Document Type:	Statistical Analysis Plan
Official Title:	A Phase 4, Randomized, Blinded, Active-Controlled Study of HTX-011 in Subjects Undergoing Different Surgical Procedures
NCT Number:	NCT06109428
Document Date:	05 April 2022

STUDY HTX-011-401

A PHASE 4, RANDOMIZED, BLINDED, ACTIVE-CONTROLLED STUDY OF HTX-011 IN SUBJECTS UNDERGOING DIFFERENT SURGICAL PROCEDURES

5 April 2022

Statistical Analysis Plan
Cohort 2 (Abdominoplasty)

Version 1

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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
CRO	Contract Research Organization
CSR	Clinical study report
DBP	Diastolic blood pressure
DM	Data management
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eDISH	Evaluation of drug-induced serious hepatotoxicity
GGT	Gamma glutamyltransferase
HCl	Hydrochloride
HR	Heart rate
IM	Intramuscular
IV	Intravenous(ly)
K-M	Kaplan-Meier
LAST	Local anesthetic systemic toxicity
LDH	Lactic dehydrogenase
LLN	Lower limit of normal
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MME	Morphine milligram equivalent
MPADSS	Modified Postanaesthetic Discharge Scoring System
NRI	Nonresponder imputation
NRS	Numeric rating scale of pain intensity
NRS-A	Numeric rating scale of pain intensity with activity
NRS-R	Numeric rating scale of pain intensity at rest
NSAID	Nonsteroidal anti-inflammatory drug
ORAE	Opioid-related adverse event
PACU	Postanesthesia care unit
PD	Pharmacodynamic
PGA	Patient's Global Assessment
PK	Pharmacokinetic(s)
PO	Oral(ly)
PR	Per rectum
PT	Preferred Term
q8h	Every 8 hours
RBC	Red blood cell
SAE	Serious adverse event

SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SDA	Study drug administration
SDTM	Study Data Tabulation Model
SDTMIG	Study Data Tabulation Model Implementation Guide
SE	Standard error
SI	Standard international
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WBC	White blood cell
WHODrug	World Health Organization Drug 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 by Heron and the statistical analyses are being performed under contract with EMB Statistical Solutions (EMB), with oversight from Heron. EMB is a contract research organization (CRO).

1.2. Data Quality Assurance

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

2. INTRODUCTION

This statistical analysis plan (SAP) is specific to Cohort 2 (abdominoplasty). A separate SAP will be provided for each cohort and each cohort will be analyzed separately following completion of that cohort.

This SAP presents a detailed plan of the statistical methods to be used during the reporting and analysis of pharmacodynamic (PD) 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 for Cohort 2. 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

Primary Objective:

The primary study objective is to assess the safety and tolerability of HTX-011 in subjects undergoing different surgical procedures.

Secondary Objective:

The secondary study objective is to characterize the bupivacaine and meloxicam PK parameters following administration of HTX-011 in these study populations.

Exploratory Objective:

The exploratory study objective is to assess the PD activity of HTX 011 in these study populations based on postoperative pain and opioid use.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 4, randomized, blinded, active-controlled, multicohort study to evaluate HTX-011 compared with bupivacaine HCl in subjects undergoing different surgical procedures. The study will include 2 cohorts, which will be conducted in parallel. Each cohort will enroll subjects undergoing a unique surgical procedure: total shoulder arthroplasty (TSA) in Cohort 1 and abdominoplasty in Cohort 2.

In each cohort, approximately 30 subjects will be randomized in a 2:1 ratio to HTX-011 or bupivacaine HCl, respectively. In both cohorts, all subjects will receive a scheduled postoperative non-opioid MMA regimen. Subjects and site personnel performing postoperative safety and PD assessments will be blinded to treatment assignments; however, unblinded site staff may collect samples for PK analysis. The Sponsor will be unblinded, but will maintain the blind when interacting with blinded site staff.

Cohort 1 (TSA)

- HTX-011 400 mg/12 mg + MMA (N=20).
- Bupivacaine HCl 0.25% 100 mg + MMA (N=10).

Cohort 2 (abdominoplasty)

- HTX-011 400 mg/12 mg + MMA (N=20).
- Bupivacaine HCl 0.25% 125 mg + MMA (N=10).

Subjects will be screened within 28 days prior to the planned surgery date. Subjects who meet the eligibility criteria will be randomized within 1 business day prior to surgery. On the day of surgery (Day 1), subjects who continue to meet the eligibility criteria will undergo surgery. Before surgery, subjects will be shown an instructional video that will describe what to expect after surgery.

During surgery, all subjects will receive a single dose of study drug (HTX-011 or bupivacaine HCl). In addition, at the discretion of the anesthesiologist/surgeon, subjects may receive intravenous (IV) fentanyl (up to 3 µg/kg body weight, not exceeding 200 µg, in Cohort 1; up to 1.5 µg/kg, not exceeding 100 µg, in Cohort 2). All subjects will receive a single dose of either IV morphine 5 to 10 mg or IV hydromorphone 1 to 2 mg just prior to the application of dermal sutures.

Subjects will remain in the facility through 72 hours postdose for PK, safety, and PD assessments. Subjects will receive a scheduled non-opioid MMA regimen throughout the 72-hour postoperative period consisting of oral (PO) acetaminophen 1 g every 8 hours (q8h) alternating with PO ibuprofen 400 mg q8h, so that an analgesic is taken approximately every 4 hours. The first dose of the postoperative MMA regimen will be administered once the subject is able to tolerate PO intake. The total combined daily dose of acetaminophen from any acetaminophen-containing product taken must not exceed 4 g (4,000 mg) as severe liver damage may occur.

Prior to discharge (Day 4), subjects will be shown an instructional video on what to expect after discharge. Subjects will be instructed at discharge to continue their scheduled MMA regimen through Day 7, while awake, and will receive instructions on how to complete the daily diary to record opioid use through the Day 15 Visit.

PK sampling will occur through Day 7. On Day 5 (96-hour timepoint), Day 6 (120-hour timepoint), and Day 7 (144-hour timepoint), PK sample collection will be performed at the study site or via a home visit. For subjects with drains, all drainage fluid will be collected and pooled over 12-hour intervals (±1 hour) through 72 hours and may be used to measure the concentrations of bupivacaine, meloxicam, and other ZYNRELEF components.

All subjects will return to the study site on Day 15 to complete End-of-Study assessments.

Postoperative Rescue Medication

During the 72-hour postoperative period, subjects should receive rescue medication only upon request for treating postoperative pain; rescue medication should not be given for pain prophylaxis. Permitted postoperative rescue medication includes the following:

- PO ibuprofen 400 mg and PO acetaminophen 500 mg (in addition to and independent from the scheduled MMA regimen), which may be administered at most only once every 12 hours as rescue. Ibuprofen and acetaminophen must be the first rescue medication given every time rescue medication is requested by the subject, provided that ≥12 hours have elapsed since the last administration of ibuprofen/acetaminophen as rescue medication and the total acetaminophen dose is ≤4 g within a 24-hour period, including both the 1g q8h administered as part of the scheduled MMA regimen and any 500 mg doses administered as rescue medication.

  Between 30 minutes and 12 hours after receiving ibuprofen and acetaminophen as rescue medication, subjects may be administered opioid rescue medication as follows, if additional rescue medication is requested.

  – PO immediate-release oxycodone (≤10 mg within a 4-hour period) OR
  – IV morphine (≤5 mg within a 4-hour period).

Combination products containing an opioid and non-opioid are not allowed. Nonsteroidal anti-inflammatory drugs (NSAIDs) or other analgesic agents are not permitted during the 72-hour postoperative period, except for ibuprofen and acetaminophen per protocol and low-dose (≤100 mg) daily acetylsalicylic acid for cardioprotection.

Prior to the administration of the first dose of rescue medication, if the subject has not already had at least 1 postoperative pain score assessed, then a numeric rating scale (NRS) of pain intensity at rest (NRS-R) score followed by an NRS of pain intensity with activity (NRS-A) score must be obtained.

Opioid Prescriptions at and After Discharge

If a subject did not receive any opioids or received <5 IV morphine milligram equivalents (MME; eg, <10 mg of oxycodone) within 12 hours prior to discharge, the subject should not receive an opioid prescription at discharge. If a subject received ≥5 IV MME within 12 hours prior to discharge, the Investigator may provide the subject with a prescription for PO immediate-release oxycodone tablets: no more than twenty 5 mg immediate release oxycodone, take 1 to 2 pills (5 to 10 mg) every 4 hours as needed. The prescription must indicate that substitutions with any other opioid-containing product are not permitted, including combination opioid/non-opioid products.

Sites will record in the electronic data capture (EDC) whether subjects are discharged with an opioid prescription and information about the opioid prescription, if provided.

All subjects (whether or not they were discharged with an opioid prescription) will be provided a daily diary to record any opioid medication use from discharge through the Day 15 Visit. Sites will record in the EDC all site- or subject-initiated contact between discharge and the Day 15 Visit and whether any contact resulted in issuing an opioid prescription.

4.2. Assessments

Safety, PK, and PD assessments will be performed. The start of study drug administration will be considered Time 0 for all assessments.

Safety Assessments

- Adverse events (AEs) from the time the subject signs the Informed Consent Form through the Day 15 Visit.
- Physical examinations.
- Vital signs, including blood pressure, heart rate, respiratory rate, and temperature.
- Wound healing assessments using the Southampton Wound Scoring System.
- Clinical laboratory tests (hematology and serum chemistry).
- Local anesthetic systemic toxicity (LAST) questionnaire

PK Assessments

Blood samples will be collected to measure the plasma concentrations of bupivacaine and meloxicam. Alpha-1 acid glycoprotein and other study drug components may be evaluated. The concentrations of bupivacaine, meloxicam, and other ZYNRELEF components may also be measured in drainage fluid in subjects with drains.

PD Assessments

- Use of rescue medication: Date, time of administration, amount, and type of all rescue medication taken from study drug administration through 72 hours. Opioid use will be recorded through Day 15.
- Pain intensity assessments using NRS-R and NRS-A will be performed from the time of study drug administration through 72 hours and on Day 15. The NRS-R score will be obtained first, after the subject has been in a resting position for at least 5 minutes. After the NRS-R score has been obtained, the NRS-A score will be obtained.
  - Cohort 1 (TSA):
    - NRS-R: Subjects should be seated comfortably or reclining.
    - NRS-A: Subjects will be asked to adduct the operated arm into the side of their body for 3 seconds.
  - Cohort 2 (abdominoplasty):
    - NRS-R: Subjects should be resting in a comfortable reclined position.
    - NRS-A: Subjects will be asked to cough.
- Discharge readiness assessment per the Modified Postanaesthetic Discharge Scoring System (MPADSS) criteria. (Note: This study instrument assesses a subject's potential readiness to be discharged and should be repeated at all scheduled timepoints. It is not meant to be used to decide whether or not to discharge a subject from the study, as subjects are required to remain in the hospital/research facility for at least 72 hours.)
- Patient Global Assessment (PGA) of pain control.
- Opioid prescription at discharge.
- Site- or subject-initiated postdischarge contact through the Day 15 Visit.
- Opioid prescription after discharge through the Day 15 Visit.
- Subject daily diary to record whether opioids were taken from discharge through the Day 15 Visit.

4.3. Endpoints

4.3.1. Primary Endpoint

- Incidence of treatment-emergent adverse events (TEAEs).

4.3.2. Secondary Endpoints

- Maximum concentration (C_{max}) of bupivacaine.
- Time of occurrence of maximum concentration (T_{max}) of bupivacaine.
- Area under the concentration-time curve from Time 0 to the time of the last quantifiable concentration (AUC_{last}) of bupivacaine.

- Area under the concentration-time curve from Time 0 extrapolated to infinity (AUC_{inf}) of bupivacaine.
- Apparent terminal half-life ($t_{½}$) of bupivacaine.

4.3.3. Other Secondary Endpoints

- PK profile of meloxicam.
- TEAEs leading to study withdrawal and SAEs.
- Change from baseline in clinical laboratory results.
- Change from baseline in vital signs.

4.3.4. Exploratory Endpoints

- Mean total postoperative opioid consumption (in IV MME) through 72 hours.
- Proportion of subjects who are opioid-free through 72 hours and through Day 15.
- Median time to first opioid rescue medication through 72 hours.
- Proportion of subjects who do not receive an opioid prescription at discharge.
- Proportion of subjects who do not receive an opioid prescription between discharge and the Day 15 Visit.
- Mean area under the curve (AUC) of the NRS scores through 72 hours.
- Proportion of subjects achieving a score of "good" or better (>1) pain control based on PGA at each timepoint.
- Proportion of subjects who first achieve a Modified Postanaesthetic Discharge Scoring System (MPADSS) score ≥9 at each timepoint.

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 PD 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/timepoint. All PD and safety analyses will be performed using descriptive statistics by treatment group (Table 1).

Table 1: Layout of Summary

HTX-011 400 mg/12 mg + MMA	Bupivacaine HCl 125 mg + MMA

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 number of 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 PD 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 PD and safety data will be listed via the SDTM datasets and selected PD and safety data will be listed via programmed listings.

5.1. Sample Size

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

5.2. Randomization, Stratification, and Blinding

Subjects who meet the Screening eligibility criteria will be randomized to either HTX-011 or bupivacaine HCl within 1 business day prior to surgery, using a computer-generated randomization scheme. Subjects do not need to be present for randomization to occur. No subject may receive study drug prior to randomization.

In each cohort, approximately 30 subjects will be randomized in a 2:1 ratio to HTX-011 or bupivacaine HCl, respectively. The randomization will be stratified by study site within each cohort.

The site's pharmacy and surgical staff will not be blinded to the treatment assignments because HTX-011 is a colored, viscous solution whereas bupivacaine HCl is a clear aqueous solution, and the volume and method of study drug administration are different between treatment groups. However, subjects will not be aware of the study drug they receive and, once surgery is completed and the subject is transferred to the postanesthesia care unit (PACU), Investigators and all site staff involved in postoperative safety and PD assessments will be blinded to the treatment assignment; however, unblinded site staff may collect samples for PK analysis. The Sponsor will be unblinded, but will maintain the blind when interacting with blinded site staff.

5.3. Analysis Populations

5.3.1. Safety Population

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

5.4. Other Important Considerations

5.4.1. 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.

5.4.2. 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 for Reporting Purposes

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

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

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

5.4.4. 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 later of the date/time of the NRS-R and NRS-A assessments at the nominal 72-hour postoperative timepoint.

However, if the date/time of the NRS-R and NRS-A assessments at the nominal 72-hour postoperative timepoint are both missing, the following will be applied depending on study endpoints.

- For AUC of the NRS scores and potential ORAEs through 72 hours, the 72-hour postoperative observation period will be defined as the start date/time of study drug administration + 72 hours.
- For analyses of opioid use (including opioid consumption in MMEs, percentage of subjects opioid-free, time to first opioid) through 72 hours, the following will be applied.
  - If the subject early terminated prior to 72 hours, the 72-hour postoperative observation period will be defined as from the start date/time of study drug administration through the time of early termination.
  - If the subject did not early terminate prior to 72 hours, the 72-hour postoperative observation period will be defined as from the start date/time of study drug administration + 72 hours.

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

5.4.5. Day 15 Visit Period

All subjects (whether or not they were discharged with an opioid prescription) will be provided a daily diary to record any opioid medication use from discharge through the Day 15 Visit. Sites will record in the EDC all site- or subject-initiated contact between discharge and the Day 15 Visit and whether any contact resulted in issuing an opioid prescription.

The Day 15 Visit has a 2-day window (ie, Day 15 ± 2 days [Study Day 13 through Study Day 17]). For analyses of opioid use and subject/site contacts, "through Day 15" is defined as follows:

- If Day 15 Visit date (or study exit date) ≥ Study Day 15 or the Day 15 Visit is missing but subject continued on study beyond Study Day 15: "through Day 15" is defined as through the Day 15 Visit date (or study exit date) or Study Day 15, whichever happens first.
- If Study Day 13 ≤ Day 15 Visit date (or study exit date) < Study Day 15: "through Day 15" is defined as through the Day 15 Visit date (or study exit date).
- If Day 15 Visit date (or study exit date) < Study Day 13: "through Day 15" is defined as through Study Day 13.

5.4.6. Visit Windows

Due to the short duration of the study, no programmatically defined visit windows are applied to map unscheduled or early termination visits to nominal scheduled visits for this study.

5.4.7. Handling of Missing and Partial Data

The amount of missing data during the primary PD 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.

In subjects who withdraw from the study prior to 72 hours, missing 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) pain intensity score observed prior to withdrawal will be used for postwithdrawal values through 72 hours. Any missing 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 pain intensity scores, any subject with missing data at a timepoint will be considered as not meeting the criterion for the endpoint at that timepoint. This is known as nonresponder imputation (NRI). Binary endpoints involving the pain intensity scores (such as proportion of subjects with an NRS score ≥7) through 72 hours will be constructed following windowed worst observation carried forward (wWOCF) (see Section 10.1.8 for details).

A table displaying the number and percentage of subjects with missing NRS pain intensity scores at each nominal timepoint and overall 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. If opioid use data collected is missing time of administration, the time of opioid use will be imputed as “00:00” for analysis.

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 randomized, 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, and subjects not completing the study by reason for withdrawal. Only 1 reason for study withdrawal will be recorded for each subject.

7. DEMOGRAPHICS, CHARACTERISTICS, AND MEDICAL HISTORY

7.1. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be presented in tables using descriptive statistics. Demographics consist of age, age category, sex, race, and ethnicity. Baseline characteristics consist of weight, height, body mass index (BMI), and history of chronic opioid use (Yes/No). 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 Safety Population.

7.2. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) version 24.1. 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 from the protocol will be recorded. Protocol deviations will be classified into one of the following categories:

- Informed consent form procedures,
- Eligibility criteria,
- Prohibited concomitant medication/therapy,
- Study procedures not done,
- Safety reporting,
- Study drug dosing/administration,
- Out of window procedure,
- Other,

Classification of deviations as important protocol violations will be decided on a case-by-case basis. All protocol deviations and important 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 Study Day 1. Concomitant medications are defined as medications that are ongoing on Study Day 1 or with a start date occurring on or after Study Day 1. Medications with start and stop dates which bracket Study Day 1, or for which missing start and/or stop dates make it impossible to determine the prior or concomitant status, will be summarized as concomitant medications.

All medications will be coded with the World Health Organization Drug Dictionary Global B3 Format (WHODrug Global B3), September 2021.

Prior and concomitant medications will be summarized separately by drug class and generic drug name. 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

All postoperative concomitant opioid pain medications with a start date/time through Day 15 (see Section 5.4.5 for details) and all acetaminophen and ibuprofen with an indication of "Pre Discharge Rescue Medication" will be included in the rescue medication summaries. Fentanyl, IV morphine, or IV hydromorphone administered on the date of surgery with a recorded indication of "Intraoperative" is considered part of intraoperative management and are not counted as rescue medication.

Incidence of opioid, acetaminophen, and ibuprofen consumption will be summarized from study drug administration (time 0) through 72 hours, through Day 15, and from 72 hours through Day 15. Summaries will be provided for usage of opioid rescue medication, any rescue medication (opioid, acetaminophen, and/or ibuprofen), acetaminophen only, and ibuprofen only.

8.3. Surgery Procedure

Summaries will include duration of surgery (min), length of incision (cm), use of drains (Yes or No), and estimated blood loss (mL). Duration of surgery will be calculated as end time minus start time, reported in minutes.

8.4. Study Treatment

All subjects will receive a single dose of study drug (HTX-011 or bupivacaine HCl) intraoperatively. The extent of exposure to study drug 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.

9. 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).

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 physical examination finding, laboratory value, vital sign result, ECG finding, or abnormal wound healing finding deemed clinically significant by the Investigator 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 24.1. Only TEAEs will be presented in AE tables. 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.

9.2. Safety Endpoints

9.2.1. Primary Endpoint

The primary endpoint is the incidence of TEAEs. The incidence of TEAEs table will include only 1 occurrence of a PT per subject. For a given PT, if a subject reports that PT multiple times, that subject will only be counted once since unique subject counts will be presented. Similar to the analysis of PTs, for a given SOC if a subject reports multiple TEAEs within the same SOC, that subject will only be counted once at the SOC level since unique 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 HTX-011 incidence. For tables showing incidence by PT only, the PTs will be sorted in descending order of HTX-011 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 TEAE possibly related to study drug
- Number of subjects with at least 1 severe TEAE
- Number of subjects with at least 1 TEAE leading to study withdrawal
- Number of SAEs
- Number of subjects with at least 1 SAE
- Number of subjects with at least 1 SAE possibly related to study drug
- Number of subjects with fatal TEAEs

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

9.2.1.1. Relationship of Adverse Events to Study Drug

The incidence of TEAEs possibly related to study drug will be presented in a table by SOC and PT.

9.2.1.2. Severity of Adverse Event

The incidence of severe TEAEs will be presented in a table by SOC and PT.

9.2.1.3. Potential Opioid-related Adverse Events

Incidence of TEAEs that are potential ORAEs, regardless of whether a subject actually received an opioid medication, will be presented by PT. Prespecified PTs that constitute potential ORAEs include the following:

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

9.2.1.4. Local Inflammatory Adverse Events

To enable a broad and comprehensive analysis of TEAEs potentially related to adverse effects on wound healing, local inflammatory TEAEs will be reviewed by searching the clinical database using a custom list of PTs created by Heron (Table 2).

Table 2. Potential Local Inflammatory Adverse Events by Preferred Term

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

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

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

9.2.1.5. Potential NSAID-Related Adverse Events

Potential NSAID-related adverse events will be identified based on the literature (Essex, Zhang et al. 2013). The incidence of potential NSAID-related adverse events will be presented in a table by SOC and PT.

9.2.1.6. Local Anesthetic Systemic Toxicity (LAST) Assessment

Subjects will be assessed with a LAST questionnaire 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 potential LAST symptom with a breakdown of each symptom for overall and by each visit. Potential LAST questionnaire results will also be listed.

9.2.1.7. Potential LAST Adverse Events

Symptoms that may be attributable to LAST will be reviewed by searching the safety database using a custom list of PTs created by Heron (Table 3).

Table 3: Potential LAST Adverse Events

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

Abbreviation: PT, Preferred Term.

The incidence of potential LAST TEAEs will be presented in a table by SOC and PT. Potential LAST TEAEs will also be listed separately.

9.2.1.8. 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.

9.2.2. Other Secondary Endpoints

9.2.2.1. Serious Adverse Events

Only treatment-emergent SAEs will be included for summary. The incidence of 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 multiple SAEs that are mapped to the same PT , then that PT will only be incremented by 1 since subject counts will be presented. As with PTs, 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. All SAEs will also be listed separately.

9.2.2.2. Treatment Emergent Adverse Events Leading to Study Withdrawal

All TEAEs reported with an action taken of "Withdrawal from Study" on the eCRF will be presented in a listing.

9.2.2.3. Change from Baseline in Clinical Laboratory Results

Laboratory assessments will be performed by a central laboratory (hematology and serum chemistry) or locally (pregnancy test, drug screen, and COVID-19 test). 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 scheduled visit (Screening, 72 hours, and Day 15), derived baseline, 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 a 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 out-of-range values for hematology and chemistry will be presented separately in addition to listings of all laboratory values.

9.2.2.3.1. Hematology

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

9.2.2.3.2. 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, and total protein.

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) 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 out-of-range liver function values will be summarized at each visit for the categories below. Subjects with out-of-range liver function values will be presented in a 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

9.2.2.3.3. Urine Pregnancy Test, Urine Drug Screen, and COVID-19 Test

Urine pregnancy test results (women of child-bearing potential), urine drug screen results, and COVID-19 test results will be listed.

9.2.2.4. Change from Baseline in Vital Signs

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 postdose at 24, 48, 72 hours; and early termination (if applicable).

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

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 out-of-range vital sign values will be presented in a data listing as well. The criteria for out-of-range vital sign values are shown in Table 4:

Table 4: Out-of-Range Vital Signs Values

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

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

9.2.3. Other Safety Endpoints

9.2.3.1. Electrocardiogram

A 12-lead ECG (single) will be performed at screening and if an AE of suspected LAST occurs, an ECG (triplicate) will be obtained. All ECG results will be listed. For the triplicate ECGs, the average of the triplicate values will also be listed. The corrected QT interval will be calculated using the Fridericia formula ($\mathrm{QTcF} = \mathrm{QT}/\sqrt[3]{60/\mathrm{HR}}$).

9.2.3.2. Physical Examination

Physical examination will be performed at Screening, 72 hours, and early termination (if applicable). Physical examination data will be listed only.

9.2.3.3. Wound Healing Assessment

Surgical wound healing will be assessed using the Southampton Wound Scoring System at 72 hours, Day 15, and early termination (if applicable). A summary of wound healing assessment results will be produced, showing the number and percentage of subjects at each visit, at worst value post-baseline, and at last value post-baseline, by grade with subgrade breakdown and by Grade 0/I and Grade II/III. Wound healing assessment results will also be listed.

10. PHARMACODYNAMIC ANALYSIS

10.1. Exploratory Endpoints

All analyses of PD data will be conducted using the Safety Population. Statistical hypothesis testing will not be performed on any PD results.

10.1.1. Mean Total Postoperative Opioid Consumption (in Intravenous Morphine Milligram Equivalents [IV MME]) Through 72 hours

Analyses of opioid consumption will be based on observed data only.

Determination of morphine equivalents

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

Table 5 displays the MME along with the analgesic windows of selected opioid rescue medications for wWOCF purposes. Protocol-allowed postoperative opioid rescue medications are marked with "✓". Opioid medications that are not protocol-allowed will be logged as protocol violations, but will still be subject to MME conversion for analysis.

Table 5: Analgesic Windows and IV MME for Opioid Rescue Medications

Medication	Route	Window (h)	MME Factor	Protocol Allowed
CODEINE	PO	6	0.05	
HYDROMORPHONE HYDROCHLORIDE	PO	4	1.33	
HYDROMORPHONE HYDROCHLORIDE	IV	4	6.67	
FENTANYL	IV	1	50.00	
HYDROCODONE	PO	6	0.40	
MORPHINE	IV	4	1.00	✓
MORPHINE	PO	4	0.33	
MORPHINE	IM	4	1.00	
MORPHINE	PR	4	1.00	
OXYCODONE	IV	4	1.00	

Medication	Route	Window (h)	MME Factor	Protocol Allowed
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: h, hour; IM, intramuscular; IV, intravenous; MME, morphine milligram equivalent; PO, oral; PR, per rectum.
Note: MME = opioid dose × MME factor.

Analysis method

Rescue medication (opioids, acetaminophen, and ibuprofen) consumption is collected from start of study drug administration (Time 0) through Day 15. Total opioid consumption will be tabulated using descriptive statistics for overall opioids, as well as oxycodone and morphine separately, for the following periods: 0-24 hours, 0-48 hours, 0-72 hours, 24-72 hours, 0-Day 15, 72 hours through Day 15, and discharge through Day 15. In addition, opioid consumption in the following 24 hour time blocks will be summarized: [24-48) and [48-72). Subjects who did not use an opioid rescue medication during a period of interest will have their dose set to 0 for that period.

Total acetaminophen and total ibuprofen taken as rescue medication in milligrams (mg) will be analyzed as described for total opioid consumption.

10.1.2. Proportion of Subjects Who Are Opioid-Free Through 72 Hours and Through Day 15

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 using descriptive statistics. The proportion of subjects who are opioid-free through Day 15 will be defined and analyzed in a similar way.

Additionally, the proportion of subjects who are opioid free for 0-24 hours, 0-48 hours, 24-72 hours, 0 through Day 15, 72 hours through Day 15, and discharge through Day 15 will be defined and analyzed similarly.

10.1.3. Median Time to First Opioid Rescue Medication Through 72 Hours

Median time in hours to first opioid rescue medication through 72 hours will be summarized using K-M estimates of the median time along with associated 95% CI. Subjects who withdraw from the study prior to 72 hours or who complete the 72-hour timepoint without having taken opioid rescue medication will be censored at the time of study withdrawal or at 72 hours, whichever is earlier.

10.1.4. Proportion of Subjects Who Do Not Receive an Opioid Prescription at Discharge

If a subject has not received any opioids or received <5 IV morphine milligram equivalents (MME; eg, <10 mg PO oxycodone) within 12 hours prior to discharge, the subject should not receive an opioid prescription at discharge. If a subject received ≥5 IV MME (eg, ≥10 mg PO oxycodone) in the 12 hours prior to discharge, the subject may be provided with a prescription for PO immediate-release oxycodone (twenty 5 mg pills; take 1 to 2 pills every 4 hours as needed). Sites will record whether subjects are discharged with an opioid prescription and information about the opioid prescription.

The proportion of subjects who do not receive an opioid prescription at discharge will be summarized using descriptive statistics.

In addition, the proportion of subjects who received an opioid prescription at discharge, the proportion of subjects who received an opioid prescription at discharge and received ≥5 IV MME within 12 hours prior to discharge, and the number of pills prescribed will also be summarized.

10.1.5. Proportion of Subjects Who Do Not Receive an Opioid Prescription Between Discharge and the Day 15 Visit

Sites will record all site-initiated or subject-initiated contact between discharge and the Day 15 visit and whether any result in issuing an opioid prescription. The proportion of subjects who do not receive an opioid prescription after discharge through Day 15 will be summarized using descriptive statistics.

In addition, the proportion of subjects who initiate contact with the site or receive site-initiated contact to discuss pain related to surgery will be summarized.

10.1.6. Proportion of Subjects Who Do Not Receive an Opioid Prescription Through Day 15

After discharge, sites will record all site-initiated or subject-initiated contact between discharge and the Day 15 visit and if any result in issuing an opioid prescription. Subjects who do not receive an opioid prescription through Day 15 is defined as those who do not receive an opioid prescription either at discharge or from discharge through Day 15.

Proportion of subjects who do not receive an opioid prescription through Day 15 will be summarized using descriptive statistics.

10.1.7. Proportion of Subjects Who are Opioid-Free Through 72 Hours and Remain Opioid-Free Through Day 15

Among subjects who are opioid-free through 72 hours (ie, MME=0 through 72 hours), the proportion of subjects who remain opioid-free from 72 hours through Day 15 will be summarized using descriptive statistics.

10.1.8. Mean Area Under the Curve (AUC) of the NRS Scores Through 72 Hours

During the first 72 hours following surgery, the NRS-R and NRS-A scores are measured at hours 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, and 72. The NRS-R and NRS-A scores will be analyzed separately.

Using the trapezoidal rule and letting P_t = the NRS pain intensity score at time t, then:

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

is the trapezoidal area between timepoints 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 mean $AUC_{0\text{-}72}$ of the NRS scores will be analyzed using descriptive statistics.

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 5 in Section 10.1.1 for predefined analgesic windows for each opioid medication.

In addition, analyses will be performed on AUC of NRS without adjusting the NRS pain intensity scores for the use of opioid rescue medications (ie, without applying wWOCF).

In addition, the mean $AUC_{0\text{-}8}$, $AUC_{0\text{-}12}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}48}$, $AUC_{24\text{-}48}$, $AUC_{48\text{-}72}$, $AUC_{24\text{-}72}$, and $AUC_{12\text{-}72}$ of the NRS scores will be analyzed in the same way as the $AUC_{0\text{-}72}$ of NRS scores.

10.1.9. Proportion of Subjects with an NRS Score ≥7 at Each Timepoint and Through 72 Hours

Proportions of subjects with an NRS score ≥7 at each timepoint will be summarized using descriptive statistics.

Proportions of subjects with an NRS score ≥7 at any timepoint through 72 hours as well as through 24 and 48 hours will be analyzed similarly.

10.1.10. Proportion of Subjects Achieving a Score of "Good" or Better (>1) Pain Control Based on PGA at Each Timepoint

PGA of pain control is a 4-point scale in which subjects rate how well their pain has been controlled (Rothman, Vallow et al. 2009). The possible responses to the question are:

- 0: Poor
- 1: Fair

- 2: Good
- 3: Excellent

The proportion of subjects answering in each category will be reported at each timepoint (24 hours, 48 hours, 72 hours, and Day 15). The proportion of subjects achieving a score of "good" or better (>1) pain control based on PGA will be analyzed at each timepoint using descriptive statistics.

10.1.11. Proportion of Subjects Who First Achieve an MPADSS Score ≥9 at Each Timepoint

Discharge readiness will be assessed using the MPADSS criteria, which considers a number of clinical variables: vital signs, ambulation, nausea/vomiting, pain, and surgical bleeding (Chung 1995). The proportion of subjects who first achieve an MPADSS score ≥9 by each timepoint will be analyzed cumulatively (ie, by 2 hours, by 4 hours, by 6 hours, by 8 hours, etc.) using descriptive statistics.

10.1.12. Subgroup Analyses

Subgroup analyses will be performed for the following subgroups:

- Subjects with a prior history of chronic opioid use
- Subjects without a prior history of chronic opioid use

The following PD endpoints will be summarized for each of the subgroups:

- Mean AUC of the NRS-R and NRS-A scores through 72 hours (0-72 hours)
- Mean total postoperative opioid consumption (in IV MME) through 72 hours (0-72 hours).
- Proportion of subjects who are opioid-free through 72 hours (0-72 hours) and through Day 15 (0-Day 15).

Subgroup analysis may also be performed for additional endpoints.

11. INTERIM ANALYSIS

11.1. Interim Analysis

No formal interim analysis is planned.

11.2. Data Safety Monitoring Board

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

12. REFERENCES

Chung, F. (1995). "Discharge criteria--a new trend." Can J Anaesth **42**(11): 1056-1058.

Essex, M. N., R. Y. Zhang, M. F. Berger, S. Upadhyay and P. W. Park (2013). "Safety of celecoxib compared with placebo and non-selective NSAIDs: cumulative meta-analysis of 89 randomized controlled trials." Expert Opin Drug Saf **12**(4): 465-477.

Rothman, M., S. Vallow, C. V. Damaraju and D. J. Hewitt (2009). "Using the patient global assessment of the method of pain control to assess new analgesic modalities in clinical trials." Current Medical Research and Opinion **25**(6): 1433-1443.

APPENDIX 1. IMPUTATION OF PARTIAL AND MISSING DATES

Incomplete Adverse Event Start Date

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, 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, there is no need to impute an 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	05APR2022	Initial version, based on protocol version 3.2 (10MAR2022)

Signature Page for VV-CLIN-005465 v2.0

Approval Task	[redacted] 06-Apr-2022 00:00:57 GMT+0000

Approval Task	[redacted] 06-Apr-2022 06:23:13 GMT+0000

Signature Page for VV-CLIN-005465 v2.0