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STUDY HTX-011-302

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, SALINE PLACEBO- AND ACTIVE-CONTROLLED, MULTICENTER STUDY OF HTX-011 VIA LOCAL ADMINISTRATION FOR POSTOPERATIVE ANALGESIA AND DECREASED OPIOID USE FOLLOWING UNILATERAL OPEN INGUINAL HERNIORRHAPHY (EPOCH 2)

24 October 2017

Statistical Analysis Plan

Version 2

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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.

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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
IRS	Integrated Rank of Silverman
IRT	Interactive response technology
ITT	Intent-to-Treat
IV	Intravenous(ly)
K-M	Kaplan-Meier
LAST	Local Anesthetic System Toxicity
LDH	Lactic dehydrogenase
LLN	Lower limit of normal
LOCF	Last observation carried forward
LSMD	Least-squares mean difference
MedDRA	Medical Dictionary for Regulatory Activities
MME	Morphine milligram equivalency
MPADSS	Modified Postanaesthetic Discharge Scoring System
NRI	Nonresponder imputation
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
PACU	Post-Anesthesia Care Unit
PGA	Patient’s Global Assessment
PGIC	Patient’s Global Impresson of Change
PK	Pharmacokinetic(s)

PO	Administered orally
PR	Per rectum
PRN	As needed
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
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 pharmacokinetics (PK) assessments in the study. Planned PK analysis will be presented in a separate PK 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 as follows:

- To compare the efficacy and duration of analgesia following local administration of HTX-011 with saline placebo during the first 72 hours following unilateral open inguinal herniorrhaphy

The secondary objectives are as follows:

- To compare the efficacy and duration of analgesia for HTX-011 with bupivacaine HCl without epinephrine during the first 72 hours following surgery in this study population
- To compare the effect of HTX-011 with saline placebo and bupivacaine HCl without epinephrine on opioid load during the first 72 hours following surgery in this study population
- To assess the safety and tolerability of HTX-011 in this study population
- To further establish the pharmacokinetic (PK) parameters of bupivacaine and meloxicam in HTX-011 in this study population

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 3, randomized, double-blind, saline placebo- and active-controlled, multicenter study in subjects undergoing unilateral open inguinal herniorrhaphy. This study will evaluate the efficacy and safety profile of HTX-011 on clinical outcomes (eg, level of pain, avoidance of opioids, etc.) in subjects treated with a single intraoperative dose of study drug administered via instillation into the surgical site.

Approximately 400 subjects will be randomized to 1 of the following 3 treatment group in a 2:2:1 ratio:

- HTX-011, 300 mg/9 mg (bupivacaine/meloxicam doses), 10.3 mL, via instillation into the surgical site (160 subjects)
- Bupivacaine HCl without epinephrine 0.25%, 75 mg (30 mL), via injection into the surgical site (160 subjects)
- Saline placebo, 10.3 mL, via instillation into the surgical site (80 subjects)

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

- Discharge readiness assessment per the Modified Postanaesthetic Discharge Scoring System (MPADSS) criteria
- Patient Global Assessment (PGA) of pain control

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)
- Physical examinations
- Wound healing assessment
- Vital signs collections
- Local Anesthetic Systemic Toxicity (LAST) assessment

4.3. Endpoints

4.3.1. Efficacy Endpoints

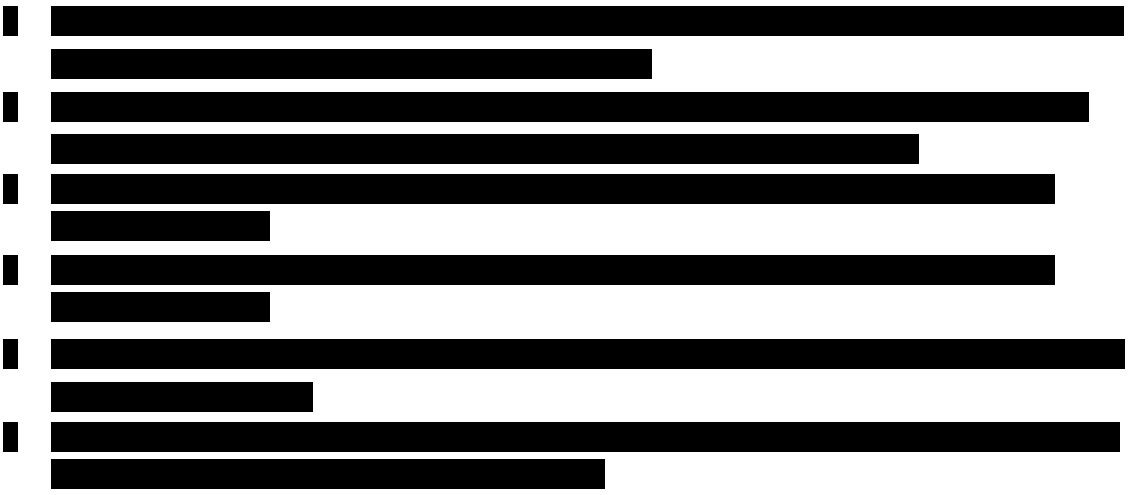
The primary efficacy endpoint is:

- Mean area under the curve (AUC) of the NRS-A pain intensity scores through 72 hours (AUC_{0-72}) for HTX-011 compared with saline placebo

The key secondary efficacy endpoints via hierarchical testing are:

1. Mean AUC_{0-72} of the NRS-A pain intensity scores for HTX-011 compared with bupivacaine HCl
2. Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with saline placebo
3. Proportion of subjects who are opioid-free through 72 hours for HTX-011 compared with bupivacaine HCl
4. Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with bupivacaine HCl

[redacted]



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 ECG data
- Change from baseline in vital signs
- Wound healing assessment at 72 hours and on Day 10 and Day 28

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 (SE). 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 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 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.

5.1. Sample Size

Based on a previous Phase 2 study of HTX-011 in subjects undergoing unilateral open inguinal herniorrhaphy, estimates of the relevant parameters for each of the primary and key secondary endpoints are as follows:

Parameter	Saline Placebo	Bupivacaine HCl	HTX-011 300 mg/9 mg
Pain intensity AUC_{0-72}: Mean (SD)	400 (150)	350 (150)	275 (200)
Opioid consumption (mg): Mean (SD)	30 (25)	23 (25)	12 (25)
Proportion of opioid-free subjects	10%	20%	40%

Assuming these estimates and using Satterthwaite's t-test with $\alpha = 0.05$, 2-sided for the continuous endpoints and Fisher's exact test with $\alpha = 0.05$, 2-sided for the categorical endpoints, 160 subjects in the HTX-011 group, 160 subjects in the bupivacaine HCl active control group, and 80 subjects the saline placebo control group provides at least 90% power to detect a statistically significant difference between the HTX-011 group and each of the control groups for each of the primary and key secondary endpoints.

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. 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. However, subjects will not be aware of the study drug they are receiving, and once surgery is completed and the subject is transferred to the PACU, the Investigator and all site staff involved in safety and efficacy assessments will be blinded to the treatment assignment until after database lock. The Sponsor's study team will also be blinded to the treatment assignments with the exception of the clinical trial material (CTM) and clinical observer staff.

The randomization will be based on a centralized computer-generated blocked randomization algorithm created by an IRT provider.

A subject's treatment group assignment will not be broken until database lock 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

The primary endpoint of $AUC_{0\text{-}72}$ of NRS-A will be a comparison of HTX-011 with saline placebo under the following hypothesis:

$$H_0: \mu_{\text{HTX-011}} = \mu_{\text{saline placebo}}$$
$$H_a: \mu_{\text{HTX-011}} \neq \mu_{\text{saline placebo}}$$

The primary endpoint will be carried out using an analysis of variance (ANOVA) model with treatment as the main effect, comparing HTX-011 with saline placebo at a significance level of 5%. Results will be expressed as mean AUCs and SDs, least-square mean differences (LSMD) and SEs with associated 95% CI, and p-values.

The first key secondary endpoint involving $AUC_{0\text{-}72}$ of NRS-A comparing HTX-011 with bupivacaine HCl will be analyzed similarly to the methods described for the primary endpoint.

Total postoperative opioid consumption through 72 hours will be summarized using descriptive statistics. The Shapiro-Wilk test will be used to examine the assumption of normality. If this test is statistically significant (ie, $p \leq 0.05$) then the assumption of normality is violated and the total postoperative opioid consumption through 72 hours will be analyzed

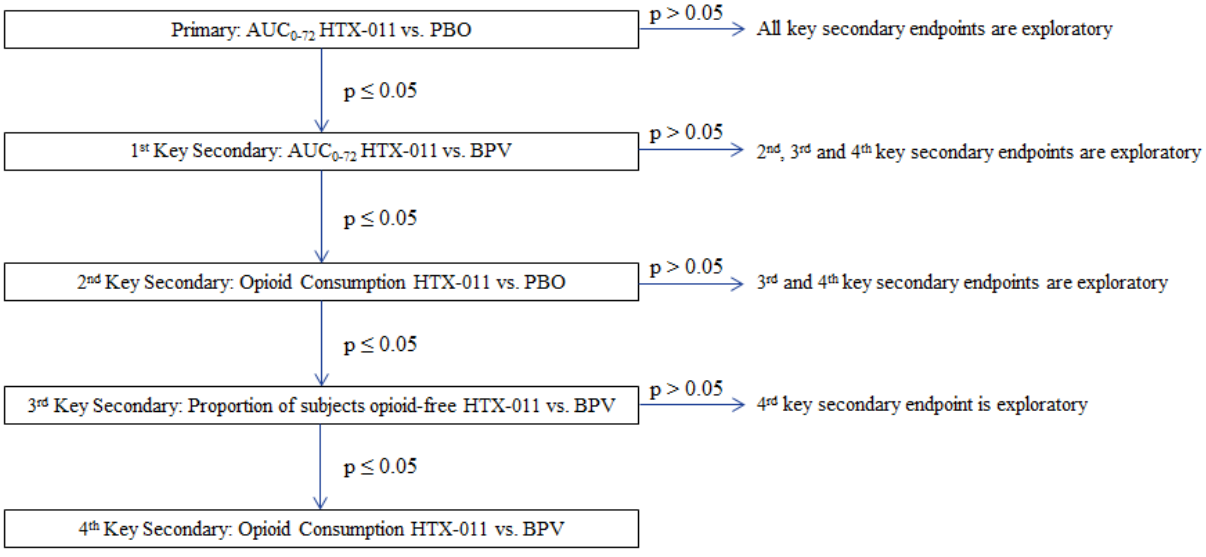
using a Wilcoxon rank sum test. Results will be expressed as median (range) and p-values. However, if the assumption of normality holds (ie, Shapiro-Wilk p-value >0.05), then the total postoperative opioid consumption through 72 hours will be analyzed using an ANOVA model with treatment as the main effect. Results will be expressed as means, SDs, and LSMD and SEs with associated 95% CI, and p-values.

The proportion of subjects who are opioid-free postoperatively through 72 hours will be analyzed using Fisher's exact test. Results will be expressed as the number and percentage of subjects meeting the relevant endpoint, differences in proportions with 95% CI, and p-values.

In order to account for multiple hypothesis testing on the primary endpoint and on each of the 4 key secondary endpoints, a strict testing hierarchy will be applied to control study-wise alpha level at 0.05. If the primary endpoint is statistically significant ($p \leq 0.05$), then the first key secondary endpoint will be tested. If the first key secondary endpoint is statistically significant, then the second key secondary endpoint will be tested. Sequential testing will continue in this manner down the key secondary endpoint list until an endpoint fails to meet statistical significance, after which all subsequent key secondary endpoints will be considered exploratory (

Figure 1). If the primary endpoint is not statistically significant, then all key secondary endpoints will be considered exploratory.

Figure 1. Hierarchical test procedure for primary and key secondary endpoints



Abbreviations: BPV, bupivacaine HCl; PBO, saline placebo

5.4. Analysis Populations

5.4.1. Intent-to-Treat (ITT) Population

The ITT Population will consist of all subjects who are randomized and receive study drug. This analysis 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.

5.4.2. Per Protocol Population

The Per Protocol Population will consists of all subjects in the ITT Population who do not receive a prohibited rescue medication prior to 72 hours and who have no important protocol violations prior to 72 hours. This population will be used for sensitivity analyses on the primary and key secondary endpoints.

5.4.3. Safety Population

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

5.5. Other Important Considerations

5.5.1. 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.

5.5.2. 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 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. 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 study drug administration 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.

5.5.5. 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.

5.5.6. 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.

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). Analyses 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, 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 Per Protocol 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

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 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.

Demographics and baseline characteristics will be presented for the ITT Population, the Safety Population, and the Per Protocol Population. Demographics will also 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 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, 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. Reasons for excluding subjects from the Per Protocol Population will be summarized for the ITT population by treatment and overall.

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 classification dictionary (WHODrug), September 1, 2016.

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 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 medication with indication of "Post Operative Pain"
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 5.5.4 for details)

Opioid rescue medication in morphine milligram equivalency (MME) dose (see Section 9.2 for details) and non-opioid rescue medication dose 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 the ITT population.

8.3. Surgery Procedure

The side of body subject to the surgical procedure (left or right), type of mesh, and the duration of surgery will be summarized. Duration will be calculated as completion time minus start time, reported in minutes. In addition, summary statistics will be provided for length of incision in centimeters.

8.4. Study Drug

For all subjects, treatment will consist of a single 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 ITT Population. Table 1 displays the planned treatment groups being studied.

Table 1. Planned Treatment Groups

Treatment	Planned Sample Size
HTX-011 300 mg/9 mg (10.3 mL)	160
Saline placebo (10.3 mL)	80
Bupivacaine HCl 75 mg (30 mL)	160

See Section 5.3 for details on multiple endpoint handling for primary and key secondary endpoints.

The following treatment comparisons will be tested for each efficacy endpoint.

1. HTX-011 300 mg/9 mg vs. saline placebo
2. HTX-011 300 mg/9 mg vs. bupivacaine HCl 75 mg

In addition, the following comparison will be tested for AUC of NRS-A and NRS-R pain intensity scores only: bupivacaine HCl 75 mg vs. saline placebo.

Subgroup analyses will be performed for the primary and key secondary efficacy endpoints where applicable. The following are the pre-defined subgroups:

- Age at screening (18-44, 45-54, 55-64, 65-74, 75-84, and ≥ 85)
- Sex (female, male)
- Race (black, white, other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)

If any of the subgroups has fewer than 20 total subjects, then that subgroup will either not be performed (eg, if there are fewer than 20 males) or will be pooled with another subgroup (eg, if there are fewer than 20 subjects in the 55-64 age group).

9.1. Primary Efficacy Endpoint

The primary estimand to address the efficacy objectives is the mean AUC of NRS-A pain intensity scores through 72 hours (AUC_{0-72}) adjusted for use of opioid rescue medication via wWOCF, comparing the estimated treatment difference between HTX-011 and saline placebo using ANOVA with missing data imputed using LOCF for interval censored pain intensity scores and WOCF for right-censored pain intensity scores in the ITT Population.

The primary efficacy endpoint is the mean AUC of the NRS-A pain intensity scores through 72 hours (AUC_{0-72}) for HTX-011 compared with saline placebo.

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:

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

The primary endpoint of mean $AUC_{0\text{-}72}$ of the NRS-A pain intensity scores will be analyzed using an ANOVA model with randomized treatment as the main effect, comparing HTX-011 with saline placebo at a significance level of 5%. Results will be expressed as mean AUCs, SDs, and LSMD and SEs with associated 95% CI, and p-values.

To adjust for the duration effect of opioid rescue medication, 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/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 $AUC_{0\text{-}72}$ of the NRS-A pain intensity scores using wWOCF will also be plotted with associated SEs in a bar chart. A forest plot showing the overall result and the result for each of the subgroups will also be presented.

The $AUC_{0\text{-}12}$, $AUC_{0\text{-}24}$, $AUC_{24\text{-}48}$, $AUC_{0\text{-}48}$, and $AUC_{48\text{-}72}$ of the NRS-A pain intensity scores will be analyzed similarly as for the $AUC_{0\text{-}72}$ of the NRS-A pain intensity scores, with appropriate adjustments to the calculations to reflect the time periods of interest. Mean $AUC_{0\text{-}24}$, and mean $AUC_{0\text{-}48}$ 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 analyses will be performed on the primary endpoint:

1. Reproducing the primary analysis but without adjusting the NRS-A pain intensity scores for the use of opioid rescue medications (ie, without applying wWOCF)
2. Reproducing the primary analysis on the Per Protocol Population

9.2. Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints via hierarchical testing are:

1. Mean AUC of the NRS-A scores through 72 hours (AUC_{0-72}) for HTX-011 compared with bupivacaine HCl
2. Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with saline placebo
3. Proportion of subjects who are opioid-free through 72 hours for HTX-011 compared with bupivacaine HCl
4. Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with bupivacaine HCl

The endpoint involving AUC of NRS-A will be analyzed similarly to the methods described for the primary endpoint in Sections 9.1.1 and 9.1.2.

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 compared with bupivacaine HCl using Fisher's exact test. Descriptive statistics, differences in proportions, p-values, and exact 95% CI based on Farrington-Manning score statistics (Chan and Zhang 1999) will be presented.

The endpoints involving postoperative opioid consumption will be analyzed as follows:

Determination of morphine equivalents

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

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 or oral paracetamol (no more than 1 gram [1000 mg] in a 6-hour window). For subjects administered any acetaminophen/paracetamol-containing product, the total combined daily dose must not exceed 4 grams (4000 mg) as severe liver damage may occur. No other

analgesic agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), 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 opioid rescue medications are checked. Opioid 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	IM	4	1.00	
MORPHINE	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	

Abbreviations: hr, hour; IM, intramuscular; IV, intravenous; MME, morphine milligram equivalency; 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 opiate, for overall opioids, and for acetaminophen/paracetamol 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. Only postoperative opioid consumption will be subject to hypothesis testing for the relevant key secondary endpoints.

The Shapiro-Wilk test will be used to examine the assumption of normality. If this test is statistically significant (ie, $p \leq 0.05$) then the assumption of normality is violated and the total postoperative opioid consumption during each period of interest will be analyzed using a Wilcoxon rank sum test. Results will be expressed as median (range) and p-values. However, 1if the 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 SEs 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 SEs.

Mean total postoperative opioid consumption in MME through 24 and 48 hours will be analyzed similarly, with appropriate adjustments to the calculations to reflect the time periods of interest.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.4. Other Efficacy Analyses

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

- 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 72 hours who also are < 4 at Day 10
  - The proportion of subjects with an NRS-A pain intensity score < 4 at 72 hours who are also < 4 at Day 28
  - The proportion of subjects with an NRS-A pain intensity score < 4 at 72 hours and at Day 10
  - The proportion of subjects with an NRS-A pain intensity score < 4 at 72 hours 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 72 hours who also are < 4 at Day 10
  - The proportion of subjects with an NRS-R pain intensity score < 4 at 72 hours who are also < 4 at Day 28
  - The proportion of subjects with an NRS-R pain intensity score < 4 at 72 hours and at Day 10
  - The proportion of subjects with an NRS-R pain intensity score < 4 at 72 hours and at Day 28

- Mild or no pain in in the absence of opioid rescue medication use
  - The proportion of subjects with an NRS-A pain intensity score < 4 at 72 hours with no opioid rescue medication use through 72 hours
  - The proportion of subjects with an NRS-R pain intensity score < 4 at 72 hours with no opioid rescue medication use through 72 hours

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).

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 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 in the HTX-011 column. For tables showing incidence by PT only, the PTs will be sorted in descending order of incidence in the HTX-011 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

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. 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. 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
- Incidence of ORAEs through the 72-hour postoperative observation period
- Incidence of ORAEs in the subset of subjects who received at least 1 opioid rescue medication during the 72-hour postoperative observation period
- Incidence of ORAEs through the 72-hour postoperative observation period in the subset of subjects who received at least 1 opioid rescue medication during 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 were reviewed by searching the safety database using a custom list of PTs created by Heron from 4 MedDRA SOCs (Table 3).

Table 3. Local Inflammatory Adverse Events by System Organ Class and Preferred Term

General disorders and administration site conditions	Infections and infestations	Injury, poisoning and procedural complications	Skin and subcutaneous tissue disorders
• Impaired healing	• Cellulitis • Incision site cellulitis • Incision site infection • Infection • Medical device site cellulitis • Post procedural cellulitis • Postoperative wound infection • Purulent discharge • Wound infection	• Incision site complication • Incision site erythema • Incision site haemorrhage • Incision site vesicles • Postoperative wound complication • Wound complication • Wound dehiscence	• Blister • Blood blister • Erythema[a]

[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. 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 (Table 4).

Table 4. LAST-Related Adverse Events by System Organ Class and Preferred Term

Nervous system disorders	Cardiac disorders	Vascular disorders	Respiratory, thoracic and mediastinal disorders
• Dysguesia • Paresthesia oral • Tinnitus • Visual impairment • Tremor • Muscle twitching • Dizziness • Seizure	• Bradycardia • Arrhythmia • Cardiac arrest	• Hypotension	• Respiratory arrest

Incidence of LAST-related TEAEs will be presented in a table by SOC and 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. Local Anesthetic System Toxicity Assessment

A LAST assessment questionnaire will be provided on a regular basis to monitor for early neurologic and cardiac signs and symptoms of LAST. A summary of LAST assessment results will be produced, showing the number and percentage of subjects with any sign of LAST symptom with breakdown of each symptom for overall and by each visit. LAST assessment results will also be listed.

10.3. 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, and Day 10), 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.

10.3.1. 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).

10.3.2. 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 clinically relevant abnormalities in Liver Function Tests will be summarized at each visit for each treatment group 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 x ULN
    - ≥ 2 x ULN
    - ≥ 3 x ULN
    - ≥ 4 x ULN
    - ≥ 5 x ULN
- Total bilirubin ≥ 2 x ULN
- ALP:
    - ≥ 1.5 x ULN
    - ≥ 2 x ULN
- ALT ≥ 3 x ULN and AST ≥ 3 x ULN
- ALT ≥ 3 x ULN and total bilirubin ≥ 2 x ULN
- AST ≥ 3 x ULN and total bilirubin ≥ 2 x ULN
- Hy's Law: (ALT or AST ≥ 3 x ULN) and ALP < 2 x ULN and total bilirubin ≥ 2 x ULN

10.3.3. Urine Pregnancy Test and Urine Drug Screen

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

10.4. 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 and at 4, 18, 24, 48, and 72 hours. ECG parameters include heart rate (beats/min), PR interval (ms), RR interval (ms), QRS interval (ms), QT interval (ms), and QTcF interval (ms). Overall interpretations of ECG results are also included.

ECG assessments will be performed in triplicate, and the mean value of the observed triplicates will be used for each ECG parameter. Summary statistics of ECG parameters and change from Baseline in ECG parameters will be presented using descriptive statistics at each scheduled visit by treatment group. Shift from baseline of overall ECG interpretation at each postoperative timepoint will also be provided.

The number and percentage of subjects with clinically relevant abnormalities will be presented using summary table as well as data listing at each postoperative timepoint.

- QTcF values > 450 ms, > 480 ms, and > 500 ms
- Change from Baseline in QTcF values > 30 ms and > 60 ms
- QT values > 500 ms

All ECG assessments will be listed.

10.6. Physical Examination

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

10.7. Wound Healing Assessment

Wound healing assessment according to the Southampton Wound Scoring System (Bailey, Karran et al. 1992) is performed at 72 hours, on Day 10, and on Day 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.

11. INTERIM ANALYSIS

11.1. Interim Analysis

No formal interim analyses are planned.

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 monthly 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	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	15AUG2017	Initial version, based on protocol version 3 (30JUL2017)
2	24OCT2017	Second version. • Added hours 24-48 and hours 48-72 intervals to analyses of AUC for NRS-A and NRS-R, and total opioid consumption • Added summaries for local inflammatory AEs • Added summaries for local anesthetic system toxicity (LAST) AEs

Signature Page for VV-CLIN-000444 v1.0

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