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STUDY HTX-034-101

A Phase 1b/2, Randomized, Blinded, Active-Controlled Study of Escalating Doses of HTX-034 for Postoperative Analgesia in Subjects Undergoing Unilateral, Distal, First Metatarsal Bunionectomy With Osteotomy and Internal Fixation

24 May 2021

Statistical Analysis Plan

Version 2.0

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

Approved by: _____ Date: _____

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Approved by: _____ Date: _____

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Chief Medical Officer
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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC_{last}	Area under the plasma concentration-time curve from Time 0 to the time of the last quantitative plasma concentration
BMI	Body mass index
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CINV	Chemotherapy-induced nausea and vomiting
C_{max}	Maximum concentration
CME	Clinically Meaningful Event
CRO	Contract research organization
CSR	Clinical study report
CV	Cardiovascular
DM	Data management
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ePRO	Electronic patient-reported outcome
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GI	Gastrointestinal
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IRC	Interim Review Committee
IV	Intravenous(ly)

Abbreviation	Definition
LAST	Local anesthetic systemic toxicity
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
LSMD	Least Squares Mean Difference
MME	Morphine milligram equivalents
MPADSS	Modified Postanaesthetic Discharge Scoring System
NK_1	Neurokinin-1
NRS	Numeric rating scale of pain intensity
NRS-A	NRS score with activity
NRS-R	NRS score at rest
NSAID	Nonsteroidal anti-inflammatory drug
OBAS	Overall benefit of analgesia score
ORAE	Opioid-related adverse event
OR-SDS	Opioid-Related Symptom Distress Scale
PACU	Postanesthesia care unit
PGA	Patient Global Assessment
PK	Pharmacokinetic(s)
PO	By mouth, orally
SAE	Serious adverse event
SAP	Statistical analysis plan
SE	Standard error
SD	Standard deviation
SDTM	Study Data Tabulation Model
SJS	Stevens-Johnson Syndrome
TEAE	Treatment-emergent adverse event
T_{max}	Time of occurrence maximum concentration
ULN	Upper limit of normal
US	United States
WOCF	Worst observation carried forward
wWOCF	Windowed worst observation carried forward

Note: Abbreviations defined in the text but not used again in the text are not included in this List of Abbreviations. Abbreviations used only in a table or figure are also excluded from this List of Abbreviations; they are defined in the table or figure footnotes.

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 Precision for Medicine, Oncology and Rare Disease (Precision) for Phase 1b and by Heron for Phase 2, and the statistical analyses are being performed under contract with Precision, with oversight from Heron. Precision is a contract research organization (CRO).

1.2. Data Quality Assurance

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

2. INTRODUCTION

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

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

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

3. OBJECTIVES

Primary Objectives:

- To evaluate the safety and tolerability of single-dose administration of escalating doses of HTX-034 in subjects undergoing bunionectomy (Phase 1b).
- To evaluate the efficacy of HTX-034 in subjects undergoing bunionectomy (Phase 2).

Secondary Objectives:

- To evaluate the efficacy of escalating doses of HTX-034 in this study population (Phase 1b).
- To evaluate the safety and tolerability of HTX-034 in this study population (Phase 2).
- To characterize the PK profile of HTX-034 in this study population (Phase 1b and Phase 2).

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 1b/2, randomized, blinded, active-controlled study. Phase 1b will evaluate escalating doses of HTX-034 compared with bupivacaine HCl (without epinephrine). The Phase 2 will be a dose-expansion phase to evaluate additional subjects treated with the HTX-034 dose selected based on Phase 1b compared with bupivacaine HCl (without epinephrine).

Subjects will be screened within 28 days prior to the planned surgery date. Subjects who meet the screening eligibility criteria will be randomized to receive HTX-034 or bupivacaine HCl. On the day of surgery (Day 1), subjects who continue to meet the eligibility criteria will undergo a bunionectomy under regional anesthesia with no more than 20 mL of 1% lidocaine without epinephrine administered as a Mayo block. During surgery, the use of intravenous (IV) fentanyl up to 4 μg/kg will be permitted for intraoperative pain control per site practice. Near the completion of surgery, a single dose of study drug (HTX-034 or bupivacaine HCl) will be administered into the surgical site.

Subjects will remain in the hospital/research facility for 7 days (Phase 1b) or 3 days (Phase 2) from the start of study drug administration to undergo postoperative safety, PK, and efficacy assessments. All subjects in Phase 1b will perform self-assessments of pain intensity during the post-surgery inpatient period (at hours 1, 2, 4, 8, 12, 18, 24, 36, 48, 60, 72, evening Day 4, and twice daily on Day 5 through Day 8) and will record the use of postoperative rescue medication through the Day 15 Visit. Subjects in Phase 2 will also perform self-assessments of pain intensity, during the post-surgery inpatient period (at hours 1, 2, 4, 8, 12, 18, 24, 36, 48, 60, 72) and during the outpatient period (evening Day 4, and twice daily on Day 5 through Day 8). After discharge, follow-up PK samples will be collected at home visits by a healthcare professional on Days 9, 10, 11, and 22 in Phase 1b or at the study site on Days 8, 15, and 29 in Phase 2 to characterize the PK profile of HTX-034. Subjects will return to the study site on Day 8 (subjects in Phase 2 only) and on Days 15, 29, and 43 (all subjects) for follow-up assessments. A serum drug test for opioids will be performed at the Day 8 Visit (subjects in Phase 2 only) and at the Day 15 Visit (all subjects).

Phase 1b (Dose Escalation)

There are 2 planned sequential dose cohorts (Table 1). Cohort 1 will evaluate a single dose level of HTX-034. Cohort 2 will evaluate individualized doses of HTX-034; the amount administered will be determined for each subject by the surgeon at the time of surgery and will be based on the volume sufficient to coat the pain-generating tissues, while ensuring there is not an excess that could be expressed from the site during closure.

Each cohort will include a total of approximately 16 subjects (with a minimum of 10 subjects per cohort evaluable for PK). Within each cohort, subjects will be randomized in a 3:1 ratio to receive either HTX-034 (n=12) or bupivacaine HCl (n=4).

Table 1: Summary of Dose Cohorts in Phase 1b

	HTX-034				Bupivacaine HCl 0.5% Dose (Volume)
Cohort	Syringe Volume to Withdraw	Syringe Volume to Expel[a]	Actual Volume Administered[b]	Dose to Administer[c]	
Cohort 1	1 mL	1 mL	0.73 mL	21.7 mg/4.3 mg/0.6 mg	50 mg (10 mL)
Cohort 2	2 mL	1.3 mL to 2 mL	1.03 mL to 1.73 mL	30.6 mg/6.1 mg/0.9 mg to 51.5 mg/10.3 mg/1.5 mg	50 mg (10 mL)

[a] Syringe volume to expel in Cohort 2 will be determined by the Investigator at the time of administration based on the volume sufficient to coat the pain-generating tissues, while ensuring there is not an excess that could be expressed from the site during closure. The volume to expel will range between 1.3 mL and 2 mL.

[b] Actual volume administered takes into account the volume retained in syringe and Luer lock applicator (0.27 mL) after study drug administration.

[c] Dose to administer is based on actual volume administered, which will be determined by weighing syringes before and after study drug administration. HTX-034 doses list the bupivacaine dose first followed by the aprepitant dose and then the meloxicam dose.

Dose escalation to Cohort 2 will be guided by safety data from Cohort 1. After all subjects in Cohort 1 have completed the Day 29 Visit, an internal Interim Review Committee (IRC) will review the data. If the IRC deems it appropriate, the next dose cohort may begin to enroll.

Dose escalation will not take place if any of the following occur:

- ≥2 subjects in a dose cohort experience a serious adverse event (SAE) reported by the Investigator and confirmed by Sponsor to be possibly related to HTX-034.
- ≥2 subjects experience a moderate or severe treatment-emergent adverse event (TEAE) compatible with local anesthetic systemic toxicity (LAST) reported by the Investigator and confirmed by the Sponsor to be possibly related to HTX-034.
- ≥2 subjects treated with HTX-034 who have a wound healing complication of Grade IV or V using the Southampton Wound Scoring System.

Phase 2 (Dose Expansion)

Following a review of the Phase 1b data, up to approximately 40 additional subjects will be randomized to 1 of 2 HTX-034 dose levels or to bupivacaine HCl in a 2:1:1 ratio at the same doses assessed in Phase 1b.

- HTX-034 high dose: 30.6 mg/6.1 mg/0.9 mg to 51.5 mg/10.3 mg/1.5 mg (20 subjects).

- HTX-034 low dose: 21.7 mg/4.3 mg/0.6 mg (10 subjects).
- Bupivacaine HCl 0.5%: 50 mg (10 subjects).

All subjects in Phase 2 will be inpatient for 3 days.

4.2. Assessments

Safety, PK, and efficacy assessments will be performed. The start of HTX-034 or bupivacaine HCl administration will be considered Time 0 for all assessments.

Safety assessments will include the following:

- AEs from the time the subject signs the ICF through the Day 43 Visit.
- LAST questionnaire.
- 12-lead electrocardiograms (ECG) (in triplicate).
- Physical examinations.
- Vital signs, including blood pressure, resting heart rate, respiratory rate, and body
- temperature.
- Wound healing assessments using the Southampton Wound Scoring System (Phase 1b and Phase 2) and a wound healing questionnaire (Phase 2 only).
- Clinical laboratory tests (hematology and serum chemistry).
- Bone healing assessment (X-ray of surgical site).

Efficacy assessments will include:

- Pain intensity assessments using a numeric rating scale of pain intensity score at rest (NRS-R) and NRS score with activity (NRS-A). NRS-R scores are always assessed prior to NRS-A scores.
  - *NRS-R*: Subjects should be seated/recumbent with the surgically attended leg elevated or lying supine. Measurements should be obtained after the subject is in the resting position for at least 5 minutes.
  - *NRS-A*: Subjects should be seated with the plantar surface of the ball of the surgically attended foot touching the floor (no weight-bearing).
  - Subjects will record their pain intensity scores in an electronic patient-reported outcome (ePRO) device after surgery through Day 8.
- Use of postoperative rescue medication through the Day 15 Visit: Date, time of administration, amount, and type of all rescue medication taken will be recorded.
- Opioid prescription at discharge.
- Opioid prescription after discharge through the Day 15 Visit.

- Patient Global Assessment (PGA) of pain control.
- Overall benefit of analgesia score (OBAS).
- Opioid-Related Symptom Distress Scale (OR-SDS) questionnaire.
- Modified Postanaesthetic Discharge Scoring System (MPADSS) assessment.

4.3. Study Endpoints

4.3.1. Primary Endpoint

- Incidence of TEAEs (Phase 1b).
- Mean area under the curve (AUC) of the numeric rating scale of pain intensity (NRS) scores through 72 hours (AUC_{0-72}) for the pooled Phase 1b and Phase 2.

4.3.2. Secondary Endpoints

Safety

- Incidence of SAEs.
- Change from baseline in clinical laboratory results.
- Change from baseline in vital signs.
- Change from baseline in ECGs.
- Incidence of TEAEs (Phase 2).

Efficacy

- Mean AUC of NRS scores through the Day 8 Visit.
- Total postoperative opioid consumption (in IV morphine milligram equivalents [MME]) through the Day 8 Visit.
- Proportion of subjects who are opioid-free through the Day 15 Visit.

4.3.3. Other Endpoints

- Incidence of potential opioid-related adverse events (ORAEs) and potential LAST-related TEAEs.
- Wound healing assessment results at each assessed timepoint.
- Bone healing X-ray results at each assessed timepoint.
- Proportion of subjects with an NRS score ≥7 at each timepoint and through the Day 8 Visit.
- Proportion of subjects who do not receive an opioid prescription through the Day 15 Visit.
- Proportion of subjects achieving a score of "good" or better (>1) pain control based on PGA at each timepoint.
- Mean OBAS at each timepoint.

- OR-SDS scores by symptom dimension.
- Proportion of subjects who first achieve an 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 efficacy measures will also include the standard error (SE). Categorical data will be summarized by the frequency and percent of subjects. Data will be displayed in all listings sorted by subject number and visit/study day. When count data are presented, the percent will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where necessary to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in that treatment group within the population of interest, unless otherwise stated. Non-zero percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places. Additional rounding rules are as follows:

- If the original value has 0 decimal places: mean, median will have one decimal place and SD and SE will have 2 decimal places
- If the original value has 1 decimal place: mean, 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.

5.1. Sample Size

The sample size in Phase 1b was selected empirically without a formal statistical assumption and will be sufficient to characterize the PK profile for HTX-034.

Based on results from Phase 1b of this study and a Phase 3 bunionectomy study of HTX-011 (Study HTX-011-301), a sample size of 40 subjects in Phase 2 (2:1:1 ratio of HTX-034 high

dose:HTX-034 low dose:bupivacaine HCl) when pooled with Phase 1b (Table 2) will provide 82% power to detect a statistical significant difference between the HTX-034 high dose and bupivacaine HCl for the primary endpoint, assuming mean (SD) AUC_{0-72} of NRS pain scores were 272 (122) for HTX-034 in Phase 1b and 394 (154) for bupivacaine HCl in Phase 3 using Satterthwaite's t-test with $\alpha = 0.05$, 2-sided.

Table 2: Sample Size Per Phase

	HTX-034 High Dose	HTX-034 Low Dose	Bupivacaine HCl
Phase 1b Safety Population	13	11	9[a]
Planned Phase 2 Safety Population	20	10	10
Pooled Phase 1b and Phase 2	33	21	19

[a] Pooled across cohorts.

5.2. Randomization, Stratification, and Blinding

Subjects who meet the Screening eligibility criteria will be randomized to either HTX-034 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. The randomization will be based on centralized, computer-generated, stratified randomization by site. Section 4.1 provides further details on the randomization schedule for each dose cohort.

The site's pharmacy and surgical staff will not be blinded to the treatment assignments because HTX-034 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 safety, efficacy, and PK assessments will be blinded to the treatment assignment. Sponsor staff directly interacting with blinded site personnel will maintain the blind. The data for Cohorts 1 and 2 may be unblinded after Phase 1b is complete.

The study blind should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the study drug he/she received.

5.3. Analysis Populations

5.3.1. Safety Population

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

5.4. Table Layout and Pooling

Data from the bupivacaine HCl treatment groups in Phase 1b will be pooled across dose cohorts as well as pooled across Phase 1b and Phase 2. Each HTX-034 dose cohort will be analyzed separately in each phase as well as pooled with the same dose cohort across Phase 1b and Phase 2.

Table 3 displays the planned treatment groups being studied.

Table 3. Planned Treatment Groups

Study Phase	Dose Cohort	Inpatient Period	Treatment Group	Actual/Planned Treated Subjects[a]
1b	1	7 Day	HTX-034 low dose	11
			Bupivacaine HCl 0.5% 50 mg (10 mL)	5
	2	7 Day	HTX-034 high dose	13
			Bupivacaine HCl 0.5% 50 mg (10 mL)	4
2		3 Day	HTX-034 high dose	20
			HTX-034 low dose	10
			Bupivacaine HCl 0.5% 50 mg (10 mL)	10

[a] Number of actual treated subjects are presented for Phase 1b while number of planned treated subjects are presented for Phase 2.

All efficacy and safety data will be summarized for each of the three treatment groups (bupivacaine HCl, HTX-034 Low Dose, HTX-034 High Dose) by phase and each of the three treatment groups will be pooled across Phase 1b and Phase 2 (Table 4).

Table 4. Layout of Summary Tables

Phase 1b			Phase 2			Pooled Phase 1b/2		
HTX-034 Low Dose (N=XX)	HTX-034 High Dose (N=XX)	Bupivacaine HCl 50 mg (N=XX)	HTX-034 Low Dose (N=XX)	HTX-034 High Dose (N=XX)	Bupivacaine HCl 50 mg (N=XX)	HTX-034 Low Dose (N=XX)	HTX-034 High Dose (N=XX)	Bupivacaine HCl 50 mg (N=XX)

Note: HTX-034 doses (bupivacaine/aprepitant/meloxicam) are as follows: 21.7 mg/ 4.3 mg/ 0.6 mg for HTX-034 Low Dose, 30.6 mg/ 6.1 mg/ 0.9 mg to 51 5 mg/ 10.3 mg/ 1.5 mg for HTX-034 High Dose.

5.5. Other Important Considerations

5.5.1. Definition of Baseline

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

5.5.2. Calculation of Change and Percent Change from Baseline

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

$C_t = M_t - M_B$, where:

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

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

$P_t = 100*(C_t/M_B)$

5.5.3. Study Day Calculation for Reporting Purposes

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

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

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

5.5.4. 72-Hour Postoperative Period

The 72-hour postoperative period will be defined as the period of time from the start date/time of study drug administration to the latest date/time of the NRS-R and NRS-A assessments at the nominal 72-hour postoperative timepoint on the ePRO device. Subjects who have a reported NRS-R or NRS-A pain intensity score at the nominal 72-hour postoperative timepoint will be considered as having completed the 72-hour postoperative period.

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

- For the analysis of AUC, the 72-hour postoperative period will be defined as the start date/time of study drug administration + 72 hours.
- For the analyses of opioid use (including opioid MME consumption and opioid-free status) through 72 hours, the following rules will be applied to the analytic opioid data based on concomitant medications (morphine and other non-oxycodone use) and ePRO device data (oxycodone use).
  - If the subject early terminates 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.

5.5.5. Day 8 Postoperative Period

The Day 8 postoperative period is intended to capture 7 days (168 hours) of data from the start of study drug administration.

The Day 8 postoperative period will be defined as the period of time from the start date/time of study drug administration to the latest date/time of the NRS-R and NRS-A assessments at the nominal 168 hour timepoint on the ePRO device. Subjects who have a reported NRS-R or NRS-A pain intensity score at the nominal 168 hour timepoint will be considered as having completed the Day 8 postoperative period.

However, if the date/time of the NRS-R and NRS-A assessments at nominal 168 hour timepoint are both missing, the following will be applied depending on the study endpoint.

- For the analysis of AUC, the Day 8 postoperative period will be defined as the start date/time of study drug administration + 168 hours.
- For the analyses of opioid use (including opioid MME consumption and opioid-free status) through the Day 8 postoperative period, the following rules will be applied to the analytic opioid data based on concomitant medications (morphine and other non-oxycodone use) and ePRO device data (oxycodone use).
    - If the subject early terminates prior to the 168 hour timepoint, the Day 8 postoperative 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 the 168 hour timepoint, the Day 8 postoperative period will be defined as from the start date/time of study drug administration + 168 hours.

5.5.6. Day 15 Postoperative Period

The Day 15 postoperative period will be defined as the period of time from the start date/time of study drug administration to the Day 15 visit date.

If the Day 15 visit date is missing, the following rules will be applied.

- If the subject early terminates prior to Study Day 15, the period is defined as the start date/time of study drug administration to the date of early termination.
- If the subject continues beyond Study Day 15, the period is defined as the start date/time of study drug administration + 14 days (ie, from the date of surgery to Study Day 15).

5.5.7. 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.

5.5.8. Handling of Missing and Partial Data

For any pain score data that is missing through the 168 hour timepoint in subjects who complete the Day 8 postoperative period, the pain intensity scores (NRS-R or NRS-A) will be imputed via last observation carried forward (LOCF), in which the most recent postdose non-missing value is used for the 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.

For binary endpoints (i.e. endpoints 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 defined by 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-R score ≥ 7) through the 168 hour timepoint will be constructed following both LOCF alone and windowed worst observation carried forward (wWOCF) (see Section 10.1.1 for details).

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

All other efficacy results will be analyzed using observed data unless otherwise specified.

All safety results will be summarized using observed data 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 A. No other partial dates will be imputed.

Rescue medication recorded in concomitant medications with missing start times will be imputed to “00:01” for that day.

6. SUBJECT DISPOSITION

A summary of the disposition of subjects will include the frequency and percentage of subjects for the following categories: enrolled (signed the informed consent form), failed screening prior to randomization with reasons for screen failure, randomized, primary reason for study withdrawal after randomization but prior to dosing, Safety Population, completed the 72-hour postoperative period, completed Day 8 Postoperative period, completed Day 15 Postoperative period, completed the study, and subjects not completing the study by reason for withdrawal.

Only one reason for study withdrawal will be recorded for each subject. Study completion is defined as subjects who completed the Day 43 Visit.

7. DEMOGRAPHICS, CHARACTERISTICS, AND MEDICAL HISTORY

7.1. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be presented in tables using descriptive statistics. Demographics consist of age, age category, sex, race, and ethnicity. Baseline characteristics consist of weight, height, and body mass index (BMI). A subject's age in years is calculated using the integer part of the difference in number of days between the date that informed consent is signed and date of birth divided by 365.25, or what 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 23.0. Medical history will be summarized for the Safety Population and will display the frequency 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
- Other

Protocol deviations will be further subclassified as related to COVID-19 (Yes/No).

Protocol deviations meeting the following criteria will be classified as important PDs:

- Subject who entered the study even though they did not satisfy entry criteria.

- Subject who developed withdrawal criteria during the study but were not withdrawn.
- Subject who received wrong study drug or incorrect dose of study drug.
- Subject who received a prohibited concomitant medication during the study.

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

All medications will be coded with the World Health Organization Drug Dictionary Global B3 Format (WHODrug Global B3), March 2019.

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 concomitant opioid pain medications and acetaminophen with a start date/time within the Day 15 postoperative period (see Section 5.5.6 for details) will be included in the rescue medication summaries. An exception will be fentanyl administered on the date of surgery with a recorded indication of "Intraoperative"; this is considered part of intraoperative management and is not counted as rescue medication.

Incidence of opioid and acetaminophen consumption will be summarized from study drug administration (time 0) through 72 hours, through Day 8 (See Section 5.5.5), and through Day 15 and from 72 hours through Day 15. Summaries will be provided for usage of no opioid rescue medication, any rescue medication (opioid and/or acetaminophen), and acetaminophen only.

8.3. Surgery Procedure

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

8.4. Study Treatment

All subjects will receive a single dose of study drug (HTX-034 or bupivacaine HCl) intraoperatively while undergoing bunionectomy. The extent of exposure to study drug will be reported in the CSR as the number of subjects who received study drug in the Safety Population. A summary of treatment compliance will not be produced, by definition it will be 100% for the Safety Population.

Since subjects in Phase 1b Cohort 2 and Phase 2 HTX-034 high dose group receive individualized doses of HTX-034, the weight of the syringe before and after HTX-034 administration will be collected on eCRF to calculate the dose of HTX-034 administered.

Component doses of bupivacaine, aprepitant and meloxicam in HTX-034 will also be summarized with descriptive statistics. Component doses in milligrams (mg) will be calculated as follows:

Given that D = (Total pre-dose weight – Total post-dose weight) in grams(g),

Bupivacaine dose (mg) = D *25 mg/g

Aprepitant dose (mg) = D *5 mg/g

Meloxicam dose (mg) = D *0.75 mg/g.

9. SAFETY ANALYSES

All analyses of safety data will be conducted on the Safety Population. Statistical hypothesis testing will not be performed on any safety data. No imputation of missing safety data will be performed except in the case of partial AE and concomitant medication onset dates (Appendix A).

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.

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 23.0. 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. 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.

9.1.2. Severity of Adverse Event

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

9.1.3. Adverse Events Leading to Study Withdrawal

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

9.1.4. Death

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. Safety Endpoints

9.2.1. Primary Endpoint

9.2.1.1. Incidence of Treatment-Emergent Adverse Events (Phase 1b)

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 only 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 overall HTX-034 incidence. For tables showing incidence by PT only, the PTs will be sorted in descending order of pooled HTX-034 High Dose 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 subjects with at least 1 potential ORAE
- Number of subjects with at least 1 potential LAST TEAE.
- Number of treatment-emergent SAEs (TESAEs)
- Number of subjects with at least 1 TESAE
- Number of subjects with at least 1 TESAE possibly related to study drug
- Number of subjects with fatal TEAEs

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

9.2.2. Secondary Endpoints

9.2.2.1. Incidence of Serious Adverse Events

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

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

Incidence of TESAEs will be presented in a table by SOC and PT. The incidence of TESAE tables will include only 1 occurrence of a PT per subject. For a given PT, if a subject reports the same TESAE multiple times, that subject will only be counted once since unique subject counts will be presented. Similar to the analysis of PTs, if a subject reports multiple TESAEs within the same SOC, that subject will only be counted once since unique subject counts will be presented. All SAEs will also be listed separately.

Incidence of TESAEs related to study drug will also be summarized by SOC and PT.

9.2.2.2. Change from Baseline in Clinical Laboratory Results

Laboratory assessments will be performed by a central laboratory (hematology, serum chemistry, and serum drug test) or locally (pregnancy test and urine 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 serum chemistries including actual values and change from Baseline values will be presented for clinical laboratory tests with numeric values. These tables will include each visit (Screening, Baseline, 72-hours, Day 8, and Day 15, and Day 29), 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 will be flagged simply with "L".

Listings of out-of-range values for hematology and serum chemistries will be presented separately in addition to listings of all laboratory values.

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

Serum 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 out-of-range liver function values will be summarized at each visit for the following categories. Subjects with out-of-range liver function values 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

Urine Pregnancy Test, Urine Drug Screen, and Serum Drug Tests

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

Listings of subjects with a positive opioid serum test on Day 8 (Phase 2 only) and Day 15 (Phase 1b and 2) will be generated.

9.2.2.3. Change From Baseline in Vital Signs

Vital signs including systolic blood pressure, diastolic blood pressure, resting heart rate, body temperature, and respiration rate will be collected at screening, on Day 1 before surgery, and post-treatment at 30, 60, and 90 minutes, 2, 4,12,18, 24, 36, 48, 60, and 72 hours, Day 8 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 5 :

Table 5: 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.

9.2.2.4. Change from Baseline in Electrocardiograms

12-lead ECGs will be performed at baseline, 24 hours, 48 hours, 72 hours, Day 8, and early termination (if applicable).

ECG parameters include RR interval (ms), QT interval (ms), and QTcF (Fridericia) interval (ms). Overall interpretations of ECG results are also included. QTcF will be calculated and used in tabular summaries, according to,

$QTcF = QT\ interval / (RR\ interval)^{1/3}$.

Site reported ECG parameters and calculated QTcF will be provided in listings.

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

The frequency and percentage of subjects with the following clinically relevant abnormalities will be presented in summary tables and data listings at each postoperative timepoint.

- QTcF values > 450 ms, > 480 ms, and > 500 ms.

- Change from Baseline in QTcF values > 30 ms and > 60 ms.

9.2.2.5. Incidence of Treatment-Emergent Adverse Events (Phase 2)

Incidence of TEAEs will be summarized for Phase 2 as a secondary endpoint as described in Section 9.2.1.1.

9.2.3. Other Safety Endpoints

9.2.3.1. Potential 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 potentially opioid-related include the following:

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

Incidence of potential ORAEs will be presented separately as follows:

- Incidence of potential ORAEs
- Incidence of potential ORAEs through the Day 8 postoperative periods
- Incidence of potential ORAEs in the subset of subjects who received at least 1 opioid rescue medication during the Day 8 postoperative periods
- Incidence of potential ORAEs through the Day 8 postoperative periods in the subset of subjects who received at least 1 opioid rescue medication during the Day 8 postoperative periods

9.2.3.2. Potential Local Anesthetic Systemic Toxicity Assessment

A LAST assessment questionnaire will be administered on a regular basis to monitor for early neurologic and cardiac signs and potential symptoms of 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.

9.2.3.3. Potential Local Anesthetic Systemic Toxicity (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 6).

Table 6. 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.

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

9.2.4. Wound Healing Assessment Results at Each Assessed Timepoint

Surgical wound healing will be assessed in both Phase 1b and Phase 2 using the Southampton Wound Scoring System at Day 8 and on Day 15, Day 29, Day 43, and early termination (if applicable). A summary of wound healing assessment results will be produced, showing the proportion of subjects in each category at each visit, at last post-baseline visit, and at worst value post-baseline by grade with subgrade breakdown. Wound healing assessment results will also be listed.

In addition, surgical wound healing will also be assessed in Phase 2 using a wound healing assessment questionnaire at the same timepoints as Southampton Wound Scoring System. A summary of wound healing assessment results will be produced, showing the number and percentage of subjects with symptom absence/presence, and if present, symptoms expected (as applicable), abnormal not clinically significant (NCS) or abnormal clinically significant (CS) at each visit for each symptom, overall for each symptom, and overall for all symptoms.

Wound healing data collected at unscheduled visits will be included in listings and will contribute to the worst and last post-dose assessment summaries for wound healing assessment using Southampton (Phase 1b/2) and to overall summaries for wound healing assessment using questionnaire (Phase 2 only). Unscheduled wound healing results will not be windowed for the purposes of assigning a nominal visit.

9.2.5. Bone Healing X-ray Results at Each Assessed Timepoint

Bone healing assessments based on X-rays of the surgical site will be assessed at Day 29, Day 43, and early termination (if applicable). A summary of bone healing assessment X-ray results will be produced, showing the frequency and percentage of subjects at each visit, at last post-baseline visit, and at worst value post-baseline. Bone healing assessment results will also be listed.

9.3. Additional Safety Analyses

9.3.1. Physical Examinations

Physical examination will be performed at Screening, Day 29, and early termination (if applicable). Physical examination data will be listed only.

10. EFFICACY ANALYSES

10.1. Efficacy Endpoints

Unless otherwise specified, statistical testing will be done in Phase 1b and 2 for all efficacy endpoints and will be two-sided at an alpha of 0.05, for each endpoint. Unadjusted p-values will be reported. The family-wise error rate will not be controlled for at an alpha of 0.05 for multiple comparisons. In general, descriptive statistics will be reported for all efficacy endpoints. The statistical comparison will be performed between HTX-034 High Dose vs bupivacaine HCl, and HTX-034 Low Dose vs bupivacaine HCl by phase and pooled across Phase 1b and Phase 2.

The following statistical tests will be performed on efficacy endpoints:

The analysis of mean AUC of NRS scores will be carried out using an analysis of variance (ANOVA) model with treatment as the main effect, comparing HTX-034 with bupivacaine HCl at a significance level of 5%. Results will be expressed as mean AUCs and SDs, least-square mean differences (LSMD) and SEs with associated 95% CI, and p-values.

Total postoperative opioid rescue medication consumption through a specified time period will be summarized using descriptive statistics. The total postoperative opioid rescue medication consumption through the specified time period will be analyzed using a Wilcoxon rank sum test.

Proportion-type endpoints will be analyzed using Fisher's exact test. Results will be expressed as the frequency and percentage of subjects meeting the relevant criteria for the endpoint, differences in proportions across treatment arms with exact 95% CIs, and corresponding p-values.

Mean OBAS score and overall composite OR-SDS score will be analyzed using the Wilcoxon rank sum test.

10.1.1. Primary Endpoint

10.1.1.1. Mean area under the curve (AUC) of the NRS scores through 72 hours (AUC0-72) for the Pooled Phase 1b and Phase 2

During the Day 8 postoperative period, the NRS is measured at hours 1, 2, 4, 8, 12, 18, 24, 36, 48, 60, 72, evening Day 4, Day 5 8AM, Day 5 8PM, Day 6 8AM, Day 6 8PM, Day 7 8AM, Day 7 8PM, and 168 hours. 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*. Respective actual times at nominal timepoints will be used to compute trapezoidal widths. The $AUC_{0\text{-}168}$ is thus calculated as follows:

$$AUC_{0-168} = \int_{1}^{168} f(t)dt \approx \sum_{i=2}^{168}(t_i - t_{i-1})\frac{P_{i-1} + P_i}{2}$$

Mean $AUC_{0\text{-}72}$ of the NRS-A pooled high dose HTX-034 vs pooled bupivacaine is considered the primary efficacy endpoint.

To adjust for the duration effect of opioid rescue medication, the wWOCF method will be implemented as the primary analysis method for endpoints involving NRS pain intensity scores. In this method, pain intensity scores observed during the analgesic window (duration of effect) of any opioid rescue medication will be replaced with the worst (highest) postdose nonmissing NRS pain intensity score observed prior to the rescue medication window, with the following exception: if the NRS pain intensity score for a windowed observation is higher than the worst pre-window score, then it will **not** be replaced. wWOCF will be performed following LOCF (ie, perform LOCF first, then apply wWOCF). See Table 7 in Section 10.2 for predefined analgesic windows for each opioid medication.

In addition, mean AUC of the NRS-R scores through the Day 8 Visit ($AUC_{0\text{-}168}$) of NRS-R will be analyzed similarly as the $AUC_{0\text{-}168}$ of NRS-A scores.

10.1.2. Sensitivity Analyses

Sensitivity analyses include reproducing the primary analysis but without adjusting the NRS pain intensity scores for the use of opioid rescue medications (ie, without applying wWOCF).

10.2. Secondary Efficacy Endpoints

10.2.1. Mean AUC of NRS Scores Through Day 8 Visit

The following means of $AUC_{0\text{-}24}$, $AUC_{0\text{-}72}$, $AUC_{0\text{-}168}$, $AUC_{24\text{-}72}$, $AUC_{24\text{-}168}$, and $AUC_{72\text{-}168}$ of the NRS-A and NRS-R scores will be analyzed with appropriate adjustment to the calculation to reflect the time period of interest. Statistical testing will be performed between groups for the AUCs mentioned above.

In addition, the mean NRS scores will be summarized at each assessed timepoint.

10.2.2. Total Postoperative Opioid Consumption (in IV MME) Through the Day 8 Visit

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

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

Determination of MME

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

Postoperative rescue medication through the first 72 hours after surgery will consist of 1 or more of the following 3 medications: oral (PO) acetaminophen (1,000 mg within a 6-hour window; not to exceed 4,000 mg per day), PO immediate-release oxycodone (≤10 mg within a 4-hour period), and/or IV morphine (≤10 mg within a 2-hour period). The choice of rescue medication will be at the site's discretion. Combination products containing an opioid and a non-opioid are not allowed. Nonsteroidal anti-inflammatory drugs (NSAIDs) are not permitted; no other analgesic agents are permitted.

After 72 hours, the following medications are recommended to treat pain when necessary in a step-wise fashion:

1. PO acetaminophen as needed (1,000 mg no more frequently than every 6 hours; not to exceed 4,000 mg per day).
2. PO immediate-release oxycodone (≤10 mg within a 4-hour period) only if acetaminophen fails to adequately manage pain.

Morphine is not permitted after 72 hours. NSAIDs are not permitted; no other analgesic agents are permitted.

After the Day 15 Visit, postoperative pain should be managed per institutional standard of care.

Table 7 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 7: Analgesic Windows and Morphine Milligram Equivalents 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	
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 equivalents; PO, by mouth (orally); PR, per rectum.
Note: Morphine Equivalent = Opioid Dose × MME factor.

Analysis method

Rescue medication (opioids and acetaminophen) consumption is collected from start of study drug administration (time 0) through the Day 15 Visit. 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, 0-Day 8, 0-Day 15, 24 hours-Day 8, 24-72 hours, 72 hours - Day 8, 72 hours -Day 15, Day 8-Day 15, and discharge through Day 15. In addition, opioid consumption in 24 hour time blocks up to Day 15 will be summarized: [0-24), [24-48), [48-72), [72-96), [96-120), [120-144), [144-168), [168-192), [192-216), [216-240), [240-264), [264-288), [288-312), [312-336), and [336-360] hours. 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 consumption in milligrams (mg) will be analyzed similarly as total opioid consumption.

10.2.3. Proportion of Subjects Who are Opioid-free Through the Day 15 Visit

Opioid-free status will be determined based on observed data from concomitant medications and ePRO device data.

Subjects who have a total MME postoperative opioid dose = 0 through Day 15 will be characterized as "opioid-free" through Day 15. The proportion of subjects who are opioid-free through Day 15 will be summarized using descriptive statistics. Additionally, the proportion of subjects who are opioid free 0-24 hours (ie, MME=0 through 24 hours), and proportion of subjects who are opioid free 0-48 hours, 0-72 hours, 0-Day 8, 24 hours-Day 8, 24-72 hours, 72 hours-Day 15, Day 8-Day 15, and discharge through Day 15 hours will be analyzed similarly.

10.3. Other Efficacy Endpoints

10.3.1. Proportion of subjects with an NRS score ≥7 at each timepoint and through the Day 8 Visit

The proportion of subjects with an NRS (NRS-R and NRS-A) score ≥7 (ie, severe pain) at each timepoint, 0-Day 8 Visit, 0-72 hours, and 72 hours-Day 8 Visit.

10.3.2. Proportion of subjects who do not receive an opioid prescription through the Day 15 Visit

The site will record all site- or subject-initiated contacts between discharge and the Day 15 visit and if any resulted in issuing an opioid prescription. The proportion of subjects who do not receive an opioid prescription through the Day 15 Visit will be summarized using descriptive statistics, which includes the site's response of 'No' to "Did the subject receive an Opioid prescription?" at discharge and the subject not receiving any opioid prescriptions after discharge through Day 15. In addition, 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 receive an opioid prescription at discharge and the number of pills prescribed among these subjects will also be summarized.

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

10.3.3. Proportion of subjects achieving a score of "good" or better (>1) pain control based on PGA at each timepoint

Subjects will be asked to evaluate their pain control over the preceding 24 hours using a 4-point PGA scale (Rothman, Vallow et al. 2009) on Days 2, 3, and 4. The possible responses are as follows:

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

The proportion of subjects answering in each category will be reported at each timepoint (Days 2, 3, and 4). The proportion of subjects achieving a score of "good" or better (>1) pain control based on PGA will be summarized at each timepoint using descriptive statistics.

10.3.4. Mean OBAS at each timepoint

Subjects will be asked to evaluate their overall benefit of analgesia using a 7-item, multidimensional, quality assessment questionnaire (Lehmann, Joshi et al. 2010). The 7 items address pain, vomiting, itching, sweating, freezing, dizziness, and overall satisfaction with postoperative pain. Each of the 7 items is rated on a scale of 0-4 as follows:

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

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

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

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

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

10.3.5. OR-SDS scores by symptom dimension

Subjects will be asked about 10 opioid-related symptoms experienced over the preceding 24 hours: fatigue, drowsiness, inability to concentrate, nausea, dizziness, constipation, itching, difficulty with urination, confusion, and retching/vomiting on Days 2, 3, and 4. Each symptom will be assessed according to the following dimensions:

- Frequency
- Severity
- Bothersomeness

using categorical scales according to methods developed by Portenoy et al. (1994) and described in Appendix C. Clinically Meaningful Events will be determined by the symptom scores on Days 2, 3, and 4 according to the following definitions per Apfelbaum el al. (2004) and Zhao et al. (2004) :

Dimension	Scale Definition	Definition of a CME (a response of):
Frequency	0 = Did not have 1 = Rarely 2 = Occasionally 3 = Frequently 4 = Almost Constantly	Frequently to almost constantly
Severity	0 = Did not have 1 = Slightly Severe 2 = Moderately Severe 3 = Severe 4 = Very Severe	Moderate to very severe
Bothersomeness	0 = Did not have 0.8 = Not at all 1.6 = A little bit 2.4 = Somewhat 3.2 = Quite a bit 4.0 = Very much	Quite a bit to very much bothered

If at least one dimension had a response that fit the CME definition, a CME for that symptom will be recorded. For the symptom of retching/vomiting, the number of episodes is recorded for the Frequency OR-SDS score and if the subject vomited at least once then the subject will have a CME for the Frequency dimension.

The following OR-SDS scores will be calculated for each subject and summarized by descriptive statistics:

- OR-SDS score by each symptom and dimension.
- Symptom specific score. Computed as the average of scores across dimensions per specific symptom.
- Dimension-specific composite score. Computed by averaging across symptom scores for each dimension (i.e. frequency, severity, or bothersomeness).
- Overall composite score. Computed as the average of the symptom specific scores.

Treatment groups will be compared based on the Wilcoxon Rank Sum test on the overall composite symptom score and dimension specific composite scores. The proportion of subjects per treatment group with one or more CMEs and corresponding p-value will be presented with the OR-SDS summaries. OR-SDS summary scores and the proportion of subjects with at least one CME will be presented by assessed timepoints on Days 2, 3, and 4, as well as proportion of subjects with at least one CME through Day 4.

In addition, total number of CMEs will be calculated for each subject for Days 2, 3, and 4, and through Day 4. For each subject and each day the total number of CMEs is the sum of CMEs across symptoms and ranges from 0 to 10. For each subject the total number of CMEs through Day 4 is the sum of total number of CMEs at Days 2, 3, and 4 and ranges from 0 to 30. The total number of CMEs will be compared between treatment groups using a Wilcoxon rank sum test at assessed timepoints with p-values reported.

10.3.6. 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). This study instrument assesses a subject's potential readiness to be discharged. It is not meant to be used to decide whether or not to discharge a subject from the study. Subjects are required to remain in the hospital/research facility for 7 days (Phase 1b) or 3 days (Phase 2).

The proportion of subjects who first achieve an MPADSS score ≥9 at each timepoint will be analyzed cumulatively (i.e., through 2 hours, through 4 hours, through 6 hours, through 8 hours, etc.) using descriptive statistics.

11. INTERIM ANALYSES

11.1. Interim Analysis

An interim analysis may occur when at least 16 subjects in a dose-escalation cohort complete the Day 29 Visit. An internal IRC will review unblinded, summary-level data from each cohort to make decisions on the next cohort. The internal IRC will be composed of 1 Sponsor representative from the Clinical Research, Biometrics, Pharmacovigilance, Regulatory, and Pharmaceutical and Translational Sciences functions. The IRC will operate under a written, detailed IRC Charter.

11.2. Data Safety Monitoring Board

An independent Data Safety Monitoring Board 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, including regular review of AEs laboratory results, and other safety assessment results.

12. REFERENCES

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APPENDIX A. 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 B. DOCUMENT REVISION HISTORY

Version	Date	Notes/Revisions
1	14DEC2020	Initial version, based on protocol version 6 (03NOV2020)
2	24MAY2021	Second version, based on protocol versions 7 (05FEB2021) and 8 (09MAR2021) • Updated sections on study design, assessments, and endpoints to align with protocol v7 • Updated Section 4 to incorporate pooled analysis across Phase 1b and Phase 2 to align with protocol v7 • Updated Section 5.1 on the Phase 2 sample size to align with protocol v8 • Updated analysis for protocol deviation in Section 7.3 to align with Protocol Deviation Management Plan v2.0 • Added analysis for wound healing questionnaire to account for corresponding assessment added to protocol v7

APPENDIX C. OPIOID-RELATED SYMPTOM DISTRESS SCALE

We have listed 10 symptoms below. Read each one carefully. If you have had the symptom during the past 24 hours, let us know how OFTEN you had it, how SEVERE it was usually and how much it DISTRESSED OR BOTHERED you by placing an 'X' in the appropriate box. If you DID NOT HAVE the symptom, please place an 'X' in the box marked "Did not have".

For the symptom "retching/vomiting" below, you will indicate the actual **number** of episodes you experienced.

During the last 24 hours, did you have any of the following?

Symptoms	Did not have	(If yes), how often did you have it?				(If yes), how severe was it usually?				(If yes), how much did it distress or bother you?				
		Rarely	Occasionally	Frequently	Almost constantly	Slight	Moderate	Severe	Very severe	Not at all	A little bit	Somewhat	Quite a bit	Very much
Fatigue	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Drowsiness	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Inability to concentrate	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Nausea	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Dizziness	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Constipation	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Itching	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Difficultly with urination	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Confusion	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Retching/vomiting	☐	__ # of episodes				☐	☐	☐	☐	☐	☐	☐	☐	☐

Adapted with permission from the Memorial Symptom Assessment Scale by Portenoy, et al; OR-SDS© 2004 Pfizer Inc., Jeffrey L. Apfelbaum and Tong J. Gan.

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