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STATISTICAL ANALYSIS PLAN

STUDY HTX-011-220

A Phase 2, Open-Label Study of the Pharmacokinetics and Safety of HTX-011 Administered Postpartum to Women Undergoing a Planned Caesarean Section

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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.

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Classification
AUC	Area under the curve
bpm	Beats per minute
BMI	Body mass index
BUN	Blood urea nitrogen
C-section	Caesarean section
CRO	Contract Research Organization
CSR	Clinical Study Report
DBP	Diastolic blood pressure
DM	Data management
DMSO	Dimethyl sulfoxide
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDISH	Evaluation of drug-induced serious hepatotoxicity
GGT	Gamma glutamyltransferase
HR	Heart rate
IM	Intramuscular
IV	Intravenous(ly)
LAST	Local anesthetic systemic toxicity
LDH	Lactic dehydrogenase
LLN	Lower limit of normal
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMA	multimodal analgesic
MME	Morphine milligram equivalency

Abbreviation	Term
NRS	Numeric Rating Scale
NRS-A	Numeric Rating Scale with activity
NRS-R	Numeric Rating Scale at rest
ORAE	Opioid-related adverse event
PK	Pharmacokinetic(s)
PO	Administered orally
PR	Per rectum
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
TEG POE	tri(ethylene glycol) poly(orthoester) polymer
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHODrug	World Health Organization Drug classification dictionary
WOCF	Worst observation carried forward
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). The data management (DM) is being performed under contract with EMB Statistical Solutions (EMB) and the statistical analyses are being performed under contract with Precision for Medicine, Oncology and Rare Disease (Precision for Medicine), with oversight from Heron. EMB and Precision for Medicine are Contract Research Organizations (CROs).

1.2. Data Quality Assurance

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

2. INTRODUCTION

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

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

This SAP should be read in conjunction with the study protocol and the electronic case report forms (eCRFs).

3. OBJECTIVES

The primary objective is to characterize the PK of bupivacaine, meloxicam, dimethyl sulfoxide (DMSO), and HTX-011 tri(ethylene glycol) poly(orthoester) polymer (TEG-POE) water-soluble end products in expressed breast milk and plasma following postpartum administration of HTX-011 in women undergoing a planned Caesarean section (C-section).

The secondary objective is to assess the safety and tolerability of HTX-011 administered alone or as part of a scheduled, non-opioid multimodal analgesic (MMA) regimen in this study population.

The exploratory objective is to characterize the efficacy and duration of analgesia during the first 72 hours following administration of HTX-011 alone or as part of a scheduled, non-opioid MMA regimen in this study population.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 2, open-label, multi-cohort study of HTX-011 administered postpartum either alone or as part of a scheduled, non-opioid MMA regimen in women undergoing a planned C-section who must have chosen prospectively to not breast-feed their newborn. The study will include up to 3 cohorts. Cohorts will be conducted sequentially.

4.1.1. Study Overview

In Cohort 1, subjects will receive HTX-011 300 mg/9 mg. In Cohort 2, subjects will receive HTX-011 400 mg/12 mg and a scheduled, non-opioid MMA regimen. PK (in expressed breast milk and plasma), safety, and efficacy will be assessed in Cohorts 1 and 2. An optional dose-expansion cohort (Optional Cohort 3) may be conducted after Cohort 2 to further evaluate the safety and efficacy of HTX-011 400 mg/12 mg and a scheduled, non-opioid MMA regimen. No PK assessments will be conducted in Optional Cohort 3.

Cohort 1

Approximately 15 subjects will be treated in Cohort 1. Subjects will be screened within 28 days prior to the planned surgery date. Eligible subjects will be enrolled and undergo a C-section under ropivacaine spinal anesthesia on Day 1. In addition to ropivacaine spinal anesthesia, management of intraoperative anesthesia will be in accordance with the prevailing institutional practice/anesthesiologist's preference as long as it does not include bupivacaine or meloxicam. After delivery of the newborn baby, all subjects will receive a single dose of HTX-011 300 mg/9 mg (bupivacaine/meloxicam doses) administered via instillation into the surgical site.

Cohort 2

Up to approximately 12 subjects will be treated in Cohort 2 to ensure adequate breast milk collection in at least 6 subjects. Subjects will be screened within 28 days prior to the planned surgery date. On the day of surgery (Day 1), eligible subjects will be administered oral (PO) acetaminophen 975 mg to 1 g approximately 2 hours prior to the start of anesthesia. Subjects will undergo a C-section under spinal anesthesia with ropivacaine up to 20 mg, intrathecal morphine sulfate injection (DURAMORPH®) 50 µg, and intrathecal fentanyl 20 µg. After delivery of the newborn baby, all subjects will receive a single dose of HTX-011 400 mg/12 mg administered via instillation into the surgical site. Following surgery, subjects will receive a scheduled, non-opioid MMA regimen while awake during the first 5 days after surgery (ie, Days 1 through 6) consisting of PO acetaminophen 975 mg to 1 g every 6 hours alternating with PO ibuprofen 400 mg every 6 hours.

Postoperative Follow Up for Cohorts 1 and 2

Subjects will remain in the hospital/research facility for a minimum of 72 hours after the start of HTX-011 administration to undergo postoperative assessments. Assessments will include the collection of breast milk and blood samples for PK analyses, and safety and efficacy assessments. After the 72-hour postoperative procedures and assessments have been completed, subjects may be discharged in accordance with institutional practice/Investigator preference. Sites will record if subjects are discharged with an opioid prescription and information about the opioid prescription.

At discharge, each subject will be provided a breast milk log to record breast milk expression during the follow-up period. A visiting healthcare professional will visit each subject once a day on Days 5, 6, 8, 9, and 10 to collect breast milk and blood samples for PK analyses. On Day 7 and Day 11, a visiting healthcare professional will visit the subject to collect only the breast milk samples, and the subject will return to the study site to undergo additional assessments. In Cohort 1 only, a visiting healthcare professional will visit the subject on the Day 16 Visit and collect a final blood sample and a final expressed breast milk sample for PK analyses. All subjects will return to the study site for a Day 28 Visit to undergo final study assessments.

Optional Cohort 3

After a review of data from Cohort 2, up to approximately 24 subjects may be treated in Optional Cohort 3. Subjects in Optional Cohort 3 will undergo a C-section under spinal anesthesia with ropivacaine up to 20 mg, intrathecal Duramorph 50 to 200 μg, and intrathecal fentanyl 20 μg. Subjects will receive the same HTX-011 dose and scheduled, non-opioid MMA regimen as Cohort 2 (pre- and postoperatively), and will follow the same schedule of events as Cohort 2 with the exception of PK assessments. Breast milk and blood samples for PK analysis will not be collected in Optional Cohort 3.

After at least 6 subjects have been administered HTX-011 in Cohort 1 and completed the Day 16 Visit breast milk collection, the Sponsor will conduct an analysis of PK data. If there are sufficient breast milk and plasma data to fulfill the primary objective, the study may be stopped and no more subjects will be enrolled.

4.1.2. Postoperative Rescue Medications:

Subjects should receive rescue analgesic medication only upon request for pain control, as needed, during the 72-hour postoperative observation period. Rescue medication should not be given for pain prophylaxis, but only for treating postoperative pain. Prior to the administration of the first dose of rescue medication, if the subject has not already had at least 1 postoperative pain score assessed, then a numeric rating scale of pain intensity (NRS) score must be obtained. Subjects who are not medically ready for discharge at 72 hours may receive the same analgesic rescue medication as described below to treat postoperative pain until discharge.

Cohort 1 Rescue Medication

Postoperative rescue medication during the 72-hour postoperative period will comprise any 1 or more of the following medications as needed: PO ibuprofen ≤600 mg within a 6-hour period, PO/intravenous (IV) acetaminophen ≤1 gram (1,000 mg) within a 6-hour period, PO immediate-release oxycodone ≤5 mg within a 4-hour period, and IV morphine ≤10 mg within a 2-hour period. For subjects administered any acetaminophen-containing product, the total combined

daily dose of acetaminophen must not exceed 4 grams (4,000 mg) in a 24-hour period. Combination products containing an opioid and non-opioid are not allowed. The recommended analgesic medication after discharge will be in accordance with the prevailing institutional practice/Investigator preference; however, any drug formulation containing bupivacaine or meloxicam is prohibited through the Day 16 Visit.

Cohort 2 and Optional Cohort 3 Rescue Medication

Postoperative rescue medication during the 72-hour postoperative period will initially consist of ibuprofen 400 mg PO (in addition to the scheduled MMA regimen), which may be administered at most only once every 12 hours. If pain persists approximately 30 minutes following ibuprofen rescue medication, the following rescue medications are permitted upon subject request for additional pain control: PO immediate-release oxycodone ≤5 mg within a 4-hour period and/or IV morphine ≤10 mg within a 2-hour period.

4.2. Assessments

Safety assessments will include the following:

- Adverse events (AEs)
- Potential local anesthetic systemic toxicity (LAST) symptoms questionnaire
- Vital signs
- 12-lead electrocardiograms (ECGs)
- Wound healing assessments using the Southampton Scale
- Clinical laboratory tests (hematology and serum chemistry)
- Physical examinations

Efficacy assessments will include the following:

- Pain intensity assessments using the numeric rating scale of pain intensity at rest (NRS-R)
- Pain intensity assessments using the numeric rating scale of pain intensity with activity (NRS-A) (Cohort 2 and Optional Cohort 3 only)
- Opioid rescue medication through 72 hours
- Opioid prescription at discharge

4.3. Endpoints

4.3.1. Safety Endpoints

The safety endpoints are:

- Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), opioid-related adverse events (ORAEs), and potential LAST-related TEAEs
- Change from baseline in clinical laboratory results

- Change from baseline in vital signs
- Wound healing assessment results at 24 hours, 72 hours, Day 7, Day 11, and Day 28

4.3.2. Exploratory Endpoints

The exploratory endpoints are:

- Mean area under the curve (AUC) of the NRS-R scores through 72 hours (AUC_{0-72})
- Mean AUC_{0-72} of the NRS-A scores (Cohort 2 and Optional Cohort 3 only)
- Total postoperative opioid consumption (in IV morphine milligram equivalents [MME]) through 72 hours
- Proportion of subjects who are opioid-free through 72 hours
- Proportion of subjects who receive an opioid prescription at discharge

5. GENERAL STATISTICAL CONSIDERATIONS

Continuous data will be presented using descriptive statistics: number of subjects (n), mean, standard deviation (SD), median, minimum and maximum. Descriptive statistics on efficacy measures will also include the standard error (SE). Categorical data will be summarized by the number and percent of subjects. Data will be displayed in all listings sorted by treatment group, subject number and visit/study day. When count data are presented, the percent will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where necessary to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in that treatment group within the population of interest, unless otherwise stated. Non-zero percentages will be rounded to 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 and median will have one decimal place and SD and SE will have 2 decimal places
- If the original value has 1 decimal place: mean and median 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, SD, and SE will all have 3 decimal places

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

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

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

programmed using SAS® v. 9.4 or higher. All efficacy and safety data will be listed via the SDTM datasets and selected efficacy and safety data will be listed via programmed listings.

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

5.1. Sample Size

The sample size for each cohort was selected empirically without formal statistical assumptions. Up to approximately 51 female subjects will be enrolled and dosed: approximately 15 subjects in Cohort 1, up to approximately 12 subjects in Cohort 2, and up to approximately 24 subjects in Optional Cohort 3.A minimum of 6 to 8 subjects is considered sufficient for the PK objective (Draft FDA Guidance for Industry, Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling, February 2005).

5.2. Randomization, Stratification, and Blinding

This is an open-label study.

5.3. Analysis Populations

5.3.1. Safety Population

The Safety Population will include all subjects who receive HTX-011. Subjects in this population will be included in all disposition, demographics, safety, and efficacy analyses.

5.3.2. Analysis Table Layout

All analyses will be performed on the Safety Population and summarized using descriptive statistics (Table 1).

Table 1: Layout of Summary

Without optional cohort 3 in the study:

Cohort 1 HTX-011 300 mg/9 mg (N=XX)	Cohort 2 HTX-011 400 mg/12 mg + MMA (N=XX)	Total (N=XX)

Total column will not be included in the efficacy analyses.

With optional cohort 3 in the study:

HTX-011 300 mg/9 mg Cohort 1 (N=XX)	HTX-011 400 mg/12 mg + MMA			Overall (N=XX)
	Cohort 2 (N=XX)	Cohort 3 (N=XX)	Total (N=XX)	

Overall column will not be included in the efficacy analyses.

5.4. Other Important Considerations

5.4.1. Definition of Baseline

Unless otherwise specified, baseline is defined as the last observed measurement, whether scheduled or unscheduled, prior to study drug administration.

5.4.2. 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:

$P_t = 100*(C_t/M_B)$

5.4.3. Study Day Calculation and Time 0 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.

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

5.4.4. 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-R pain intensity score assessment at the nominal 72-hour postoperative timepoint.

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

5.4.5. Visit Windows

Due to the short duration of the study, no programmatically calculated visit windows are defined for this study.

5.4.6. Handling of Missing and Partial Data

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

For any NRS 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.

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

A table displaying the number and percentage of subjects with missing NRS-R and NRS-A (cohort 2 and optional cohort 3) pain intensity scores at each nominal timepoint will be produced.

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

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

6. SUBJECT DISPOSITION

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

7. DEMOGRAPHICS, CHARACTERISTICS, AND MEDICAL HISTORY

7.1. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be presented in tables using descriptive statistics. Demographics consist of age, 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.

Demographics and baseline characteristics will be presented for the Safety Population.

7.2. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) version 22.0. 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
- Study Procedures Not Done
- Safety Reporting
- Study Drug Dosing/Administration
- Out of Window Procedure and/or Visit
- Other

Classification of deviations as major protocol violations will be decided on a case-by-case basis according to the Protocol Deviation Plan. All protocol deviations and major protocol deviations will be presented in a summary table by protocol deviation category for the Safety Population.

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 (WHODrug) Global B3 Format, March 1, 2019.

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

Except non-opioid MMA regimens for cohort 2 and optional cohort 3, all concomitant opioid pain medications, ibuprofen, and acetaminophen with a start date/time within the 72-hour postoperative period (see Section 5.4.4 for details), regardless of whether or not they had an indication of "Post Operative Pain", will be included in rescue medication analyses. Exceptions are ropivacaine, morphine sulfate injection (DURAMORPH®), and fentanyl administered perioperatively on the date of surgery for intraoperative pain management, which are not counted as rescue medications.

Opioid rescue medication in IV MME dose (see Section 10.2 for details), ibuprofen, and acetaminophen 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 Safety Population.

8.3. Surgery Procedure

The length of surgical (skin) incision in centimeters and the duration of surgery in minutes will be summarized. Duration of surgery will be calculated as completion time minus start time. The time of clamping of the umbilical cord will be listed.

8.4. Study Drug

For all subjects, treatment will consist of a single dose of HTX-011. As such, extent of exposure will be reported in the CSR as the number of subjects in the Safety Population. A summary of treatment compliance will not be produced, as by definition it will be 100% for the Safety Population. Duration of study drug administration will be calculated as study drug stop time minus start time as reported in the Study Drug Administration eCRF. Duration of study drug administration in minutes will be listed.

9. SAFETY ANALYSIS

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

9.1. 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 22.0. 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.

9.1.1. Incidence of Treatment Emergent Adverse Events

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

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

- Number of TEAEs
- Number of subjects with at least 1 TEAE
- Number of subjects with at least 1 possibly related TEAE

- Number of subjects with at least 1 severe TEAE
- Number of subjects with at least 1 TEAE leading to study withdrawal
- Number of subjects with at least 1 ORAE
- Number of 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.

9.1.2. Relationship of Adverse Events to Study 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.

9.1.3. 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.

9.1.4. 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.

9.1.5. Adverse Events Leading to Study Withdrawal

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

9.1.6. Opioid-related Adverse Events

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

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

Incidence of ORAEs will be presented separately as follows:

- Incidence of ORAEs
- Incidence of ORAEs through the 72-hour postoperative observation period in the subset of subjects who received at least 1 opioid rescue medication during the 72-hour postoperative observation period

9.1.7. Potential Local Anesthetic Systemic Toxicity (LAST)-Related Adverse Events

The symptoms that are potentially related to LAST will be reviewed by searching the clinical database using a custom list of PTs created by Heron (Table 2).

Table 2: Potential LAST-Related Adverse Events by Preferred Term

Any PT that includes “arrhythmia”	Hypotension	Seizure
Any PT that includes “bradycardia”	Muscle twitching	Tinnitus
Cardiac arrest	Paraesthesia	Tremor
Dizziness	Paraesthesia oral	Vision blurred
Dysgeusia	Respiratory arrest	Visual impairment

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

9.1.8. 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.

9.2. Local Anesthetic Systemic Toxicity Questionnaire

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

9.3. 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, 24 hours [hematology only], 72 hours, and Day 11), 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.

9.3.1. 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).

9.3.2. 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 the following liver function ranges will be summarized at each visit, Maximum Post-Baseline, and Last Post-Baseline. Subjects with laboratory values that meet the following liver function ranges 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
- Potential Hy's Law: (ALT or AST ≥ 3 x ULN) and ALP < 2 x ULN and total bilirubin ≥ 2 x ULN

9.3.3. Urine Drug Screen

Urine drug screen results will be listed.

9.4. 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, 72 hours, Day 28, and Early Termination (if applicable).

Summary tables including actual values and changes from baseline for each visit will be presented.

The number and percentage of subjects with out-of-range vital sign values will be presented using data from any postdose visit (including unscheduled visits). Subjects with our-of-range vital signs will be presented in data listing as well. The criteria for out-of-range vital signs are shown in Table 3.

Table 3: Out-of-Range Vital Signs Values

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

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

9.5. Electrocardiogram

12-lead ECG (triplicate) is performed at screening, 72 hours, and Early Termination (if applicable). 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. Shift from baseline of overall ECG interpretation at each postoperative timepoint will also be provided.

The number and percentage of subjects with ECG findings meeting criteria identified in the ICH Guideline E14 on Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (Oct 2005), 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.

9.6. Physical Examination

Physical examination is performed at Screening, 72 hours, and Early Termination (if applicable). Physical examination data will be listed only.

9.7. Wound Healing Assessment

Surgical wound healing will be assessed using a wound healing assessment- Southampton wound scoring system at 24 hours, 72 hours, Day 7, Day 11, Day 28, and Early Termination (if applicable). A summary of wound healing assessment results will be produced, showing the number and percentage of subjects within each Southampton category at each visit and at any timepoint. Wound healing assessment results will also be listed.

10. EFFICACY (EXPLORATORY) ANALYSIS

All efficacy analyses will be carried out using the Safety Population. No statistical hypothesis testing will be performed.

10.1. Mean AUC of NRS-R and NRS-A

During the first 72 hours following surgery, the NRS-R and NRS-A (Cohort 2 and optional Cohort 3 only) are measured at hours 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72. Using the trapezoidal rule and letting P_t = the NRS-R/NRS-A pain intensity score at time t, then:

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

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

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

To adjust for the duration effect of opioid rescue medication, wWOCF method will be implemented. 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-R/NRS-A pain intensity score observed prior to the rescue medication window, with the following exception: if the NRS-R/NRS-A 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 4 in Section 10.2 for predefined analgesic windows for each opioid medication.

The $AUC_{0\text{-}12}$, $AUC_{0\text{-}24}$, $AUC_{24\text{-}48}$, $AUC_{0\text{-}48}$, $AUC_{24\text{-}72}$, and $AUC_{48\text{-}72}$ of the NRS-R/NRS-A pain intensity scores will be analyzed similarly as for the $AUC_{0\text{-}72}$ of the NRS-R/NRS-A pain intensity scores, with appropriate adjustments to the calculations to reflect the time periods of interest.

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

10.2. Total Postoperative Opioid Consumption (in IV MME)/ Ibuprofen and Acetaminophen Consumption Through 72 Hours

Determination of morphine equivalents

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

Postoperative rescue medication permitted during the 72-hour postoperative period comprises any 1 or more of the following medications as needed: PO ibuprofen ≤600 mg within a 6-hour period, PO/IV acetaminophen ≤1 gram (1,000 mg) within a 6-hour period, PO immediate-release oxycodone ≤5 mg within a 4-hour period, and IV morphine ≤10 mg within a 2-hour period. For subjects administered any acetaminophen-containing product, the total combined daily dose of acetaminophen must not exceed 4 grams (4,000 mg) in a 24-hour period. Combination products containing an opioid and non-opioid are not allowed.

Table 4 displays the IV MME along with the analgesic windows of selected opioid rescue medications for wWOCF purposes. Protocol-allowed postoperative opioid rescue medications are checked. Opioid medications that are not protocol-allowed will be logged as protocol violations, but will still be subject to MME conversion for analysis.

Table 4: 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 opioid, for overall opioids, for ibuprofen, and for acetaminophen during the following periods: 0-24, 24-48, 0-48, 48-72, 24-72, and 0-72 hours. Subjects who did not use a specific rescue medication during a period of interest will have their dose set to 0 for that period. For cohort 2 and optional cohort 3, the non-opioid MMA regimens (acetaminophen and ibuprofen) are indicated by an eCRF check box of 'Scheduled Background MMA' for the indication of concomitant medications. The non-opioid MMA regimens are not counted as rescue medications and therefore will be excluded from the above average daily use and total use analyses of rescue medications. A summary for the average daily use and total use of the scheduled postoperative non-opioid MMA regimens (acetaminophen and ibuprofen) over 0-24, 0-48, and 0-72 hours will be provided for cohort 2 and optional cohort 3.

10.3. Proportion of Subjects Who Are Opioid-Free Through 72 Hours

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

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

10.4. Proportion of Subjects Who Receive an Opioid Prescription at Discharge

A summary of the proportion of subjects who receive an opioid prescription at discharge, as recorded on the eCRF, will be provided.

11. INTERIM ANALYSIS

11.1. Interim Analysis

No formal interim analyses are planned; however, the data will be reviewed on an ongoing basis. After at least 6 subjects have been administered HTX-011 in Cohort 1 and completed the Day 16 Visit breast milk collection, the Sponsor will conduct an analysis of PK data. If there are sufficient breast milk and plasma data to fulfill the primary objective, the study may be stopped and no more subjects will be enrolled.

11.2. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will not be involved with the conduct of this study. The internal Product Safety and Risk Management Committee will monitor safety data on a periodic basis throughout the study (ie, monthly unless more frequent monitoring is necessary due to high enrollment or safety concern), including regular review of ECG findings, AEs, LAST assessments, wound healing assessments, and SAEs.

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	18 February 2021	Initial version, based on protocol version 6 (10SEP2020)

Signature Page for VV-CLIN-004612 v1.0

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