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HTX-011-211

A PHASE 2B, RANDOMIZED, CONTROLLED STUDY OF HTX-011 ADMINISTERED VIA PECTORAL NERVE BLOCK IN SUBJECTS UNDERGOING UPPER EXTREMITY SURGERY FOR AUGMENTATION MAMMOPLASTY

04 January 2018

Statistical Analysis Plan

Version 3.0

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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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Vice President, Biometrics
Heron Therapeutics, Inc.

Approved by: _____ Date: _____

[redacted]
Vice President, Clinical Research
Heron Therapeutics, Inc.

TABLE OF CONTENTS

List of Abbreviations

Abbreviation	Term
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Classification
AUC	Area under the curve
bpm	Beats per minute
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence interval
CRO	Contract Research Organization
CSR	Clinical Study Report
CTM	Clinical trial materials
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
HR	Heart rate
IM	Intramuscular
IRC	Interim Revivew Committee
IRS	Integrated Rank of Silverman
ITT	Intent-to-Treat
IWRS	Interactive web response system
IV	Intravenous(ly)
K-M	Kaplan-Meier
LDH	Lactic dehydrogenase
LLN	Lower limit of normal
LOCF	Last observation carried forward
LSMD	Least-squares mean difference
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MME	Morphine milligram equivalency
MPADSS	Modified Postanaesthetic Discharge Scoring System
NRI	Non-responder imputation
NRS	Numeric Rating Scale
NRS-A	Numeric Rating Scale with activity
NRS-R	Numeric Rating Scale at rest
NSAID	Nonsteroidal anti-inflammatory drug
OBAS	Overall benefit of analgesia score
ORAE	Opioid-related adverse event
PACU	Post-Anesthesia Care Unit
PcNB	Pectoral nerve block

PGA	Patient's Global Assessment
PK	Pharmacokinetic(s)
PO	Administered orally
PR	Per rectum
PRN	As needed
PT	Preferred term
q4h	Every 4 hours
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
SEM	Standard error of the mean
SI	Standard international
SOC	System Organ Class
SPI	Summed pain intensity
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHODrug	World Health Organization Drug classification dictionary
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 Clinical Operations, DM, and Biostatistics departments at the 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 blinded 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 during the reporting and analysis of efficacy and safety data collected in this study. This SAP does not include the planned analysis and reporting of the pharmacokinetic (PK) assessments and the Holter assessments in the study. Planned PK analyses will be presented in a separate PK analysis plan and planned Holter analyses will be presented in a separate Holter analysis plan.

This SAP was prepared prior to data analysis to provide full details of analyses to be presented in the Clinical Study Report (CSR), including a technical and 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 objective of the study is:

- To compare the efficacy and duration of analgesia following bilateral ultrasound-guided lateral and medial pectoral nerve block with HTX-011 to bupivacaine hydrochloride (HCl) without epinephrine and saline placebo in subjects undergoing upper extremity surgery.

The secondary objectives are:

- To evaluate the efficacy and duration of analgesia for HTX-011 administered using different techniques in this study population.
- To evaluate additional efficacy parameters in this study population.
- To characterize the bupivacaine and meloxicam pharmacokinetic (PK) profiles of HTX-011 in this study population.
- To determine the optimal administration technique of HTX-011 in this surgical model.
- To further assess the safety and tolerability of HTX-011 in this study population.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

HTX-011-211 is a Phase 2B, randomized, double-blind, active- and saline placebo-controlled, multicenter study in subjects undergoing bilateral submuscular augmentation mammoplasty under general anesthesia. This study will evaluate the efficacy and safety profile of HTX-011 on clinical outcomes (eg, level of pain, duration of analgesia, avoidance of opioids, etc.) in subjects treated with a single preoperative dose of study drug administered by bilateral ultrasound-guided lateral and medial pectoral nerve block (PcNB) and/or instillation within 4 hours prior to the surgical procedure.

A total of up to approximately 240 subjects who meet eligibility criteria will each be randomized into one of up to 4 sequential cohorts in the study. Interim analyses will be performed on the data collected in each cohort after at least 80% of the planned subjects in that cohort have completed their 72-hour postoperative assessments and their pain intensity and opioid use data have been entered into the eCRF. An internal Interim Review Committee (IRC), composed of 1 Sponsor representative from each of the Clinical Research, Biometrics, Pharmacovigilance, Regulatory, and Pharmaceutical and Translational Sciences functions will review unblinded summary-level data in order to make a determination to proceed with the next cohort and to select the dose of HTX-011 that will be studied in the next cohort. Detailed responsibilities of the IRC will be presented in an IRC charter.

Cohort 1

Approximately 24 subjects will be randomized to 1 of the following 3 treatment groups in a 2:1:1 ratio:

- HTX-011 60 mg (2.1 mL) via bilateral ultrasound-guided lateral and medial PcNB (12 subjects)
- Bupivacaine HCl without epinephrine 0.25% (50 mg, 20 mL) via bilateral ultrasound-guided lateral and medial PcNB (6 subjects)
- Saline placebo (2.1 mL) via bilateral ultrasound-guided lateral and medial PcNB (6 subjects)

Cohort 2

Cohort 2 was planned as an optional cohort. Following a review of the results from Cohort 1, the IRC recommended initiating enrollment in Cohort 2 and randomizing approximately 48 subjects to 1 of the following 3 treatment groups in a 2:1:1 ratio:

- HTX-011 (a single dose recommended by IRC of 120 mg/3.6 mg [bupivacaine/meloxicam doses], 4.1 mL) via bilateral ultrasound-guided lateral and medial PcNB (24 subjects)
- Bupivacaine HCl without epinephrine 0.25% (50 mg, 20 mL) via bilateral ultrasound-guided lateral and medial PcNB (12 subjects)
- Saline placebo (volume matching HTX-011 in Cohort 2) via bilateral ultrasound-guided lateral and medial PcNB (12 subjects)

Cohort 3

Cohort 3 was planned as an optional cohort. Following a review of the results from Cohort 2, the IRC recommended initiating enrollment in Cohort 3 and randomizing approximately 48 subjects to 1 of the following 3 treatment groups in a 2:1:1 ratio:

- HTX-011 (a single dose recommended by IRC of 240 mg/ 7.2 mg [bupivacaine/meloxicam doses], 8.2 mL) via bilateral ultrasound-guided lateral and medial PcNB (24 subjects)
- Bupivacaine HCl without epinephrine 0.25% (50 mg, 20 mL) via bilateral ultrasound-guided lateral and medial PcNB (12 subjects)
- Saline placebo (volume matching HTX-011 in Cohort 3) via bilateral ultrasound-guided lateral and medial PcNB (12 subjects)

Cohort 4

Cohort 4 was planned as an optional cohort. Following a review of the results from Cohort 3, the IRC recommended initiating enrollment in Cohort 4 and randomizing approximately 120 subjects to 1 of the following 4 treatment groups in a 4:4:1:1 ratio:

- HTX-011 (a single dose recommended by IRC of 400 mg/12 mg [bupivacaine/meloxicam doses], 13.7 mL) via bilateral ultrasound-guided lateral and medial pectoral nerve block (48 subjects)

- HTX-011 (a single dose recommended by IRC of 400 mg/12 mg [bupivacaine/meloxicam doses], 13.7 mL) via instillation into the intended space for the implant, with 200 mg/6 mg, 6.8 mL per side, and saline placebo (volume matching HTX-011 in Cohort 4) via bilateral ultrasound-guided lateral and medial pectoral nerve block for masking (48 subjects)

- Bupivacaine HCl without epinephrine 0.25% (50 mg, 20 mL) via bilateral ultrasound-guided lateral and medial pectoral nerve block (12 subjects)

- Saline placebo (volume matching HTX-011 in Cohort 4) via bilateral ultrasound-guided lateral and medial pectoral nerve block (12 subjects)

It is anticipated that this trial will be performed at approximately 5 study sites in the United States (US).

4.2. Assessments

Efficacy assessments will include the following:

- Pain intensity scores using the Numeric Rating Scale (NRS) with activity (NRS-A)
- Pain intensity scores using the NRS at rest (NRS-R)
- Use of opioid rescue medication
- Patient's Global Assessment (PGA) of pain control
- Assessments of discharge readiness per the Modified Postanaesthetic Discharge Scoring System (MPADSS)
- Subject's satisfaction with postoperative pain control
- Overall benefit of analgesia score (OBAS)

Safety assessments will include the following:

- Adverse event (AE) recording
- Clinical safety laboratory tests (hematology and serum chemistry)
- Physical examinations
- Wound healing assessment
- Vital signs collections
- ECG
- Continuous Holter monitoring
- Motor function assessment
- Sensory function assessment (cold test)
- Blinded assessor's satisfaction with return of sensory and motor function

See the latest version of the study protocol for the timing of procedures and assessments.

4.3. Endpoints

4.3.1. Efficacy Endpoints

The primary efficacy endpoint is:

- Mean area under the curve (AUC) of the NRS-A pain intensity scores through 24 hours (AUC_{0-24}).

The secondary efficacy endpoints are:

- Mean total postoperative opioid consumption (in morphine equivalents) through 24, 48, and 72 hours.
- Median time in hours to first opioid rescue administration through 72 hours.
- Mean AUC of the NRS-A pain intensity scores at the following intervals: 0-6, 0-12, 12-24, 24-48, 0-48, 48-72, and 0-72 hours.
- Mean AUC of the NRS-R pain intensity scores at the following intervals: 0-6, 0-12, 12-24, 0-24, 24-48, 0-48, 48-72, and 0-72 hours.
- Mean NRS-R pain intensity scores at each assessed timepoint.
- Mean NRS-A pain intensity scores at each assessed timepoint.
- Integrated Rank Analysis of Silverman using the NRS-A pain intensity AUC scores and total opioid consumption through 24, 48, and 72 hours.
- Proportion of subjects achieving a score of "good" or better (>1) pain control based on PGA at 24, 48, and 72 hours, and on Day 28.
- Proportion of subjects who are pain free at rest (defined as an NRS-R pain intensity score of 0 or 1) at each assessed timepoint.
- Proportion of subjects who are pain free with activity (defined as an NRS-A pain intensity score of 0 or 1) at each assessed timepoint.
- Proportion of subjects who are opioid free through 24, 48, and 72 hours.
- Proportion of subjects who are opioid-free from 72 hours through Day 10 and Day 28.
- Proportion of subjects who first achieve a MPADSS score ≥ 9 at 2, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours.
- Mean subject's satisfaction with postoperative pain control at 24, 48, and 72 hours, and on Day 10.
- Mean OBAS at 24, 48, and 72 hours and on Day 28.

4.3.2. Safety Endpoints

The safety endpoints are:

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

- Time to return of motor function.
- Loss of sensation in the breast at 15, 30, and 60 minutes after the start of ultrasound-guided study drug administration.
- Time to return of sensory function.
- Blinded assessor's satisfaction with return of sensory and motor function at 24, 48, and 72 hours and on Day 10.

5. GENERAL STATISTICAL CONSIDERATIONS

Unless specified otherwise, all statistical analyses will be performed using a two-sided hypothesis test at the 5% level of significance. All p-values will be rounded to 4 decimal places. If a p-value is less than 0.0001, it will be reported as "< 0.0001". If a p-value is greater than 0.9999, it will be reported as "> 0.9999".

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 of the mean (SEM). Categorical data will be summarized by the number and percent of subjects. Confidence intervals (CI) will be 95% and two-sided, unless otherwise stated. Data will be displayed in all listings sorted by cohort, 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 one 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 one decimal place and SD and SEM 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 SEM will have 3 decimal places.
- If the original value has 2 or more decimal places: mean, median, CI, SD, and SEM 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. 1.3 or higher, conforming to the SDTM

Implementation Guide (SDTMIG) v. 3.1.3 or higher. Datasets, tables, listings, and figures will be programmed using SAS® v. 9.2 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.

5.1. Sample Size

The sample size of up to approximately 240 subjects in this study was selected empirically without formal statistical assumptions.

5.2. Randomization, Stratification, and Blinding

Subjects will be randomized to receive HTX-011, bupivacaine HCl, or saline placebo. The randomization will not be stratified. Subjects will not be aware of the study drug they are receiving. The site's pharmacy and surgical staff will not be blinded to the treatment assignments because HTX-011 is a colored and viscous liquid in contrast to bupivacaine HCl and saline placebo, and the volume of study drug to be administered varies by treatment group. Once surgery is completed and the subject is transferred to the Postanesthesia Care Unit (PACU), the Investigator and all site staff involved in the safety and efficacy assessments, as well as the clinical staff at the CRO involved with study conduct and data collection will be blinded to treatment assignments until after database lock. The Sponsor's study team will also be blinded to the treatment assignments with the exception of the clinical trial materials (CTM) staff, the clinical observers, the bioanalytical staff, and an unblinded statistician who will perform the randomization and interim analysis data reviews, but will otherwise be uninvolved in the conduct of the study.

An internal IRC consisting of 1 Sponsor representative from each of the Clinical Research, Biometrics, Pharmacovigilance, Regulatory, and Pharmaceutical and Translational Sciences functions will be unblinded to summary-level data during the interim analyses conducted between cohorts. The IRC will operate under a written, detailed IRC charter.

The randomization will be based on a blocked algorithm and will be done centrally via an interactive web response system (IWRS).

A subject's treatment group assignment will not be broken until the end of the study unless emergency medical treatment of that subject depends upon knowledge of the assigned treatment.

The Sponsor retains the right to break a subject's treatment code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

5.3. Statistical Hypotheses and Multiple Endpoint Handling

For the purposes of statistical hypothesis testing, data from subjects randomized to receive saline placebo will be pooled across cohorts into a single saline placebo treatment group, and data from subjects randomized to receive bupivacaine HCl will be pooled across cohorts into a single bupivacaine HCl treatment group. Data from subjects randomized to receive HTX-011 will neither be pooled across dose levels nor be pooled across methods of administration within a dose level. The primary comparison on the primary endpoint for each HTX-011 group will be against the pooled saline placebo group under the following hypotheses:

$$H_0: \mu_{\text{HTX-011}} = \mu_{\text{Saline Placebo}}$$
$$H_a: \mu_{\text{HTX-011}} \neq \mu_{\text{Saline Placebo}}$$

Comparisons of HTX-011 against the pooled bupivacaine HCl will be considered secondary comparisons. Different doses of HTX-011 will **not** be pooled for testing purposes.

As this is a Phase 2b study without a prospective statistical power calculation, there will be no adjustments made to any hypothesis test due to multiple comparisons or multiple endpoints.

5.4. Analysis Populations

5.4.1. Intent-to-Treat (ITT) Population

The ITT Population will consist of all subjects who are randomized and do not screen fail on Day 0. This analysis population will be used in subject disposition reporting only. The randomized treatment assignment will be used for analysis in this population.

5.4.2. Modified ITT (mITT) Population

The mITT Population will consist of all subjects in the ITT Population who have at least 1 post-treatment NRS-A pain intensity score. This population will be used as the primary analysis population for all efficacy endpoints. The randomized treatment assignment will be used for analysis in this population.

5.4.3. Safety Population

The Safety Population will consist of all subjects who receive any amount of study drug. This population will be used for all summaries of safety data. The actual treatment assignment will be used for analysis.

5.5. Other Important Considerations

5.5.1. Definition of Baseline

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

5.5.2. 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:

$P_t = 100*(C_t/M_B)$

5.5.3. Study Day Calculation for Reporting Purposes

The end of surgery will be considered as Time 0 for all efficacy and safety assessments, except where otherwise specified. 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.

5.5.4. Visit Windows

Due to the short duration of the study and the primary efficacy analyses occurring during the 3-day postoperative period of subject hospitalization, no programmatically calculated visit windows are defined for this study.

5.5.5. Handling of Missing and Partial Data

The amount of missing data during the 3-day postoperative primary efficacy analysis period is expected to be very low due to the protocol-required 3-day hospitalization of all subjects following surgery. Any data that is missing 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 nonmissing values within the same treatment group at the relevant timepoint will be used. Predose values will not be carried forward to postdose timepoints.

For binary endpoints (those involving proportions of subjects) not involving the NRS-R or NRS-A, any subject with missing data at a timepoint will be considered as not meeting the

endpoint at that timepoint. This is known as nonresponder imputation (NRI). Binary endpoints involving the NRS-R or NRS-A (such as proportion of subjects who are pain-free) through 72 hours will be constructed following windowed worst observation carried forward (wWOCF) (see Section 9.1.1 for details). Binary endpoints involving NRS-R or NRS-A on Day 10 or Day 28 (such as proportion of subjects with NRS score < 4 on Day 10) will be constructed using NRI.

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

For median time in hours to first opioid rescue administration through 72 hours, subjects who complete the 72 hour observation period without receiving an opioid or discontinue from the study prior to 72 hours without receiving an opioid will be censored at the time of completion or discontinuation, whichever is earlier.

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 randomized, subjects in the ITT Population, subjects in the mITT Population, subjects in the Safety Population, subjects completing the 72-hour postoperative observation period, subjects completing study (Day 28), subjects withdrawn from study with the primary 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

The demographics and baseline characteristics will be presented in tables using descriptive statistics. The demographics consist of age, age category, sex, race, and ethnicity. The baseline characteristics consist of weight, height, body mass index (BMI), nicotine status, and alcohol use. A subject's age in years is calculated using the integer part of the difference in number of days between the date that informed consent is signed and date of birth divided by 365.25, or 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 years old.

Demographics and baseline characteristics will be presented for the mITT Population and demographics only will be presented for all subjects enrolled who fail screening.

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 body system.

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, ECG, PE, etc)
- Safety reporting
- Randomization/blinding
- Study drug dosing/administration
- Visit schedule/windows

Classification of deviations as important protocol violations will be decided on a case-by-case basis without knowledge of the treatment assigned and before database lock. Protocol deviations will be presented in a summary table by protocol deviation category and treatment. Important protocol deviations will also be listed separately from all protocol deviations.

8. TREATMENTS AND MEDICATIONS

8.1. Prior and Concomitant Medications

Prior medications are defined as medications with a stop date occurring before Study Day 1. Concomitant medications are defined as medications that are ongoing on Study Day 1 or with a start date occurring on or after Study Day 1. Medications with start and stop dates which bracket Study 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 classification dictionary (WHODrug).

Prior and concomitant medications will be summarized separately by drug class and preferred term (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 medications and concomitant medications will be summarized for the Safety Population.

8.2. Surgery Procedure

The type of implant (silicone or saline), implant size per side, and the duration of surgery will be summarized. Duration will be calculated as completion time minus start time, reported in minutes.

8.3. Study Drug

For all subjects, treatment will consist of a single preoperative dose of study drug or a combination of a preoperative dose of study drug plus an intraoperative dose of study drug. As such, extent of exposure will be reported in the CSR as the number of subjects by treatment received in the Safety Population. A summary of treatment compliance will not be produced, as by definition it will be 100% for the Safety Population.

9. EFFICACY ANALYSIS

All efficacy analyses will be performed on the mITT Population. Timepoints for efficacy analysis are relative to the end time of surgery. Table 1 displays the planned cohorts and treatment groups being studied, with an assigned letter designation to each treatment group to facilitate statistical hypothesis testing.

Table 1. Planned Cohorts and Treatment Group Designations

Cohort	Group	Treatment	Administration Method	Sample Size
1	A	HTX-011 60 mg/1.8 mg (2.1 mL)	PcNB	12
	B	Bupivacaine HCl 50 mg (20 mL)	PcNB	6
	C	Saline placebo (2.1 mL)	PcNB	6
2	D	HTX-011 120 mg/3.6 mg(4.1 mL)	PcNB	24
	E	Bupivacaine HCl 50 mg (20 mL)	PcNB	12
	F	Saline placebo (4.1 mL)	PcNB	12
3	G	HTX-011 240 mg/7.2 mg (8.2 mL)	PcNB	24
	H	Bupivacaine HCl 50 mg (20 mL)	PcNB	12
	J	Saline placebo (8.2 mL)	PcNB	12
4	K	HTX-011 400 mg/12 mg (13.7 mL)	PcNB	48
	L	HTX-011 400 mg/12 mg (13.7 mL)	instillation	48
	M	Bupivacaine HCl 50 mg (20 mL)	PcNB	12
	N	Saline placebo (13.7 mL)	PcNB	12

Abbreviations: PcNB, pectoral nerve block.

As detailed in Section 5.3, for the purposes of statistical hypothesis testing, data from subjects randomized to receive saline placebo (Groups C+F+J+N) will be pooled across cohorts into a single saline placebo treatment group, and data from subjects randomized to receive bupivacaine HCl (Groups B+E+H+M) will be pooled across cohorts into a single bupivacaine HCl treatment group. Data from subjects randomized to receive HTX-011 will neither be pooled across dose levels nor be pooled across methods of administration within a dose level. Each of the HTX-011 treatment groups will be tested against the pooled saline placebo treatment group and against the pooled bupivacaine HCl treatment group.

There will be no hypothesis testing performed against any of the individual saline placebo or bupivacaine HCl groups.

9.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the mean AUC of the NRS-A pain intensity scores through 24 hours ($AUC_{0\text{-}24}$).

9.1.1. Primary Analysis

During the first 24 hours following surgery, the NRS-A is measured at hours 1, 2, 4, 6, 8, 12, and 24. 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 $AUC_{0\text{-}24}$ is thus calculated as follows:

$$AUC_{0-24} = \int_{1}^{24} f(t)dt \approx \sum_{i=2}^{24} (t_i - t_{i-1}) \frac{P_{i-1} + P_i}{2}$$

The primary endpoint of mean $AUC_{0\text{-}24}$ of the NRS-A pain intensity scores will be analyzed using an analysis of variance (ANOVA) model with randomized treatment as the main effect. Each HTX-011 group as well as the pooled groups specified in Section 9 will be tested against each of the pooled control groups. Results will be expressed as mean AUCs, SDs, and least-squares mean differences (LSMD) and standard errors (SE) with associated 95% CIs, and p-values.

To adjust for the duration effect of opioid rescue medication, the windowed worst observation carried forward (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 pre-window score, then it will **not** be replaced. wWOCF will be performed following LOCF (ie, perform LOCF first, then apply wWOCF). See Table 2 in Section 9.2 for predefined analgesic windows for each opioid medication.

The mean $AUC_{0\text{-}24}$ of the NRS-A pain intensity scores using wWOCF will also be plotted with associated SEM in a bar chart.

9.1.2. Sensitivity Analyses

One sensitivity analysis will be performed on the primary endpoint: reproducing the primary analysis but 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 listed in Section 4.3.1.

9.2.1. Analyses

Secondary Endpoint: Mean total postoperative opioid consumption (in morphine equivalents) through 24, 48, and 72 hours

Determination of morphine equivalents

Use of opioid rescue medication will be summarized by preferred term. All opiate dosages and formulations will have the morphine milligram equivalency (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) and/or intravenous morphine (no more than 10 mg within a 2-hour period as needed). No other analgesic agents, including nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, are permitted during the 72-hour postoperative observation period.

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

Table 2. Analgesic Windows and Morphine Milligram Equivalents for Opioid Rescue Medications

Medication	Route	Window (hr)	MME Factor	Protocol Allowed
CODEINE	PO	6	0.05	
DILAUDID	PO	4	1.33	
DILAUDID	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	Intramuscular (IM)	4	1.00	
MORPHINE	Per rectum (PR)	4	1.00	
OXYCODONE	IV	4	1.00	
OXYCODONE	IM	4	1.00	
OXYCODONE	PO	6	0.50	✓
SUFENTANIL	PO	2	500.00	
TRAMADOL	IV	6	0.06	
TRAMADOL	PO	6	0.04	

Analysis method

Opioid rescue medication use is collected from hours 0-72. Average daily use and total use will be tabulated using descriptive statistics for each opiate and overall during the following periods: hours 0-24, hours 0-48, and hours 0-72. Subjects who did not use a specific opioid rescue medication during a period of interest will have their dose set to 0 for that period.

The Shapiro-Wilk test will be used to examine the assumption of normality. If this test is statistically significant (ie, $p<0.05$) then the assumption of normality is violated and the total postoperative opioid consumption during each period of interest will be analyzed using Wilcoxon rank sum test. Results will be expressed as median (range) and p-values. However, if assumption of normality holds (ie, Shapiro-Wilk p-value ≥ 0.05), then the total postoperative opioid consumption during each period of interest will be analyzed using an

ANOVA model with randomized treatment as the main effect. Results will be expressed as means, SDs, and LSMD and SE with associated 95% CI, and p-values.

The mean total postoperative opioid consumption will also be plotted in a bar chart for each time period with associated SEM.

Secondary Endpoint: Median time in hours to first opioid rescue administration through 72 hours

Median time in hours to first opioid rescue administration will be plotted using Kaplan-Meier (K-M) curves, displaying 1-*S(t)*. K-M estimates of the median times will be presented along with their associated 95% CI in a table. Treatment group comparisons will be summarized with hazard ratios and their associated 95% CI and p-values from the generalized Wilcoxon test. Subjects who withdraw from the study prior to hour 72 or who complete the hour 72 visit without having taken rescue medication will be censored at the time of study withdrawal or at hour 72, whichever is earlier.

Secondary Endpoints: Mean AUC of the NRS-A pain intensity scores at the following intervals: 0-6, 0-12, 12-24, 24-48, 0-48, 0-72, and 48-72 hours and Mean AUC of the NRS-R pain intensity scores at the following intervals: 0-6, 0-12, 12-24, 0-24, 24-48, 0-48, 48-72, and 0-72 hours

Each of these 2 endpoints will be analyzed similarly to the methods described for the primary endpoint in Sections 9.1.1 and 9.1.2, with appropriate adjustments to the calculations to reflect the time periods of interest. Mean $AUC_{0\text{-}48}$ and mean $AUC_{0\text{-}72}$ will also be plotted in a bar chart for NRS-A and mean $AUC_{0\text{-}24}$, $AUC_{0\text{-}48}$ and mean $AUC_{0\text{-}72}$ will also be plotted in a bar chart for NRS-R.

Secondary Endpoints: Mean NRS-A pain intensity scores at each timepoint and mean NRS-R pain intensity scores at each timepoint

Mean pain intensity scores at each timepoint will be summarized with descriptive statistics. Mean NRS-A scores and Mean NRS-R scores at 24, 48, and 72 hours will be analyzed with ANOVA models with randomized treatment as the main effect. Results will be expressed as means, SDs, and LSMD and SE with associated 95% CI, and p-values. Mean pain intensity scores will be plotted in a line graph over time from hours 0-72, with associated SEM at each timepoint.

Secondary Endpoint: Integrated Rank Analysis of Silverman using the NRS-A pain intensity AUC scores and total opioid consumption through 24, 48, and 72 hours

An integrated assessment combining pain intensity scores and opioid rescue medication use via the use of ranks was detailed by Silverman, et al. (Silverman, O'Connor et al. 1993). In this analysis, each subject is ranked for both the AUC of the NRS-A pain intensity scores and

total opioid rescue medication dose in MME without regard to which of the treatments being compared the subject was randomized. If there are ties, then the mean of the ranks had there been no ties is assigned to each of the tied subjects (for example, if 3 subjects are tied for 12th, then the mean of 12, 13 and 14 is assigned as the rank for those 3 subjects and the next rank starts at 15). Then the percent difference between each subject's 2 ranks and the overall mean rank is calculated, resulting in 2 percent difference ranks for each subject. Finally the 2 ranks are added together and analyzed.

Let n_1 and n_2 be the sample sizes of the relevant treatment groups. Then the overall mean rank R_N is calculated as:

$$R_N = \frac{n_1 + n_2 + 1}{2}$$

and the percent difference Δ_i between each subject's rank R_i and the overall mean rank is calculated as:

$$\Delta_i = 100\left(\frac{R_i - R_N}{R_N}\right)$$

The integrated rank of Silverman (IRS) for each subject is then calculated as:

$$IRS_i = \Delta_{i(AUC)} + \Delta_{i(MME)}$$

In this analysis lower IRS are better than higher IRS. The IRS will be rounded to the nearest integer before analysis. Summary statistics for the $IRS_{0\text{-}24}$, $IRS_{0\text{-}48}$, and $IRS_{0\text{-}72}$ will be presented, and treatment differences will be analyzed using a Wilcoxon Rank Sum test, with p-values reported.

Secondary Endpoint: Proportion of subjects achieving a score of "good" or better (>1) pain control based on PGA at 24, 48, and 72 hours, and on Day 28

The PGA of pain control is a 4-point scale in which a subject rates how well her pain has been controlled. The possible responses to the question are:

- 0: Poor
- 1: Fair
- 2: Good
- 3: Excellent

The proportion of subjects answering in each category will be reported at each timepoint. The proportion of subjects achieving a score of "good" or better (>1) pain control based on PGA will be analyzed at each timepoint using Fisher's exact test. Descriptive statistics, differences in proportions, p-values, and exact 95% CI based on the score statistic (Chan and Zhang 1999) will be presented.

Secondary Endpoint: Proportion of subjects who are pain free with activity (defined as an NRS-A pain intensity score of 0 or 1), and proportion of subjects who are pain free at rest (defined as an NRS-R pain intensity score of 0 or 1) at each assessed timepoint

Subjects with an NRS (including NRS-A or NRS-R) pain intensity score of 0 or 1 at a particular timepoint will be characterized as "pain-free" at that timepoint. The proportion of subjects who are pain-free will tabulated with numbers and percentages. The proportion of subjects who are pain-free at 24, 48, and 72 hours will be analyzed using Fisher's exact test. Descriptive statistics, differences in proportions, p-values, and exact 95% CI will be presented, along with bar charts.

Secondary Endpoint: Proportion of subjects who are opioid free through 24, 48, and 72 hours

Subjects who have a total MME opioid dose = 0 through 24 hours will be characterized as "opioid-free" at 24 hours, subjects who have a total MME opioid dose = 0 through 48 hours will be characterized as "opioid-free" at 48 hours, and subjects who have a total MME opioid dose = 0 through 72 hours will be characterized as "opioid-free" at 72 hours. The proportion of subjects who are opioid-free at each of these 3 timepoints will be analyzed using Fisher's exact test. Descriptive statistics, differences in proportions, p-values, and exact 95% CI will be presented. The proportion of subjects who are opioid free through 24, 48 and 72 hours will be plotted with bar charts.

Secondary Endpoint: Proportion of subjects who are opioid-free from 72 hours through Day 10 and Day 28

Subjects will be provided a diary to record if they took any opioid medication for their pain 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. The proportion of subjects who are opioid-free during each of these 2 periods will be analyzed using Fisher's exact test. Descriptive statistics, differences in proportions, p-values, and exact 95% CI will be presented.

Secondary Endpoint: Proportion of subjects who first achieve an MPADSS score ≥ 9 at 2, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours

Discharge readiness is assessed by the MPADSS. The proportion of subjects who first achieve an MPADSS score ≥ 9 at each timepoint will be analyzed cumulatively (ie, 2 hours, ≤ 4 hours, ≤ 6 hours, etc.) using Fisher's exact test. Descriptive statistics, differences in proportions, p-values, and exact 95% CI will be presented.

Secondary Endpoints: Mean subject's satisfaction with postoperative pain control at 24, 48, and 72 hours and Day 10

Satisfaction with postoperative pain control is collected on a scale of 1 (strongly disagree) to 5 (strongly agree) in response to the question "are you satisfied with postoperative pain control?"

Mean satisfaction at each timepoint will be summarized with descriptive statistics.

Secondary Endpoints: Mean OBAS at 24, 48, and 72 hours and on Day 28

Overall benefit of analgesia is collected using a 7-item, multidimensional, quality assessment questionnaire (Lehmann, Joshi et al. 2010) addressing pain, vomiting, itching, sweating, freezing, dizziness, and overall satisfaction with postoperative pain. Each of the 7 items is rated on a scale of 0-4 as follows:

- Item 1 (pain): 0 = "minimal pain", 4 = "maximum imaginable pain"
- Items 2-7: 0 = "not at all", 4 = "very much"

The OBAS for a subject is calculated by summing the scores in items 1-6 plus the difference between 4 and the score in item 7 for that subject:

$$OBAS = (4 - item_7) + \sum_{i=1}^{6} item_i$$

Therefore the range of possible scores goes from 0 (answering 0 to the first 6 questions and 4 to question 7) to 28 (answering 4 to the first 6 questions and 0 to question 7). Question 7 is scored inversely because it is the only question where higher scores represent better outcomes.

Mean OBAS at each timepoint will be summarized with descriptive statistics.

9.3. Other Efficacy Analyses

Analyses will be carried out on the pain intensity scores to evaluate the following:

- Acute moderate and severe pain with activity:
  - The proportion of subjects with an NRS-A pain intensity score ≥ 4 at any timepoint through 24, 48, and 72 hours
  - The proportion of subjects with an NRS-A pain intensity score ≥ 7 at any timepoint through 24, 48, and 72 hours

- Acute moderate and severe pain at rest:
  - The proportion of subjects with an NRS-R pain intensity score ≥ 4 at any timepoint through 24, 48, and 72 hours

  - The proportion of subjects with an NRS-R pain intensity score ≥ 7 at any timepoint through 24, 48, and 72 hours

- Persistent moderate and severe pain with activity:
  - The proportion of subjects with an NRS-A pain intensity score ≥ 4 at Day 10
  - The proportion of subjects with an NRS-A pain intensity score ≥ 4 at Day 28
  - The proportion of subjects with an NRS-A pain intensity score ≥ 7 at Day 10
  - The proportion of subjects with an NRS-A pain intensity score ≥ 7 at Day 28

- Persistent moderate and severe pain at rest:
  - The proportion of subjects with an NRS-R pain intensity score ≥ 4 at Day 10
  - The proportion of subjects with an NRS-R pain intensity score ≥ 4 at Day 28
  - The proportion of subjects with an NRS-R pain intensity score ≥ 7 at Day 10
  - The proportion of subjects with an NRS-R pain intensity score ≥ 7 at Day 28

- Maintenance of mild or no pain with activity:
  - The proportion of subjects with an NRS-A pain intensity score < 4 at hour 72 who also are < 4 at Day 10
  - The proportion of subjects with an NRS-A pain intensity score < 4 at hour 72 who are also < 4 at Day 28
  - The proportion of subjects with an NRS-A pain intensity score < 4 at hour 72 and at Day 10
  - The proportion of subjects with an NRS-A pain intensity score < 4 at hour 72 and at Day 28

- Maintenance of mild or no pain at rest:
  - The proportion of subjects with an NRS-R pain intensity score < 4 at hour 72 who also are < 4 at Day 10
  - The proportion of subjects with an NRS-R pain intensity score < 4 at hour 72 who are also < 4 at Day 28
  - The proportion of subjects with an NRS-R pain intensity score < 4 at hour 72 and at Day 10
  - The proportion of subjects with an NRS-R pain intensity score < 4 at hour 72 and at Day 28

Pain parameters through 72 hours will be constructed using wWOCF. Pain parameters on Day 10 or Day 28 will be constructed using NRI.

Each of the above proportions will be analyzed using Fisher's exact test. Descriptive statistics, differences in proportions, p-values, and exact 95% CI will be presented.

10. SAFETY ANALYSIS

All analyses of safety data will be conducted using the Safety Population. Statistical hypothesis testing will not be performed on any safety results. No imputation of missing

safety data will be performed except in the case of partial AE and concomitant medication onset dates (Appendix 1). Baseline for safety analysis is defined as the last data collected, whether scheduled or unscheduled, prior to the start of study drug administration.

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, 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, vital sign result, or ECG finding 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 System Organ Class (SOC), and PT. Any AEs that occur prior to 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 in the HTX-011 total column. For tables showing incidence by PT only, the PTs will be sorted in descending order of incidence in the HTX-011 total column.

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 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

Incidence of possibly related TEAEs to study drug will be presented in a table by SOC and PT. The potential relationships are "Unlikely Related" and "Possibly Related". TEAEs that are missing relationship will be presented in the summary table as "Possibly Related" but will be presented in the data listing with a missing relationship.

10.1.3. Severity of Adverse Event

Incidence of severe TEAEs will be presented in a table by SOC and PT. TEAEs that are missing severity will be presented in summary tables as "severe" 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. A 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.

Incidence of treatment-emergent SAEs will be presented in a table by SOC and PT. Incidence of possibly related SAEs will also be presented by PT. The incidence of SAE tables will include only 1 occurrence of a PT per subject. If a subject reports the same SAE 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 SAEs within the same SOC, then that SOC will only be incremented by 1 since subject counts will be presented. SAEs will also be listed separately.

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
- Somnolence
- Respiratory depression
- Urinary retention

Incidence of ORAEs will be presented separately as follows:

- Incidence of ORAEs through Day 28
- Incidence of ORAEs through 72 hours
- Incidence of ORAEs through Day 28 in the subset of subjects who received at least 1 opioid rescue medication through 72 hours
- Incidence of ORAEs through 72 hours in the subset of subjects who received at least 1 opioid rescue medication through 72 hours

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 were reviewed by searching the safety database using a custom list of PTs created by Heron as below.

- Blister
- Blood blister
- Cellulitis
- Erythema
- Impaired healing
- Incision site cellulitis
- Incision site complication
- Incision site infection
- Incision site erythema
- Incision site haemorrhage
- Incision site vesicles

- Infection
- Medical device site cellulitis
- Post procedural cellulitis
- Postoperative wound complication
- Postoperative wound infection
- Purulent discharge
- Wound complication
- Wound dehiscence
- Wound infection

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 PT. Local inflammatory TEAEs will also be listed separately.

10.1.8. Local Anesthetic System Toxicity (LAST) related Adverse Events

The symptoms that may attribute to LAST were reviewed by searching the safety database using a custom list of PTs created by Heron as below.

- Arrhythmia
- Bradycardia
- Cardiac arrest
- Dizziness
- Dysguesia
- Hypotension
- Muscle twitching
- Paresthesia oral
- Respiratory arrest
- Seizure
- Tinnitus
- Tremor
- Visual impairment

Incidence of LAST-related TEAEs will be presented in a table by PT. LAST TEAEs will also be listed separately.

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, 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, hour 24 [hematology only], 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.

10.2.1. Hematology

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

10.2.2. 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 abnormalities in Liver Function Tests (ALT, AST) will be summarized at each visit for each treatment group for the following categories:

- > 1 x ULN
- ≥ 2 x ULN
- ≥ 3 x ULN
- ≥ 4 x ULN
- ≥ 5 x ULN

10.2.3. Urine Pregnancy Test and Urine Drug Screen

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

10.3. Vital Sign Measurements

Vital signs including systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate/pulse (HR), and respiration rate will be collected at screening, on Day 0 before study drug administration, and at 24, 48, 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). The criteria for clinically relevant abnormalities are shown in Table 3.

Table 3. 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.

10.4. Electrocardiogram

12-lead ECG (triplicate) is performed at screening. Screening ECG results will be listed only, and will include each of the 3 triplicate ECGs as well as the mean values from the triplicate assessments.

10.5. Physical Examination

Physical examination is performed at Screening, 72 hours, and early termination. Physical examination results will be listed only.

10.6. Wound Healing Assessment

Wound healing assessment according to the Southampton Wound Scoring System (Bailey, Karran et al. 1992) is performed at 72 hours, and on Days 10 and 28. A summary of wound healing assessment results will be produced, showing the number and percentage of subjects at each visit by grade with subgrade breakdown. Wound healing assessment results will also be listed.

10.7. Motor Function Assessment

Motor function assessment is performed at Screening, at 6, 12, 24, 48, and 72 hours, and on Day 10. The proportion of subjects able to perform a successful motor function assessment (ie, with the elbows at the side and against the body, raise hands in front of abdomen, clasp hands together, and hold that position for at least 5 seconds) will be summarized at each timepoint. Overall time to first successful motor function assessment will be summarized. Subjects who withdraw from the study prior to hour 72 or who complete the hour 72 visit without performing a successful motor function assessment will be censored at the time of study withdrawal or at hour 72, whichever is earlier.

10.8. Sensory Function Test

The proportion of subjects with loss of sensation in the breast on the side of the dominate hand at 15, 30, and 60 minutes after the start of study drug administration will be summarized. The median time to loss of sensation in the same breast will be presented.

Following the surgical procedure, the sensory function test is performed at 6, 12, 24, 48, and 72 hours, and on Day 10. The proportion of subjects with a response of "yes" at each timepoint will be summarized. The median time to return of sensory function (the first "yes") will also be presented.

10.9. Blinded Assessor's Satisfaction with Return of Sensory and Motor Function

Satisfaction with return of sensory and motor function is collected on a scale of 1 (strongly disagree) to 5 (strongly agree) in response to the question "are you satisfied with return of sensory and motor function?"

Mean satisfaction at each timepoint will be summarized with descriptive statistics.

11. INTERIM ANALYSIS

11.1. Interim Analysis

Up to 4 interim analyses will be performed. An internal IRC composed of 1 Sponsor representative from each of the Clinical Research, Biometrics, Pharmacovigilance, Regulatory, and Pharmaceutical and Translational Sciences functions will review unblinded summary-level data from each cohort in order to make a determination to proceed with the next cohort and to select the dose(s) of HTX-011 that will be studied in the next cohort. Each interim analysis will be performed after at least 80% of the planned subjects have had their pain intensity and opioid use data through the 72-hour postoperative assessments entered into the eCRF for that cohort. Detailed responsibilities of the IRC will be presented in an IRC charter.

No adjustments to the type-1 error rate will be made in the efficacy hypothesis testing as a result of these interim analyses.

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 blinded tables and listings of accumulating data approximately bi-weekly to check enrollment, adherence to follow-up schedule, and ongoing safety results.

12. REFERENCES

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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	Set month to month 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 first dose	Missing	Set day as day of 1st dose
year = year of SDA	Month < month of first dose	Missing	Set day as last day of onset month
year = year of SDA	Month > month of first dose	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
1.0	23 DEC 2016	Initial version, based on protocol version 2 (16 DEC 2016)
2.0	08 FEB 2017	Second version, based on protocol version 3 (2 February 2017). Revised endpoint list to match new protocol version. Minor clarifications to the age ranges in demographics table, and to some of the secondary endpoint and safety analyses.
3.0	04 JAN 2018	Third version, based on protocol version 6 (15 November 2017). • Revised endpoint list to match new protocol version and updated corresponding secondary endpoint analysis • Revised sections 5.5.3 and 10.1 to update study day algorithm (ie, remove study day 0 to compliant with CDISC standard). • Modified section 9.3 to align with planned analyses in studies 209,301 and 302 • Used wWOCF as the primary method to analyze primary endpoint. The LOCF method was changed to be sensitivity analysis. • Used Shapiro-Wilk test to determine normality before choosing ANOVA or Wilcoxon rank sum test to analyze mean total opioid consumption. • Added custom lists of preferred terms for analysis of Inflammatory and LAST symptoms

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