decimal places: mean, median, and CI will have 1 decimal place and SD and SE will have 2 decimal places.
- If the original value has 1 decimal place: mean, median, and CI will have 2 decimal places and SD and SE will have 3 decimal places.
- If the original value has 2 or more decimal places: mean, median, CI, SD, and SE will all have 3 decimal places.

Minimum and maximum will always have the same decimal places as the original measure, up to a maximum of 3 decimal places. The above rounding rules will not be applied to original measures displayed in listings.

Values that are collected with "<" or ">" signs will be analyzed as the numerical value without the sign in tables and figures. In listings, these data will be reported as collected with the sign.

All efficacy and safety data will be collected electronically. Datasets will be created using the Study Data Tabulation Model (SDTM) v. 1.4 or higher, conforming to the SDTM Implementation Guide (SDTMIG) v. 3.2 or higher. Datasets, tables, listings, and figures will be programmed using SAS® v. 9.4 or higher. All efficacy and safety data will be listed via the SDTM datasets and selected efficacy and safety data will be listed via programmed listings.

All summary tables and figures will be presented by cohort. Data listings will include the cohort variable.

5.1. Sample Size

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

5.2. Randomization, Stratification, and Blinding

This is an open-label study.

5.3. Analysis Populations

5.3.1. Safety Population

The Safety Population will consist of all subjects who receive study drug. This population will be used for all summaries of efficacy and safety data.

5.4. Other Important Considerations

5.4.1. Calculation of HTX-011 Dose Received

After preparing the syringe and before administration, the weight of the syringe (to the nearest gram) containing HTX-011 will be recorded in the eCRF. After administering HTX-011, the weight of the syringe (to the nearest gram) will also be recorded in the eCRF. The calculation of the dose of study drug received is calculated as follows:

$D = W_b – W_a – 0.3$, where:

- W_b is the weight of the syringe in gram before study drug administration.
- W_a is the weight of syringe in gram after study drug administration.

Bupivacaine/meloxicam doses are calculated as follows:

Bupivacaine dose (mg) = D *25 mg

Meloxicam dose (mg) = D *0.75 mg

5.4.2. Compliance of Aprepitant

For subjects in Cohorts 2 and 4, number and percentage of subjects for each dose of aprepitant received will be summarized.

5.4.3. Definition of Baseline

Baseline data are defined as the last observed measurement collected, whether scheduled or unscheduled, prior to the start of study drug administration.

5.4.4. Calculation of Change and Percent Change from Baseline

Change from Baseline to any timepoint t (C_t) is calculated as follows:

$C_t = M_t - M_B$, where:

- M_t is the measurement of interest at timepoint t.
- M_B is the measurement of interest at Baseline.

Percent change from Baseline to any timepoint (P_t) is calculated as follows:

$P_t = 100*(C_t/M_B)$

5.4.5. Study Day Calculation for Reporting Purposes

The following convention will be used to calculate study day for reporting purposes:

- The study day of study drug administration is Study Day 1.
- For measurements that are *on or after* the date of study drug administration:
  - Study Day = date of measurement – date of study drug administration + 1.
- For measurements that are *prior* to the date of study drug administration:
  - Study Day = date of measurement – date of study drug administration.

For all subjects, the day of study drug administration should be the same day as the day of the surgical procedure.

5.4.6. Start date/time of Study Drug Administration (Time 0)

The start date/time of study drug administration is defined as the date and time of the start of HTX-011 instillation. The start date/time of study drug administration will be Time 0 for all efficacy and safety assessments.

For Cohorts 2 and 4, first dose of aprepitant study drug administration start time will be used to determine treatment emergent AE status. Otherwise, T0 is defined as HTX-011 study drug administration time.

5.4.7. 72-Hour Postoperative Observation Period

The 72-hour postoperative observation period will be defined as the period of time from the start date/time of HTX-011 to the date/time of NRS-A pain intensity score assessment at the nominal 72-hour postoperative timepoint.

Subjects who have a reported NRS-A pain intensity score at the nominal 72-hour postoperative timepoint will be considered as completing the 72-hour postoperative observation period.

5.4.8. Visit Windows

Due to the short duration of the study and the primary efficacy analyses occurring during the 72-hour postoperative period of subject hospitalization, no programmatically calculated visit windows are defined for this study.

5.4.9. Handling of Missing and Partial Data

The amount of missing data during the primary efficacy analysis period is expected to be very low due to the protocol-required 72-hour hospitalization of all subjects following surgery.

For any data that is missing through 72 hours in subjects who complete the 72-hour postoperative observation period, the NRS pain intensity scores will be imputed via last observation carried forward (LOCF), in which the most recent postdose nonmissing value is used for a subsequent missing value. If there is no postdose value available prior to the first missing value, then the median of values from subjects with observed values within the same treatment group at the relevant timepoint will be used. Predose values will not be carried forward to postdose timepoints.

In subjects who withdraw from the study prior to 72 hours, missing NRS pain intensity scores through 72 hours that were to be collected following withdrawal will be imputed via worst observation carried forward (WOCF), in which the worst (highest) NRS pain intensity score observed prior to withdrawal will be used for post-withdrawal values through 72 hours. Any missing NRS pain intensity scores prior to the point of withdrawal will be imputed via LOCF.

A table displaying the number and percentage of subjects with missing NRS-A pain intensity scores at each nominal timepoint will be produced.

All safety results will be summarized using observed cases with no imputation.

For partial dates involving AE start dates and concomitant medication start dates, the algorithms for imputation will vary depending upon the parameter; the details can be found in Appendix 1. No other partial dates will be imputed.

6. SUBJECT DISPOSITION

A summary of disposition of subjects will include the number and percentage of subjects for the following categories: subjects enrolled (signed the Informed Consent Form), subjects who failed screening with reasons for screen failure, subjects in the Safety Population, subjects completing the 72-hour postoperative observation period, subjects completing Day 28, subjects completing the Safety Follow-up on Day 42, and subjects not completing the Safety Follow-up on Day 42 by reason for withdrawal. Only 1 reason for study withdrawal will be recorded for each subject.

7. DEMOGRAPHICS, CHARACTERISTICS, AND MEDICAL HISTORY

7.1. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be presented in tables using descriptive statistics. Demographics consist of age, age category, sex, race, and ethnicity. Baseline characteristics consist of weight, height, and body mass index (BMI). A subject's age in years is recorded directly on the eCRF. The number and percentage of subjects in the following age categories will be presented: 18-44, 45-54, 55-64, 65-74, 75-84, and ≥ 85.

7.2. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) version 19.1. Medical history will be summarized for the Safety Population and will display the number and percentage of subjects with a past and/or concomitant disease or past surgeries by System Organ Class (SOC) and preferred term (PT).

7.3. Protocol Deviations

Deviations and violations from the protocol will be recorded. Protocol deviations will be classified into, but not necessarily limited to, the following categories:

- ICF procedures.
- Eligibility criteria.
- Prohibited concomitant medication/therapy.
- Laboratory assessment.
- Study procedure (eg, efficacy ratings).
- Safety reporting.
- Study drug dosing/administration
- Visit schedule/windows

Protocol deviations will be presented in a summary table by protocol deviation category.

8. TREATMENTS AND MEDICATIONS

8.1. Prior and Concomitant Medications

Prior medications are defined as medications with a stop date occurring before Day 1. Concomitant medications are defined as medications that are ongoing on Day 1 or with a start date occurring on or after Day 1. Medications with start and stop dates which bracket Day 1, or for which missing start and/or stop dates make it impossible to determine the prior or concomitant status, will be summarized as concomitant medications.

All medications will be coded with the World Health Organization Drug Dictionary Enhanced (WHODDE), September 1, 2016.

Prior and concomitant medications will be summarized separately by drug class and PT. At each level of summarization, a subject is counted once if that subject reports 1 or more medications at that level. Drug class will correspond to the Anatomical Therapeutic Classification (ATC) Level 2 term.

All prior and concomitant medications will be summarized for the Safety Population.

8.2. Rescue Medication

The following steps will be implemented to identify rescue medication in the study:

1. Select concomitant medications that are coded as an opioid analgesic (for all cohorts) or acetaminophen/paracetamol (Cohorts 1 and 2 only).
2. Identify rescue medications from Step 1 in which the start date/time of medication is within the 72-hour postoperative observation period (see Section 5.4.7 for details).

Opioid rescue medication in intravenous (IV) morphine milligram equivalent (MME) dose (see Section 9.2 for details) and non-opioid rescue medication dose (Cohorts 1 and 2 only) will be summarized for 0-24 hours, 0-48 hours, and 0-72 hours. In addition, proportions of subjects who received no rescue medication, who received opioid rescue medication only, who received non-opioid rescue medication only, and who received both opioid and non-opioid rescue medication will be summarized through 72 hours for Cohorts 1 and 2 only.

8.3. Surgery Procedure

The foot subject to the surgical procedure (left or right), length of incision in centimeters, and the duration of surgery will be summarized. Duration will be calculated as completion time minus start time, reported in minutes.

8.4. Study Drug

For all subjects, treatment will consist of a single dose of HTX-011. Cohorts 2 and 4 will also include administration of oral aprepitant on Days 1 through 3. Cohorts 3 and 4 will also receive scheduled postoperative analgesic of acetaminophen and ibuprofen during the 72-hour postoperative period. . Because a single individualized dose of HTX-011 will be given to all subjects, the actual dose received will be calculated (see Section 5.4.1 for details).

A summary of HTX-011 dose will be produced to include mean, standard deviation, median, minimum and maximum descriptive statistics for both bupivacaine and meloxicam doses, and categorical dose in bupivacaine (20-30 mg, >30-40 mg, >40-50 mg, >50-60 mg) will be summarized.

A summary of treatment compliance will be produced for aprepitant in Cohorts 2 and 4.

For subjects in Cohorts 3 and 4, average daily use and total use of protocol-specified postoperative analgesic medications will also be summarized using descriptive statistics for each analgesic (ibuprofen or acetaminophen) for hours 0-24, 0-48, and 0-72.

9. EFFICACY ANALYSIS

All efficacy summaries will be performed on the Safety Population and summarized by cohort.

Table 1 displays the planned treatment group being studied.

Table 1. Planned Treatment Group

Cohort	Treatment	Planned Sample Size
Cohort 1	HTX-011, up to but not to exceed 60 mg/1.8 mg (bupivacaine/meloxicam doses), 2.1 mL, via instillation into the surgical site	30
Cohort 2	3 single oral doses of aprepitant and HTX-011, up to but not to exceed 60 mg/1.8 mg (bupivacaine/meloxicam doses), 2.1 mL, via instillation into the surgical site	15
Cohort 3	HTX-011, up to but not to exceed 60 mg/1.8 mg (bupivacaine/meloxicam doses), 2.1 mL, via instillation into the surgical site; in addition to scheduled postoperative analgesic regimen	15
Cohort 4 (Optional)	3 single oral doses of aprepitant and HTX 011, up to but not to exceed 60 mg/1.8 mg (bupivacaine/meloxicam doses), 2.1 mL, via instillation into the surgical site; in addition to scheduled postoperative analgesic regimen	15

All efficacy analyses will consist of reporting summary statistics in tables and figures.

9.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the mean AUC of the NRS-A pain intensity scores through 72 hours ($AUC_{0\text{-}72}$).

9.1.1. Primary Analysis

During the first 72 hours following surgery, the NRS-A is measured at hours 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72. Using the trapezoidal rule and letting P_t = the NRS-A pain intensity score at time t, then:

$$(t - t_{-1})\frac{P_{t_{-1}} + P_t}{2}$$

is the trapezoidal area between times t and t_{-1}. The $AUC_{0\text{-}72}$ is thus calculated as follows:

$$AUC_{0-72} = \int_{1}^{72} f(t)dt \approx \sum_{i=2}^{72}(t_i - t_{i-1})\frac{P_{i-1} + P_i}{2}$$

To adjust for the duration effect of opioid rescue medication, the windowed WOCF (wWOCF) method will be implemented as the primary analysis method for endpoints involving NRS pain intensity scores. 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. wWOCF will be performed following LOCF/WOCF (ie, perform LOCF/WOCF first, then apply wWOCF). See Table 2 in Section 9.2 for predefined analgesic windows for each opioid medication.

The mean AUC_{0-72} of the NRS-A pain intensity scores using wWOCF will also be plotted with associated SEs in a bar chart.

The AUC_{0-12}, AUC_{0-24}, AUC_{24-48}, AUC_{0-48}, AUC_{24-72}, and AUC_{48-72} of the NRS-A pain intensity scores will be summarized similarly as for the AUC_{0-72} of the NRS-A pain intensity scores, with appropriate adjustments to the calculations to reflect the time periods of interest. Mean $AUC_{0-24,}$ and mean AUC_{0-48} of NRS-A will also be plotted with associated SEs in a bar chart.

In addition, the mean NRS-A pain intensity scores will be summarized at each assessed timepoint through Day 28. Mean NRS-A pain intensity scores will also be plotted in a line graph over time through 72 hours, with associated SEs at each timepoint.

9.1.2. Sensitivity Analyses

The following sensitivity analysis will be performed on the primary endpoint: AUC_{0-72} will be summarized using descriptive statistics without adjusting the NRS-A pain intensity scores for the use of opioid rescue medications (ie, without applying wWOCF).

9.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- 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).
- Mean AUC_{0-72} of the NRS-R pain intensity scores.

Total postoperative opioid consumption (in morphine equivalents) through 72 hours

Determination of morphine equivalents

Use of rescue medications will be summarized by preferred term. All opioid dosages and formulations will have the IV MME calculated (Opioid Morphine Equivalent Conversion Factors, Centers for Disease Control and Prevention, Atlanta, GA, May 2014).

Protocol-allowed postoperative rescue medications consist of oral (PO) immediate-release oxycodone (no more than 10 mg within a 4-hour period as needed), intravenous (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 cohorts 1 and 2. Oral acetaminophen and ibuprofen are not considered as rescue medication for Cohorts 3 and 4

rather than scheduled postoperative analgesic regimen. 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), IV acetaminophen, or combination products of opioids and NSAIDs, are permitted during the 72-hour postoperative observation period.

Table 2 displays the IV MME along with the analgesic windows of selected opioid rescue medications for wWOCF purposes. Protocol-allowed postoperative opioid rescue medications are checked. Opioid medications that are not protocol-allowed will be logged as protocol deviations, but will still be subject to IV MME conversion for analysis.

Table 2. Analgesic Windows and IV Morphine Milligram Equivalents for Opioid Rescue Medications in Preferred Terms

Medication	Route	Window (hr)	IV MME Factor	Protocol Allowed
CODEINE	PO	6	0.05	
HYDROMORPHONE HYDROCHLORIDE	PO	4	1.33	
HYDROMORPHONE HYDROCHLORIDE	IV	4	6.67	
FENTANYL	IV	1	50.00	
HYDROCODONE	PO	6	0.40	
MORPHINE	IV	4	1.00	✓
MORPHINE	PO	4	0.33	
MORPHINE	IM	4	1.00	
MORPHINE	PR	4	1.00	
OXYCODONE	IV	4	1.00	
OXYCODONE	IM	4	1.00	
OXYCODONE	PO	6	0.50	✓
PETHIDINE	IV	4	0.13	
TRAMADOL	IV	6	0.06	
TRAMADOL	PO	6	0.04	

Abbreviations: hr, hour; IM, intramuscular; IV, intravenous; MME, morphine milligram equivalent; PO, by mouth (orally); PR, per rectum.

Analysis method

Rescue medication use is collected from hours 0-72. Average daily use and total use will be tabulated using descriptive statistics for each opioid, for overall opioids, and for acetaminophen (for cohorts 1 and 2) during the following periods: hours 0-24, hours 24-48,

hours 0-48, hours 48-72, and hours 0-72. Subjects who did not use a specific rescue medication during a period of interest will have their dose set to 0 for that period.

The mean total postoperative opioid consumption will also be plotted in a bar chart for hours 0-24, hours 0-48 and hours 0-72 with associated SEs.

Proportion of subjects who are opioid-free through 72 hours

Subjects who have a total MME postoperative opioid dose = 0 through 72 hours will be characterized as "opioid-free" through 72 hours. The proportion of subjects who are opioid-free through 72 hours will be summarized.

In addition, the proportion of subjects who are opioid-free through 24 hours and through 48 hours will be summarized.

Proportion of subjects who are opioid-free through 72 hours who remain opioid-frree through Day 10 and Day 28 (Cohorts 3 and 4 only)

Using the number of subjects receiving no opioid rescue medication from 0-72 hours as the denominator, the proportion of these subjects receiving no opioid rescue medication through Day 10 and through Day 28 will be summarized. The opioid use through Day 10 and Day 28 will come from the subject diary.

Subjects will be provided a diary to record if they took any opioid medication from 72 hours through Day 28. Opioid-free from 72 hours through Day 10 is defined as answering "No" to the question "Did you take any opioid medication" on a daily basis from 72 hours through Day 10. Subjects who report "Yes" or have a missing report on any day during the period will not be considered opioid-free from 72 hours through Day 10. Opioid-free from 72 hours through Day 28 is defined similarly.

Mean AUC_{0-72} of the NRS-R pain intensity scores

AUC_{0-72} of the NRS-R pain intensity scores will be summarized similarly to the methods described for the primary endpoint in Sections 9.1.1 and 9.1.2. AUC_{0-12}, AUC_{0-24}, AUC_{24-48}, AUC_{0-48}, AUC_{24-72}, and AUC_{48-72} of the NRS-R pain intensity scores will also be summarized.

10. SAFETY ANALYSIS

All analyses of safety data will be conducted using the Safety Population. No imputation of missing safety data will be performed except in the case of partial AE and concomitant medication onset dates (Appendix 1).

10.1. Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A TEAE is any AE which occurs any time during or after study drug administration (for cohorts 1 and 3, use HTX-011 administration start time and for cohorts 2 and 4, use the first dose of aprepitant administration start time), or any AE with an onset prior to study drug administration that worsens during or after study drug administration. 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.

For an event to be a TEAE, it must meet one of the following conditions:

- Begins on Study Day 1, during or after administration of study drug.
- Begins after Study Day 1.
- Begins before Study Day 1 and worsens in severity during or after the Study Day 1 administration of study drug.

AEs with unknown onset dates or unknown end dates will be counted as TEAEs unless the event resolves before Study Day 1.

AEs will be coded using MedDRA version 19.1. Only TEAEs will be presented in AE tables, according to the SOC and PT. Any AEs that occur and resolve prior to Study Day 1 or are ongoing but do not worsen on or after Study Day 1 will be considered pretreatment AEs and will appear in the AE listing but not in TEAE tables.

10.1.1. Incidence of Treatment Emergent Adverse Events

The incidence of TEAEs table will include only 1 occurrence of a PT per subject. If a subject reports the same PT multiple times, then that PT will only be incremented by 1 since subject counts will be presented. As with the PT, if a subject reports multiple TEAEs within the same SOC, then that SOC will only be incremented by 1 since subject counts will be presented. For tables showing incidence by SOC and PT, SOCs will be sorted by the internationally agreed order and PTs will be sorted within SOC in descending order of incidence. For tables showing incidence by PT only, the PTs will be sorted in descending order of incidence.

An overall summary of TEAEs will be presented, and will include the following:

- Number of TEAEs.
- Number of subjects with at least 1 TEAE.
- Number of subjects with at least 1 possibly related TEAE.
- Number of subjects with at least 1 severe TEAE.
- Number of subjects with at least 1 TEAE leading to study withdrawal.
- Number of subjects with at least 1 ORAE.
- Number of subjects with at least 1 local inflammatory TEAE.
- Number of subjects with at least 1 potential LAST-related TEAE.
- Number of SAEs.
- Number of subjects with at least 1 SAE.
- Number of subjects with at least 1 possibly related SAE.
- Number of subjects with fatal TEAEs.

The incidence of all TEAEs will be presented by SOC and PT and separately by PT only.

10.1.2. Relationship of Adverse Events to Investigational Drug

The incidence of possibly related TEAEs will be presented in a table by SOC and PT. TEAEs that are missing relationship will be considered "Possibly Related" for the purpose of this incidence table but will be presented in the data listing with a missing relationship.

10.1.3. Severity of Adverse Event

The incidence of severe TEAEs will be presented in a table by SOC and PT. TEAEs that are missing severity will be considered "severe" for the purpose of this incidence table but will be presented in the data listing with a missing severity.

10.1.4. Serious Adverse Events

The seriousness of a TEAE should be assessed by the Investigator independently from the severity of the TEAE. An SAE is an AE occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing inpatient hospitalization, results in persistent or significant disability/incapacity, or is a congenital abnormality/birth defect.

Important medical events that may not be immediately life-threatening or result in death, or require hospitalization may be considered SAEs when, based upon medical judgment, they may jeopardize the subject or may require intervention to prevent one of the outcomes listed above.

SAEs will be presented in a listing.

10.1.5. Adverse Events Leading to Study Withdrawal

All TEAEs reported with "Withdrawal from Study" checked on the eCRF will be presented in a listing.

10.1.6. Opioid-related Adverse Events

Incidence of TEAEs that are potentially opioid-related, regardless of whether a subject actually received an opioid medication, will be presented by PT. Prespecified PTs that may be opioid-related include the following:

- Nausea
- Vomiting
- Constipation
- Pruritus
- Pruritus generalised
- Somnolence
- Respiratory depression
- Urinary retention

Incidence of ORAEs will be presented separately as follows:

- Incidence of ORAEs.
- Incidence of ORAEs through the 72-hour postoperative observation period.

10.1.7. Local Inflammatory Adverse Events

To enable a broad and comprehensive analysis of TEAEs potentially related to adverse effects on wound healing, local inflammatory TEAEs will be reviewed by searching the clinical database using a custom list of PTs created by Heron (Table 3).

Table 3. Local Inflammatory Adverse Events by Preferred Term

• Blister • Blood blister • Cellulitis • Erythema[a] • Impaired healing • Incision site cellulitis • Incision site complication • Incision site erythema	• Incision site haemorrhage • Incision site infection • Incision site oedema • Incision site rash • Incision site swelling • Incision site vesicles • Infection • Postoperative wound complication	• Postoperative wound infection • Post procedural cellulitis • Purulent discharge • Wound complication • Wound dehiscence • Wound infection • Wound secretion

[a] The Preferred Term of erythema was included in addition to incision site erythema for the most comprehensive review.

Incidence of local inflammatory TEAEs will be presented in a table by SOC and PT.

10.1.8. Potential Local Anesthetic Systemic Toxicity (LAST) related Adverse Events

The symptoms that are potentially related to LAST will be reviewed by searching the clinical database using a custom list of PTs created by Heron (Table 4).

Table 4. Potential LAST-Related Adverse Events by Preferred Term

• Arrhythmia (any preferred term with the string of "Arrhythmia") • Bradycardia (any preferred term with the string of "Bradycardia") • Cardiac arrest • Dizziness • Dysgeusia	• Hypotension • Muscle twitching • Paraesthesia • Paraesthesia oral • Respiratory arrest	• Seizure • Tinnitus • Tremor • Vision blurred • Visual impairment

Incidence of potential LAST-related TEAEs will be presented in a table by SOC and PT.

10.1.9. Death

Any subject deaths during this study will be collected and presented in a listing. The information that is presented will include date of death, days on study, cause of death (AE preferred term), and relationship of death to study drug.

10.2. Clinical Laboratory Evaluations

Laboratory assessments will be performed by a central laboratory (hematology and serum chemistry) or locally (pregnancy test and drug screen). All summaries of central laboratory data will be based on the standard international (SI) units provided by the central lab. Associated laboratory parameters such as hepatic profile, renal function, and hematology values will be grouped and presented together.

Summary tables for hematology and chemistry including actual values and change from Baseline values will be presented for clinical laboratory tests with numeric values. These tables will include each visit (Baseline and Hour 72), highest postdose value, lowest postdose value, and last postdose value.

Laboratory data will also be summarized using shift tables where appropriate. Each subject's hematology and serum chemistry values will be flagged as "low", "normal", or "high" relative to the normal ranges of the central laboratory.

Laboratory data collected at unscheduled visits will be included in listings and will contribute to tables of shifts from Baseline and in tables showing changes from Baseline to highest value, lowest value, and last value. Unscheduled laboratory results will not be windowed for the purposes of assigning a nominal visit.

Listings of laboratory values will include flags for values outside the central laboratory normal ranges that indicate how far out of the normal range an abnormal value is. For example, a value that is ≥ 3 times the upper limit of normal (ULN) but below 4 times the upper limit of normal will have a "3H" flag. Flag multipliers will show values that are 1, 2, 3, 4, 5, and 10 times relative to the ULN if high. Values that are below the lower limit of normal (LLN) will be flagged simply with "L".

Listings of abnormal values for hematology and chemistry will be presented separately in addition to listings of all laboratory values.

10.3. Hematology

The following laboratory tests will be included in hematology summary tables: hematocrit, hemoglobin, mean corpuscular volume (MCV), platelet count, red blood cell (RBC) count, and total and differential white blood cell (WBC) count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils).

10.3.1. Blood Chemistry

The following laboratory tests will be included in the blood chemistry summary tables: alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, direct bilirubin, gamma-glutamyltransferase (GGT), glucose, lactate

dehydrogenase (LDH), magnesium, phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid.

Associated laboratory parameters such as hepatic profile (ALT, albumin, ALP, AST, direct bilirubin, GGT, total bilirubin), electrolytes (bicarbonate, calcium, chloride, magnesium, phosphorus, potassium, sodium), renal profile (BUN, creatinine), and other (glucose, LDH, total protein, uric acid) will be sorted/grouped together in table and listing presentations.

Evaluation of drug-induced serious hepatotoxicity (eDISH) scatterplots of the highest postdose ALT vs. total bilirubin observed at the same draw as the high ALT value, and of the highest postdose AST vs. total bilirubin observed at the same draw as the high AST value, will be produced.

The incidence of subjects with clinically relevant abnormalities in liver function tests will be summarized at each visit for the following categories. Subjects with clinical relevant abnormalities in Liver Function Tests will be presented in data listing as well.

- ALT or AST:
  - $> 1 \times$ ULN
  - $\geq 2 \times$ ULN
  - $\geq 3 \times$ ULN
  - $\geq 4 \times$ ULN
  - $\geq 5 \times$ ULN
- Total bilirubin $\geq 2 \times$ ULN
- ALP:
  - $\geq 1.5 \times$ ULN
  - $\geq 2 \times$ ULN
- ALT $\geq 3 \times$ ULN and AST $\geq 3 \times$ ULN
- ALT ≥ 3 x ULN and total bilirubin $\geq 2 \times$ ULN
- AST ≥ 3 x ULN and total bilirubin $\geq 2 \times$ ULN
- Potential Hy's Law: (ALT or AST $\geq 3 \times$ ULN) and ALP $< 2 \times$ ULN and total bilirubin $\geq 2 \times$ ULN

10.3.2. Urine Pregnancy Test and Urine Drug Screen

Urine pregnancy test results (women of childbearing potential) and urine drug screen results will be listed.

10.4. Vital Sign Measurements

Vital signs including systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate/pulse (HR), body temperature, and respiration rate will be collected at screening, on Day

1 before surgery, and post-treatment at 30 minutes and at 1, 1.5, 2, 4, 8, 12, 18, 24, 36, 48, 60, and 72 hours.

Summary tables including actual values and changes from Baseline will be presented for vital signs.

The number and percentage of subjects with clinically relevant abnormalities will be presented using data from any postdose visit (including unscheduled visits). Subjects with clinical relevant abnormalities in vital signs will be presented in data listing as well. The criteria for clinically relevant abnormalities are shown in Table 5.

Table 5. Clinically Relevant Vital Signs Abnormalities

Vital Sign	Low	High
HR	≤50 bpm and ≥15 bpm decrease from Baseline	≥120 bpm and ≥15 bpm increase from Baseline
SBP	≤90 mmHg and ≥20 mmHg decrease from Baseline	≥160 mmHg and ≥20 mmHg increase from Baseline
DBP	≤50 mmHg and ≥15 mmHg decrease from Baseline	≥100 mmHg and ≥15 mmHg increase from Baseline

Abbreviations: bpm, beats per minute; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

10.5. Electrocardiogram

12-lead ECG (triplicate) is performed at screening only. ECG data will be listed only.

10.6. Physical Examination

Physical examination is performed at screening only. Physical examination data will be listed only.

10.7. Wound Healing Assessment

Surgical wound healing will be assessed using a wound healing assessment questionnaire on Day 7, Day 28 and the Safety Follow-Up on Day 42. A summary of wound healing assessment results will be produced, showing the number and percentage of subjects with abnormal wound healing symptoms at each visit and final assessment. Any symptoms present overall at each visit (Day 7, Day 28, Safety Follow-Up on Day 42 and the final assessment) will also be summarized.

Wound healing data collected at unscheduled visits will be included in listings and will contribute to the final assessment summary. Unscheduled wound healing results will not be windowed for the purposes of assigning a nominal visit.

11. INTERIM ANALYSIS

11.1. 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.

11.2. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will not be involved with the conduct of this study. The Sponsor will review tables and listings of accumulating data approximately monthly to check enrollment, adherence to follow-up schedule, and ongoing safety results.

APPENDIX 1. IMPUTATION OF PARTIAL AND MISSING DATES

Incomplete Dates of Adverse Event start

All AE onset dates must be entered on the eCRF as complete dates. In the rare case that all or part of an AE onset date is missing but an AE resolution date is present and after study drug administration then the AE onset date will be imputed as follows:

Year of onset	Month of onset	Day of onset	Onset date to be imputed as
Missing	Missing	Missing	Date of SDA
year = year of SDA	Missing	Nonmissing	Date of SDA
year = year of SDA	Missing	Missing	Set month and day to those of SDA
year < year of SDA	Missing	Nonmissing	set month to December
year < year of SDA	Missing	Missing	set month and day to December 31
year > year of SDA	Missing	Nonmissing	set month to January
year > year of SDA	Missing	Missing	set month and day to January 1
year = year of SDA	Month = month of SDA	Missing	Set day as day of SDA
year = year of SDA	Month < month of SDA	Missing	Set day as last day of onset month
year = year of SDA	Month > month of SDA	Missing	Set day as first day of onset month
year < year of SDA	Nonmissing	Missing	Set day as last day of onset month
year > year of SDA	Nonmissing	Missing	Set day as first day of onset month

SDA = study drug administration.

If AE resolution date is present and prior to study drug administration, no need to impute incomplete AE start date, as the AE is not treatment emergent and the event should be in the medical history.

Concomitant Medications

- If year and month are present and day is missing then set day to first day of month for start date, and set day to last day of month for end date.
- If year and day are present and month is missing then set month to January for start date, and set month to December for end date.
- If year is present and month and day are missing then set month and day to January 1 for start date, and set month and day to December 31 for end date.
- Completely missing dates will not be imputed.

If start date is completely missing and end date is not prior to study drug administration, then the medication will be classified as concomitant; if the end date is missing, then the medication will be classified as ongoing. Medications for which the start and end dates are completely missing will be classified as concomitant.

APPENDIX 2. DOCUMENT REVISION HISTORY

Version	Date	Notes/Revisions
1	05 October 2018	Initial version, based on protocol version 1 (27 September 2018)
2	04 January 2019	2nd version, based on protocol version 3 (12 December 2018)