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STUDY HTX-011-306

A PHASE 3B, OPEN-LABEL STUDY OF HTX-011 AS PART OF A SCHEDULED NON-OPIOID MULTIMODAL ANALGESIC REGIMEN IN SUBJECTS UNDERGOING TOTAL KNEE ARTHROPLASTY

01 July 2021

Statistical Analysis Plan

Version 3.0

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

Approved by: _____ Date: _____

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Heron Therapeutics, Inc.

Approved by: _____ Date: _____

[redacted]
Heron Therapeutics, Inc.

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List of Abbreviations

Abbreviation	Term
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Classification
AUC	Area under the curve
bpm	Beats per minute
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence interval
CRO	Contract Research Organization
CSR	Clinical study report
CTM	Clinical trial materials
DBP	Diastolic blood pressure
DM	Data management
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
eDISH	Evaluation of drug-induced serious hepatotoxicity
GGT	Gamma glutamyltransferase
HCl	Hydrochloride
HR	Heart rate
IM	Intramuscular
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
NRS-R	Numeric rating scale of pain intensity at rest
NSAID	Nonsteroidal anti-inflammatory drug
OBAS	Overall benefit of analgesia score
ORAE	Opioid-related adverse event
PACU	Postanesthesia care unit
PGA	Patient's Global Assessment
PK	Pharmacokinetic(s)
PO	Oral(ly)
PR	Per rectum
PRN	As needed
PT	Preferred Term
RBC	Red blood cell

SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SDA	Study drug administration
SDTM	Study Data Tabulation Model
SDTMIG	Study Data Tabulation Model Implementation Guide
SE	Standard error
SI	Standard international
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper limit of normal
US	United States
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 under contract with [redacted] and the statistical analyses are being performed under contract with [redacted], with oversight from Heron. [redacted] 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 Objective:

The primary objective is to assess pain control following HTX-011 as part of a scheduled non-opioid multimodal analgesic (MMA) regimen in subjects undergoing total knee arthroplasty (TKA).

Secondary Objectives:

- To assess total opioid use following HTX-011 as part of a scheduled non-opioid MMA regimen in this study population.
- To assess the proportion of subjects who are opioid-free after receiving HTX-011 as part of a scheduled non-opioid MMA regimen in this study population.
- To assess the safety and tolerability of HTX-011 in a multimodal setting in this study population.
- To characterize the pharmacokinetic (PK) parameters of bupivacaine and meloxicam in this study population

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 3b, open-label study to evaluate if HTX-011 administered as the foundation of a scheduled non-opioid MMA regimen can further improve pain control and lead to a greater reduction or eliminate the need for opioids following a primary unilateral TKA.

Subjects who meet the eligibility criteria will be enrolled in the study in 1 of 4 cohorts and will undergo primary unilateral TKA under bupivacaine spinal anesthesia (≤ 20 mg). All subjects will be administered a single dose of HTX-011 as follows:

- Cohort 1: Approximately 50 subjects will be administered a single dose of HTX-011 400 mg/12 mg via periarticular application into the surgical site during surgery.
- Cohort 2: Approximately 15 subjects will be administered a single dose of HTX-011 400 mg/12 mg via periarticular application into the surgical site during surgery. Drains will be prohibited.
- Cohort 3: Approximately 30 subjects will be randomized at 1:1 ratio into 2 groups. In Group A, subjects will be administered a single dose of HTX-011 300 mg/9 mg via periarticular application into the surgical site during surgery. In Group B, subjects will be administered a single dose of HTX-011 300 mg/9 mg via periarticular

application into the surgical site and 100 mg bupivacaine HCl injected into the posterior capsule during surgery. Drains will be prohibited.

- Cohort 4: Up to approximately 20 subjects will be administered a single dose of HTX-011 400 mg/12 mg via periarticular application into the surgical site during surgery.

Just before being taken to the operating room, all subjects will receive PO acetaminophen 1 g, PO celecoxib 200 mg, and PO pregabalin 300 mg. After surgery, subjects will receive a scheduled non-opioid MMA regimen for 7 days. The first dose of postoperative MMA regimen will be administered once the subject is able to tolerate PO intake. For the first 3 days after surgery, all subjects will receive PO acetaminophen 1 g every 8 hours and PO celecoxib 200 mg every 12 hours (Cohorts 1, 2 and 3) or PO acetaminophen 1 g every 8 hours and PO ibuprofen 600 mg every 6 hours (Cohort 4). For the next 4 days, the MMA regimen for all cohorts will consist of PO ibuprofen 600 mg every 6 hours alternating with PO acetaminophen 1 g every 6 hours (maximum ibuprofen dose of 2.4 g/day and maximum acetaminophen dose of 4 g/day) while the subject is awake, so that an analgesic is taken approximately every 3 hours.

4.2. Assessments

The start of HTX-011 (ie, study drug) administration will be considered Time 0 for all assessments.

Efficacy assessments will include the following:

- VAS and NRS of pain intensity at rest (NRS-R) assessments. Assessments should be performed when the subject is in the resting position (either seated comfortably or lying down) for at least 5 minutes prior to obtaining the pain scores.
- Opioid rescue medications: Date, time of administration, amount, and type of all opioid rescue medication taken from study drug administration through 72 hours.
- Discharge readiness assessment per the Modified Postanaesthesic Discharge Scoring System (MPADSS) criteria.
- Patient Global Assessment (PGA) of pain control.
- Overall benefit of analgesia score (OBAS).
- Treatment Satisfaction Questionnaire for Medication (TSQM-9).
- Time to ambulation.
- Ability to participate in scheduled rehabilitation sessions.

- Whether the subject is discharged home or to a skilled nursing facility.
- Opioid prescription at discharge.
- Site- or subject-initiated postdischarge contact through the Day 11 Visit.
- Opioid prescription after discharge through the Day 11 Visit.
- Subject daily diary to record whether opioids were taken from discharge through the Day 11 Visit

Safety assessments will include the following:

- AEs from the time the subject signs the ICF through the Day 29 Visit.
- Physical examination.
- Vital signs, including blood pressure, resting heart rate, respiratory rate, and temperature.
- Wound healing assessment using the Southampton Wound Scoring Scale.
- Clinical laboratory tests (hematology and serum chemistry).

4.3. Endpoints

4.3.1. Efficacy Endpoints

The primary efficacy endpoint is the mean area under the curve (AUC) of VAS scores from 12 to 48 hours (AUC_{12-48})

The secondary efficacy endpoints are:

- Mean AUC of VAS scores through 72 hours.
- Mean AUC of NRS-R scores through 72 hours.
- Proportion of subjects severe pain at each timepoint and through 72 hours.
- Mean total postoperative opioid consumption (in IV morphine milligram equivalents [MME]) through 72 hours.
- Proportion of subjects who are opioid-free through 72 hours and through Day 11.
- Proportion of subjects who are opioid-free through 72 hours who remain opioid-free through Day 11.
- 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 11 Visit.
- Proportion of subjects achieving a score of "good" or better (>1) pain control based on PGA at each timepoint.
- Median time to first ambulation through 72 hours.
- Proportion of subjects unable to participate in each rehabilitation session because of pain.
- Proportion of subjects who first achieve a MPADSS score ≥9 at each timepoint.
- Proportion of subjects who are discharged home vs to a skilled nursing facility.
- Mean OBAS at each timepoint.
- Mean TSQM-9 score.

4.3.2. Safety Endpoints

The safety endpoints are:

- Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and opioid-related adverse events (ORAEs).
- Change from baseline in clinical laboratory results.
- Change from baseline in vital signs.
- Wound healing assessment results at each assessed 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 number and percent of subjects. Data will be displayed in all listings sorted 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 of 115 subjects was selected empirically without formal statistical assumptions.

5.2. Randomization, Stratification, and Blinding

This is a Phase 3b, open-label, multi-cohort study. In Cohorts 1 and 2, subjects who meet the eligibility criteria are enrolled. In Cohort 3, subjects who meet the eligibility criteria are randomized in a 1:1 ratio to 2 treatment groups (Section 4.1) using a computer-generated randomization scheme.

5.3. Analysis Populations

5.3.1. Safety Population

The Safety Population will consist of all subjects who receive study drug. This population will be used for all summaries of efficacy and safety data.

5.3.2. Layout of Efficacy and Safety Analyses

All efficacy and safety analyses will be performed using descriptive statistics on the Safety Population, treatment group and cohort (Table 1). In addition, a Total column that pools cohorts 1, 2, 3 and 4 will be added to all tables except for efficacy tables.

Table 1: Layout of Summary

Cohort 1 HTX-011 400 mg/12 mg + MMA	Cohort 2 HTX-011 400 mg/12 mg +MMA	Pooled Cohorts 1 and 2 HTX-011 400 mg/ 12 mg + MMA	Cohort 3		Cohort 4 HTX-011 400 mg/12 mg +MMA	Pooled Cohorts 1, 2 and 4 HTX-011 400 mg/ 12 mg + MMA
			Group A HTX-011 300 mg/9 mg + MMA	Group B HTX-011 300 mg/9 mg + Bupi 100 mg + MMA		

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 or VAS assessments at the nominal 72-hour postoperative timepoint.

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

- For AUC, ORAE through 72 hours, and time to first ambulation 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 MME, opioid-free, time to first opioid) through 72 hours, the following will be applied.
    - If subject early terminated prior to 72 hours, the opioid use through 72 hours will be based on concomitant medication and 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 subject did not early terminate prior to 72 hours and was discharged on or after (≥) 72 hours from dosing start time, the opioid use through 72 hours will be based on concomitant medication and the 72 hour postoperative observation period will be defined as from the start date/time of study drug administration + 72 hours.
    - If subject did not early terminate prior to 72 hours and was discharged prior to (<) 72 hours, the opioid use through 72 hours will be based on concomitant medication (through discharge) and opioid diary (from the date of discharge to Day 4). In this case the 72 hour postoperative observation period will be defined as from the start date/time of study drug administration + 72 hours (or Day 4). For analysis of time to first opioid through 72 hours, if opioid collected during this period of time contains missing time (for example, as recorded in opioid diary), the time of opioid use will be imputed as “00:00” for analysis.
        - In this case only, opioid use from 72 hours through Day 11 will be defined as from Day 5 through Day 11 based on opioid diary only.

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

5.4.5. Day 11 Visit Period

Subjects will be provided a daily diary to record any opioid medication use from discharge through the Day 11 Visit. Sites will record all site- or subject-initiated contact between discharge and the Day 11 Visit and whether any contact resulted in issuing an opioid prescription.

The Day 11 Visit has a 2-day window (ie, Day 11 ±2 days [Study Day 9 through Study Day 13]). The Day 11 Visit period is defined as below and will be applied for opioid diary and subject/site call back analyses.

- If Day 11 Visit date (or study exit date) ⩾ Study Day 11 or the Day 11 Visit is missing but subject continued on study beyond Study Day 11: the Day 11 Visit period is through the Day 11 Visit date (or study exit date) or Study Day 13, whichever happens first.
- If Study Day 9 ⩽ Day 11 Visit date (or study exit date) < study day 11: the Day 11 visit period is through Day 11 Visit date (or study exit date).
- If Day 11 Visit date (or study exit date) < Study Day 9: the Day 11 Visit period is through Study Day 9.

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

For any data that is missing through 72 hours in subjects who complete the 72-hour postoperative observation period, the pain intensity scores (VAS or NRS) 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 post-withdrawal 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 severe pain) through 72 hours will be constructed following windowed worst observation carried forward (wWOCF) (see Section 9.1.1 for details).

A table displaying the number and percentage of subjects with missing VAS and 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.

For the median time in hours to first ambulation postsurgery, subjects who complete the 72-hour observation period without ambulation or discontinue from the study prior to 72 hours without ambulation will be censored at the time of completion or discontinuation, whichever is earlier. For subjects who reported an ambulation date but no corresponding ambulation time, mean imputation will be performed based on the average ambulation time among subjects within the same cohort who were able to ambulate and who reported a complete ambulation date and time.

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 (Cohort 3 only), subjects who failed screening with reasons for screen failure, subjects in the Safety Population, subjects completing the 72-hour postoperative observation period, subjects completing the study through Day 29, 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, and body mass index (BMI). A subject's age in years is calculated using the integer part of the difference in number of days between the date that informed consent is signed and date of birth divided by 365.25, or is recorded directly on the eCRF. The number and percentage of subjects in the following age categories will be presented: 18-44, 45-54, 55-64, 65-74, 75-84, and ≥ 85.

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

7.2. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) version 22.0. Medical history will be summarized for the Safety Population and will display the number and percentage of subjects with a past and/or concomitant disease or past surgeries by System Organ Class (SOC) and Preferred Term (PT).

7.3. Protocol Deviations

Deviations and violations from the protocol will be recorded. Protocol deviations will be classified into 1 of the following categories:

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

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

8. TREATMENTS AND MEDICATIONS

8.1. Prior and Concomitant Medications

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

All medications will be coded with the World Health Organization Drug 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 with a start date/time within the 72-hour postoperative period (see Section 5.4.4 for details) will be included in rescue medication analyses. An exception will be fentanyl administered perioperatively on the date of surgery for intraoperative pain management; this is not counted as rescue medication.

Opioid rescue medication in IV morphine milligram equivalency (MME) dose (see Section 9.2 for details) will be summarized for 0-24 hours, 0-48 hours, and 0-72 hours. In addition, proportion of subjects who received any rescue medication as well as each rescue within the 72-hour postoperative period will also be provided.

8.3. Surgery Procedure

Surgery details including the knee subject to the surgical procedure (left or right), incision length in centimeters, drain usage, posterior ligament (CR or PS), surgical approach, tourniquet time, estimated blood loss, 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-011) intraoperatively while undergoing TKA. As such, 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, as by definition it will be 100% for the Safety Population. Duration of study drug administration will be calculated as completion time minus start time, reported in minutes.

The proportion of subjects who received preoperative MMA regimen will be summarized by each preoperative MMA medication (ie, acetaminophen, celecoxib, and pregabalin) using descriptive statistics.

The average daily use and total use of each postoperative MMA medication (ie, acetaminophen and celecoxib for Cohorts 1-3 and acetaminophen and ibuprofen for Cohort 4) will be tabulated using descriptive statistics through 72 hours.

9. EFFICACY ANALYSIS

9.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the mean AUC of the VAS scores from 12 through 48 hours ($AUC_{12\text{-}48}$).

9.1.1. Primary Analysis

During the first 72 hours following surgery, the VAS is measured at hours 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, and 72. Using the trapezoidal rule and letting P_t = the VAS 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 $AUC_{12\text{-}48}$ is thus calculated as follows:

$$AUC_{12-48} = \int_{12}^{48} f(t)dt \approx \sum_{i=24}^{48} (t_i - t_{i-1})\frac{P_{i-1} + P_i}{2}$$

The primary endpoint of mean $AUC_{12\text{-}48}$ of the VAS 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 VAS 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 VAS pain intensity score observed prior to the rescue medication window, with the following exception: if the VAS 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 in Section 9.2 for predefined analgesic windows for each opioid medication.

9.1.2. Sensitivity Analyses

A sensitivity analyses will be performed on the primary endpoint by reproducing the primary analysis but without adjusting the VAS pain intensity scores for the use of opioid rescue medications (ie, without applying wWOCF).

9.2. Secondary Efficacy Endpoints

Mean AUC of VAS scores through 72 hours

The $AUC_{0\text{-}12}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}48}$, $AUC_{0\text{-}72}$, $AUC_{24\text{-}48}$, $AUC_{48\text{-}72}$, $AUC_{24\text{-}72}$, $AUC_{12\text{-}72}$ of the VAS pain intensity scores will be analyzed similarly as the $AUC_{12\text{-}48}$ of VAS pain intensity scores, with appropriate adjustment to the calculation to reflect the time period of interest. In addition, to explore the effect of drain usage, the $AUC_{0\text{-}12}$, $AUC_{12\text{-}48}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}48}$, $AUC_{0\text{-}72}$ of the VAS pain intensity scores will be summarized by drain usage in Cohorts 1 and 2 by the surgeon(s) who participated in Cohort 2.

In addition, the mean VAS pain intensity scores will be summarized at each assessed timepoint through Day 29. Mean VAS pain intensity scores will also be plotted in a line graph over time through 72 hours, with associated SEs at each timepoint.

Mean AUC of NRS-R scores through 72 hours

The $AUC_{0\text{-}12}$, $AUC_{12\text{-}48}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-}48}$, $AUC_{0\text{-}72}$, $AUC_{24\text{-}48}$, $AUC_{48\text{-}72}$, $AUC_{24\text{-}72}$, $AUC_{12\text{-}72}$ of the NRS-R pain intensity scores will be analyzed similarly as the $AUC_{12\text{-}48}$ of VAS pain intensity scores, with appropriate adjustment to the calculation to reflect the time period of interest using NRS-R pain intensity scores.

In addition, the mean NRS-R pain intensity scores will be summarized at each assessed timepoint through Day 29. Mean NRS-R pain intensity scores will also be plotted in a line graph over time through 72 hours, with associated SEs at each timepoint.

Proportion of subjects with severe pain at each timepoint and through 72 hours

Proportions of subjects with severe pain (an NRS score $\geq$ 7 or a VAS score $\geq$ 75 mm) at each timepoint will be summarized using descriptive statistics.

Proportions of subjects with severe pain at any timepoint through 72 hours as well as through 24 and 48 hours will be analyzed similarly.

Mean total postoperative opioid consumption (in IV morphine milligram equivalents [MME]) through 72 hours

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

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

Determination of morphine equivalents

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

Protocol-allowed postoperative rescue medications consist of oral (PO) immediate-release oxycodone (≤ 10 mg within a 4-hour period as needed), intravenous (IV) morphine (2.5 to 5 mg within a 4-hour period as needed), and/or IV hydromorphone (0.5 to 1.0 mg in a 4-hour window). Combination products containing an opioid and non-opioid are not allowed. With the exception of PO acetaminophen and PO celecoxib, which are administered as part of the scheduled MMA regimen, no other analgesic agents, including other nonsteroidal anti-inflammatory drugs (NSAIDs), are permitted during the 72-hour postoperative observation period.

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

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

Medication	Route	Window (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 equivalent; PO, oral; PR, per rectum.
Note: MME = opioid dose × MME factor.

Analysis method

Rescue medication use is collected from 0-72 hours. Average daily use and total use will be tabulated using descriptive statistics for overall opioids as well as oxycodone, morphine and hydromorphone during the following periods: 0-12, 12-48, 0-24, 24-48, 0-48, 48-72, 24-72, 12-72, and 0-72 hours. Subjects who did not use a specific rescue medication during a period of interest will have their dose set to 0 for that period. In addition, the total use, individual daily use at each study day between study day 4 and study day 11, as well as average daily use (ie, total use averaged over the number of days with non-missing diary reported) of overall opioids as well as oxycodone will be summarized after discharge through Day 11 visit (based on opioid daily diary only). For opioid consumption based on diary, MME will be calculated using observed data only.

Proportion of subjects who are opioid-free through 72 hours and through Day 11

Opioid-free status will be determined based on observed data only.

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 analyzed using descriptive statistics. The proportion of subjects who are opioid free through 24 hours (ie, MME=0 through 24 hours) and proportion of subjects who are opioid free through 48 hours (ie, MME=0 through 48 hours) will be analyzed similarly. In addition, the proportion of subjects who are opioid-free from 12 to 48 hours (ie, MME=0 from 12 to 48 hours) will also be summarized in a similar manner.

If subject was discharged on or after (≥) 72 hours from start of study drug administration, opioid-free from 72 hours through Day 11 is defined as MME=0 from 72 hours to discharge and answering "No" to the question "Did you take any opioid medication" from discharge through Day 11. If subject was discharged prior to (<) 72 hours from start of study drug administration, the opioid-free from 72 hours through Day 11 is defined as answering "No" to the question "Did you take any opioid medication" from Day 5 through Day 11 (see Section 5.4.4 for details). Subjects who report "Yes" during the period of interest will not be considered opioid-free during this period. The proportion of subjects who are opioid-free through Day 11 will be analyzed using descriptive statistics. The number of pills by overall and by opioid type (ie, oxycodone or other) taken after discharge through Day 11 as collected in daily diary will also be summarized.

In addition, opioid-free from 48 hours through day 11 (based on concomitant medication and opioid diary), from 72 hours through Day 11 (based on concomitant medication [if discharged after 72 hours] and opioid diary) and from discharge through Day 11 (based on opioid diary only) will be analyzed using descriptive statistics.

Proportion of subjects who are opioid-free through 72 hours who remain opioid-free through Day 11

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 11 will be summarized using descriptive statistics.

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.

Proportion of subjects who do not receive an opioid prescription at discharge

If a subject received ≥ 10 mg of oxycodone within 12 hours prior to discharge, the Investigator may provide the subject with a prescription of immediate-release PO oxycodone tables: no more than thirty 5 mg immediate-release oxycodone. 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.

Proportion of subjects who do not receive an opioid prescription between discharge and the Day 11 Visit

Sites will record all site-initiated or subject-initiated contact between discharge and Day 11 visit and if any result in issuing an opioid prescription. The proportion of subjects who do not receive an opioid prescription between discharge and Day 11 Visit will be summarized using descriptive statistics.

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.

Among subjects who had contact data, the proportion of subjects who report to have taken their multimodal regimen as instructed at all contacts will also be summarized.

In addition, the proportion of subjects who did not follow their MMA regimen as instructed among those who received a postdischarge opioid prescription will also be summarized.

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. 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.

Median time to first ambulation through 72 hours

Median time in hours to first ambulation postsurgery 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 ambulation will be censored at the time of study withdrawal or at 72 hours, whichever is earlier.

Proportion of subjects unable to participate in each rehabilitation session because of pain

The proportion of subjects unable to participate in each rehabilitation session because of pain at each timepoint and at any time through 72 hours will be summarized using descriptive statistics.

Proportion of subjects who first achieve an MPADSS score ≥9 at each timepoint

Discharge readiness is 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, ≤ 8 hours, etc.) using descriptive statistics.

Proportion of subjects who are discharged home vs to a skilled nursing facility

Site will record if subjects are discharged home or to a skilled nursing facility. The proportion of subjects who are discharged home vs to a skilled nursing facility will be summarized using descriptive statistics.

Mean OBAS at each timepoint

Overall benefit of analgesia is collected using a 7-item, multidimensional, quality assessment questionnaire (Lehmann, Joshi et al. 2010) addressing pain, vomiting, itching, sweating,

freezing, dizziness, and overall satisfaction with postoperative pain. Each of the 7 items is rated on a scale of 0-4 as follows:

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

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

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

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

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

Mean TSQM-9 score

Subjects will be asked to evaluate their satisfaction with their scheduled non-opioid MMA regimen for the treatment of their TKA-related pain using the TSQM-9 questionnaire (Bharmal, Payne et al. 2009).

The TSQM-9 contains 9 items which make up the Effectiveness, Convenience, and Global Satisfaction domains. Scores for each domain are computed by adding the TSQM items in each domain and then transforming the composite score into a value ranging from 0 to 100. A score can be computed for a domain only if no more than one item is missing from that domain (IQVIA 2018).

Effectiveness Domain:

([(Item 1 + Item 2 + Item 3) – 3] divided by 18) * 100

If one item is missing

([(Sum(the two completed items – 2] divided by 12) * 100

Convenience Domain:

([Sum(Item 4 to Item 6) – 3] divided by 18) * 100

If one item is missing

([(Sum(the two completed items)) – 2] divided by 12) * 100

Global Satisfaction Domain:

([Sum(Item 7 to Item 9) – 3] divided by 14) * 100

If either Item 7 or 8 is missing

([(Sum(the two completed items)) – 2] divided by 10) * 100

If Item 9 is missing

([(Sum(Item7 and Item8)) – 2] divided by 8) * 100

The scores from individual question as well as for each domain will be summarized using descriptive statistics at each timepoint.

10. SAFETY ANALYSIS

All analyses of safety data will be conducted using the Safety Population. Statistical hypothesis testing will not be performed on any safety results. No imputation of missing safety data will be performed except in the case of partial AE and concomitant medication onset dates (Appendix 1).

10.1. Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A TEAE is any AE which occurs any time during or after study drug administration, or any AE with an onset prior to study drug administration that worsens during or after study drug administration. An AE may be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not considered causally associated with the use of the study drug. Any abnormal laboratory value, vital sign result, or ECG finding deemed clinically significant by the Investigator, regardless of causal relationship, must be reported as an AE.

For an event to be a TEAE, it must meet one of the following conditions:

- Begins on Study Day 1, during or after administration of study drug
- Begins after Study Day 1
- Begins before Study Day 1 and worsens in severity during or after the Study Day 1 administration of study drug

AEs with unknown onset dates or unknown end dates will be counted as TEAEs unless the event resolves before Study Day 1.

AEs will be coded using MedDRA version 22.0. Only TEAEs will be presented in AE tables, according to the SOC and PT. Any AEs that occur and resolve prior to Study Day 1

or are ongoing but do not worsen on or after Study Day 1 will be considered pretreatment AEs and will appear in the AE listing but not in TEAE tables.

10.1.1. Incidence of Treatment Emergent Adverse Events

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

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

- Number of TEAEs
- Number of subjects with at least 1 TEAE
- Number of subjects with at least 1 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 ORAE
- 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.

10.1.2. 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.

10.1.3. Severity of Adverse Event

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

10.1.4. Serious Adverse Events

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. If a subject reports the same TESAE multiple times, then that PT will only be incremented by 1 since subject counts will be presented. As with the PT, if a subject reports multiple TESAEs 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.

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

10.1.5. Adverse Events Leading to Study Withdrawal

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

10.1.6. Potential Opioid-related Adverse Events

Incidence of TEAEs that are potential opioid-related AEs, regardless of whether a subject actually received an opioid medication, will be presented by PT. Prespecified PTs that constitute potential opioid-related AEs 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 72-hour postoperative observation period
- Incidence of potential ORAEs in the subset of subjects who received at least 1 opioid rescue medication during the 72-hour postoperative observation period
- Incidence of potential ORAEs through the 72-hour postoperative observation period in the subset of subjects who received at least 1 opioid rescue medication during the 72-hour postoperative observation period

10.1.7. Death

Any subject deaths during this study will be collected and presented in a listing. The information that is presented will include date of death, days on study, cause of death, and relationship of death to study drug.

10.2. Clinical Laboratory Evaluations

Laboratory assessments will be performed by a central laboratory (hematology and serum chemistry) or locally (pregnancy test and drug screen). All summaries of central laboratory data will be based on the standard international (SI) units provided by the central lab. Associated laboratory parameters such as hepatic profile, renal function, and hematology values will be grouped and presented together.

Summary tables for hematology and chemistry including actual values and change from Baseline values will be presented for clinical laboratory tests with numeric values. These tables will include each visit (Baseline, 72 hours, and Day 11), highest postdose value, lowest postdose value, and last postdose value.

Laboratory data will also be summarized using shift tables where appropriate. Each subject's hematology and serum chemistry values will be flagged as "low", "normal", or "high" relative to the normal ranges of the central laboratory.

Laboratory data collected at unscheduled visits will be included in listings and will contribute to tables of shifts from Baseline and in tables showing changes from Baseline to highest value, lowest value, and last value. Unscheduled laboratory results will not be windowed for the purposes of assigning a nominal visit.

Listings of laboratory values will include flags for values outside the central laboratory normal ranges that indicate how far out of the normal range 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.

10.2.1. Hematology

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

10.2.2. Blood Chemistry

The following laboratory tests will be included in the blood chemistry summary tables: alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, direct bilirubin, gamma-glutamyltransferase (GGT), glucose, lactate dehydrogenase (LDH), magnesium, phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid.

Associated laboratory parameters such as hepatic profile (ALT, albumin, ALP, AST, direct bilirubin, GGT, total bilirubin), electrolytes (bicarbonate, calcium, chloride, magnesium, phosphorus, potassium, sodium), renal profile (BUN, creatinine), and other (glucose, LDH, total protein, uric acid) will be sorted/grouped together in table and listing presentations.

Evaluation of drug-induced serious hepatotoxicity (eDISH) scatterplots of the highest postdose ALT vs. total bilirubin observed at the same draw as the high ALT value, and of the highest postdose AST vs. total bilirubin observed at the same draw as the high AST value, will be produced.

The incidence of subjects with 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

10.2.3. Urine Pregnancy Test and Urine Drug Screen

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

10.3. Vital Sign Measurements

Vital signs including systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate/pulse (HR), body temperature, and respiration rate will be collected at screening, on Day 1 before surgery, and post-treatment 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 :

Table 3: Out-of-Range Vital Signs Values

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

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

10.4. Electrocardiogram

A 12-lead ECG (triplicate) will be performed at screening. The results will be listed.

10.5. Physical Examination

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

10.6. Wound Healing Assessment

Surgical wound healing will be assessed using the Southampton Wound Scoring System at 72 hours and on Day 11, Day 29, 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 and at worst 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.

11. INTERIM ANALYSIS

11.1. Interim Analysis

No formal interim analyses are planned.

11.2. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will not be involved with the conduct of this study. The internal Product Safety and Risk Management Committee will

monitor safety data on a periodic basis throughout the study, including regular review of AEs (including SAEs), laboratory results and other safety assessments.

12. REFERENCES

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APPENDIX 1. IMPUTATION OF PARTIAL AND MISSING DATES

Incomplete Dates of Adverse Event start

All AE onset dates must be entered on the eCRF as complete dates. In the rare case that all or part of an AE onset date is missing but an AE resolution date is present and after study drug administration then the AE onset date will be imputed as follows:

Year of onset	Month of onset	Day of onset	Onset date to be imputed as
Missing	Missing	Missing	Date of SDA
year = year of SDA	Missing	Nonmissing	Date of SDA
year = year of SDA	Missing	Missing	Set month and day to those of SDA
year < year of SDA	Missing	Nonmissing	set month to December
year < year of SDA	Missing	Missing	set month and day to December 31
year > year of SDA	Missing	Nonmissing	set month to January
year > year of SDA	Missing	Missing	set month and day to January 1
year = year of SDA	Month = month of SDA	Missing	Set day as day of SDA
year = year of SDA	Month < month of SDA	Missing	Set day as last day of onset month
year = year of SDA	Month > month of SDA	Missing	Set day as first day of onset month
year < year of SDA	Nonmissing	Missing	Set day as last day of onset month
year > year of SDA	Nonmissing	Missing	Set day as first day of onset month

SDA = study drug administration.

If AE resolution date is present and prior to study drug administration, no need to impute incomplete AE start date, as the AE is not treatment emergent and the event should be in the medical history.

Concomitant Medications

- If year and month are present and day is missing then set day to first day of month for start date, and set day to last day of month for end date
- If year and day are present and month is missing then set month to January for start date, and set month to December for end date
- If year is present and month and day are missing then set month and day to January 1 for start date, and set month and day to December 31 for end date
- Completely missing dates will not be imputed

If start date is completely missing and end date is not prior to study drug administration, then the medication will be classified as concomitant; if the end date is missing, then the medication will be classified as ongoing. Medications for which the start and end dates are completely missing will be classified as concomitant.

APPENDIX 2. DOCUMENT REVISION HISTORY

Version	Date	Notes/Revisions
1	28JUN2019	Initial version, based on protocol version 3 (26JUN2019)
2	05APR2021	Updated version, based on protocol version 6 (02JUL2020) • Updated study design, treatment cohorts, endpoints, and sample size per protocol version 6 • Added layout of efficacy and Safety analyses • Added analyses of AUC of pain intensity by drain usage at site 34 • Modified the Day 11 Visit Period • Added imputation for missing ambulation time while ambulation date was reported • Added analysis for proportion of subjects who are opioid free from 12 to 48 hours • Specified that opioid MME and opioid-free analyses based on observed data only
3	01JUL2021	Updated version, based on protocol version 6 (02JUL2020). Updated Section 5.3.2 Layout of Efficacy and Safety Analyses by adding a Pooled Cohorts 1, 2, and 4 treatment column for all safety and efficacy tables and a Total column for all tables except efficacy tables.

Signature Page for VV-CLIN-004749 v1.0

Approval Task	[redacted] 2021 19:43:45 GMT+0000

Approval Task	[redacted] 20:15:39 GMT+0000

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