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STUDY HTX-011-304

A PHASE 3B, RANDOMIZED, OPEN-LABEL STUDY OF HTX-011 AS THE FOUNDATION OF A NON-OPIOID, MULTIMODAL ANALGESIC REGIMEN TO DECREASE OPIOID USE FOLLOWING UNILATERAL OPEN INGUINAL HERNIORRHAPHY

16 December 2019

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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TABLE OF CONTENTS

List of Abbreviations

Abbreviation	Term
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Classification
bpm	Beats per minute
BMI	Body mass index
BUN	Blood urea nitrogen
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
IRT	Interactive response technology
ITT	Intent-to-Treat
IV	Intravenous(ly)
LDH	Lactic dehydrogenase
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MME	Morphine milligram equivalency
NRS	Numeric Rating Scale
NRS-A	Numeric Rating Scale with activity
NRS-R	Numeric Rating Scale at rest
NSAID	Nonsteroidal anti-inflammatory drug
PACU	Post-Anesthesia Care Unit
PO	Administered orally
PR	Per rectum
PRN	As needed
PT	Preferred term
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
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-9	Treatment Satisfaction Questionnaire for Medication (9-question)
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHODDE	World Health Organization Drug Dictionary Enhanced

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) 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 functions 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 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:

Part 1:

To identify which of two postoperative non-opioid multimodal analgesic (MMA) regimens, with intraoperative administration of HTX-011 as the foundation, results in the highest proportion of subjects who do not require a prescription for postoperative opioid medication following unilateral open inguinal herniorrhaphy.

Part 2:

To confirm, in a larger study population, the proportion of subjects who do not require a prescription for postoperative opioid medication following unilateral open inguinal herniorrhaphy with intraoperative administration of HTX-011 as the foundation of a non-opioid MMA regimen selected based on the results of Part 1 of the study.

Secondary Objectives:

- To assess postdischarge opioid consumption.
- To assess subject satisfaction with the postoperative MMA regimen.

3.1. Overall Study Design and Plan

This is a Phase 3b, open-label, study to assess postoperative opioid use in subjects undergoing unilateral open inguinal herniorrhaphy with intraoperative administration of HTX-011 and a non-opioid MMA regimen. The study will be conducted in 2 sequential parts.

In Part 1, subjects will be randomized to 1 of 2 parallel cohorts, each with a different postoperative non-opioid MMA regimen. Up to approximately 45 subjects will be included in each cohort. Both cohorts will receive the same preoperative non-opioid MMA consisting of acetaminophen 1000 mg and ibuprofen 400 mg administered concurrently approximately 2 hours prior to surgery. The postoperative MMA will be different for each cohort.

- Cohort 1 MMA regimen: PO ibuprofen 600 mg every 6 hours, starting once the subject is able to tolerate PO intake. Three hours after the first dose of ibuprofen, start PO acetaminophen 1 g every 6 hours, alternating the 2 medications so that an analgesic is taken approximately every 3 hours.
- Cohort 2 MMA regimen: PO ibuprofen 600 mg and PO acetaminophen 1 g taken together every 6 hours, starting once the subject is able to tolerate PO intake.

In Part 2, each subject will be assigned to either of these MMA regimen cohorts per Investigator discretion rather than randomization.

3.2. Assessments

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

Efficacy assessments will include the following:

- Postoperative opioid administration prior to discharge, including date/time, dose, and route of administration.
- Opioid prescription at discharge, including date/time, and reason (Numeric Rating Scale at rest [NRS-R] ≥6 pain intensity score; or subject received postoperative, predischarge opioid; or both).
- Postdischarge opioid prescription details through the Day 15 visit, including date/time and dose.
- Postdischarge opioid consumption through the Day 15 visit, via patient recall.
- Subject-initiated, postdischarge, site contacts about postoperative pain related to the surgery, through the Day 15 visit, including date/time and any action taken, including whether it resulted in an opioid prescription.
- Pain intensity score at the time of discharge.
- Treatment Satisfaction Questionnaire for Medication (9-question; TSQM-9) regarding the MMA regimen.

Safety assessments will include the following:

- Adverse events (AEs) from the time the subject signs the ICF through the final on-site study visit (Day 29 in Part 1, Day 15 in Part 2); serious adverse events (SAEs) through Day 29 in both parts of the study.
- Vital signs (resting heart rate, blood pressure, respiration rate, and body temperature) at the Screening Visit, preoperatively on Day 1, at Discharge, and at the Day 15 visit.
- Part 1 only: Clinical safety laboratory tests (hematology and serum chemistry) at the Screening and Day 15 visits.

3.3. Endpoints

3.3.1. Efficacy Endpoints

The primary efficacy endpoint is:

- Proportion of subjects who do not receive a postoperative opioid prescription through the Day 15 visit.

The secondary efficacy endpoints are:

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

- Proportion of subjects who do not receive a postdischarge opioid prescription, through the Day 15 visit.
- Pain intensity scores at the time of discharge.
- Number of oxycodone pills taken between discharge and the Day 15 visit
- Mean Treatment Satisfaction Questionnaire for Medication (9-question; TSQM-9) score

3.3.2. Safety Endpoints

The safety endpoints are:

- Incidences of TEAEs and treatment-emergent SAEs

4. GENERAL STATISTICAL CONSIDERATIONS

No statistical hypothesis testing will be performed. 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 proportion of subjects by category. Data will be displayed in all listings sorted by Part, MMA regimen, 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 Part and/or MMA regimen within the population of interest, unless otherwise stated. Non-zero percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places. Additional rounding rules are as follows:

- If the original value has 0 decimal places: mean, median, and CI will have one decimal place and SD and SE will have 2 decimal places
- If the original value has 1 decimal place: mean, median, and CI will have 2 decimal places and SD and SE will have 3 decimal places
- If the original value has 2 or more decimal places: mean, median, CI, SD, and SE will all have 3 decimal places

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

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

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

4.1. Sample Size

Part 1: The sample size was selected to provide over 80% power to detect a 20% difference between Cohorts 1 and 2, assuming the proportions of subjects who do not receive a postoperative opioid prescription through Day 15 visit are 10% and 30% in the 2 groups, respectively (Fisher's exact test at $\alpha = 0.2$, 2-sided).

Part 2: The sample size will be selected, based on the preliminary results of Part 1, to provide ≥90% probability of obtaining 5% precision regarding the proportion of subjects who do not receive a postoperative opioid prescription through the Day 15 visit assuming an alpha of 0.05.

4.2. Randomization, Stratification, and Blinding

This is an open-label study. In Part 1, subjects will be randomized to one of the 2 parallel cohorts. The randomization will be based on centralized, computer-generated, stratified randomization by site. No randomization will be performed in Part 2.

4.3. Analysis Populations

4.3.1. 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.

4.4. Other Important Considerations

4.4.1. 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.

4.4.2. 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:

$$P_t = 100*(C_t/M_B)$$

4.4.3. 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.

4.4.4. Day 15 Visit Period

The Day 15 Visit period will be defined as the period of time from the date of surgery to the Day 15 visit date.

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

- If subject early terminates prior to Study Day 15, the period is defined as the date of surgery to the date of early termination.
- If subject continued up to Study Day 15 or beyond, the period is defined as the date of surgery + 14 days (ie, from the date of surgery to Study Day 15).

4.4.5. Visit Windows

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

4.4.6. Handling of Missing and Partial Data

All efficacy and 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.

5. SUBJECT DISPOSITION

A summary of the disposition of subjects will include the frequency and proportion of subjects for the following categories: subjects enrolled (signed the Informed Consent Form),

subjects who failed screening with reasons for screen failure, subjects in the Safety Population, subjects completing the Day 15 Visit , subjects completing the study, and subjects who withdrew from the study prior to dosing and after dosing. Note that only one reason for study withdrawal should be recorded for each subject and categories are mutually exclusive.

6. DEMOGRAPHICS, CHARACTERISTICS, AND MEDICAL HISTORY

6.1. 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. Demographics will also be presented for all subjects enrolled who fail screening.

6.1.1. Pain Phenotyping Questionnaire (Part 2 Only)

Subjects in Part 2 will provide responses to questions related to nicotine dependence, alcohol use, substance abuse, anxiety, depression, and catastrophism. Descriptive statistics will be provided for each question. The purpose of of the pain phenotyping analysis is to provide a quantitative assessment of whether subjects with one or more of these behaviors are associated with post-surgical opioid usage.

Each of the six baseline pain phenotyping aspects will be summarized as separate continuous total pain phenotyping scores in accordance to the Patient-Reported Outcomes Measurement Information System (PROMIS) scoring manuals (PROMIS, 2019) and the University of Michigan Hospitals and Health Center Department of Anesthesiology AOS II (Analgesic Outcomes Study) baseline patient questionnaire (Swartzman et al., 1994).

Separate univariate logistic regression models will be the primary analysis method to assess associations between each of the baseline pain phenytyping aspect scores and the odds of post-surgical opioid rescue mediation usage in subjects that were treated with HTX-011 and an MMA regimen. Odds ratios, and corresponding 95% confidence intervals will be summarized for each of the six pain phenotyping aspects.

Additional analyses will include multivariable logistic regression analysis that will include several pain phenotyping aspects and may include higher order terms as covariates. Dichotimous versions of the pain phenotyping aspect scores will also be assessed as potential

predictors.

6.2. 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).

6.3. 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 procedure
- 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 before database lock. Protocol deviations and major protocol deviations will be presented in a summary table by protocol deviation category in the Safety population.

7. TREATMENTS AND MEDICATIONS

7.1. 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 that 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 WHODrug Global B3 dictionary, dated March 2019.

Prior and concomitant medications will be summarized separately by drug class and PT. At each level of summarization, a subject is counted once if that subject reports 1 or more medications at that level. Drug class will correspond to the Anatomical Therapeutic Classification (ATC) Level 2 term.

All prior and concomitant medications will be summarized for the Safety Population.

7.2. Postoperative Opioid Rescue Medication Prior to Discharge

Following surgery and prior to discharge, opioid rescue medication may be administered per institutional standard care.

Determination of morphine equivalents

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). Table 1 displays the MME of selected opioid rescue medications.

Table 1. Morphine Milligram Equivalents for Opioid Rescue Medications[1]

Medication	Route	MME Factor
CODEINE	PO	0.05
DILAUDID	PO	1.33
DILAUDID	IV	6.67
FENTANYL	IV	50.00
HYDROCODONE	PO	0.40
MORPHINE	IV	1.00
MORPHINE	PO	0.33
MORPHINE	IM	1.00
MORPHINE	PR	1.00
OXYCODONE	IV	1.00
OXYCODONE	IM	1.00
OXYCODONE	PO	0.50
SUFENTANIL	PO	500.00
TRAMADOL	IV	0.06
TRAMADOL	PO	0.04

Abbreviations: IM, intramuscular; IV, intravenous; MME, morphine milligram equivalency; PO, by mouth (orally); PR, per rectum.

1. Morphine Equivalent = Opioid Dose X MME Factor

Use of opioid rescue medication will be summarized by PT. Opioid rescue medication in MME postsurgery through discharge will be tabulated using descriptive statistics for morphine, oxycodone, and for overall opioids. Subjects who did not use a rescue medication through discharge will have their dose set to 0. In addition, proportions of subjects who received no opioid rescue medication will be summarized through discharge. Among subjects who received opioid rescue medication prior to discharge, proportion of subjects receiving IV opioids only, oral opioids only, or both IV and oral opioids will also be summarized.

7.3. Surgery Procedure

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

7.4. Study Drug

All subjects will receive a single dose of HTX-011. As such, extent of exposure will be reported in the CSR as the number of subjects in the Safety Population. A summary of treatment compliance will not be produced, as by definition it will be 100% for the Safety Population.

In addition, duration of study drug administration (end time – start time) in minutes will be summarized by descriptive statistics that include the mean, standard deviation, median, min, and max.

8. EFFICACY ANALYSIS

Table 2 displays the planned treatment groups being studied.

Table 2. Planned Treatment Groups

Study Part	Treatment	Planned Sample Size
1	Cohort 1: HTX-011 300 mg/ 9 mg + Alternating MMA	45
	Cohort 2: HTX-011 300 mg/ 9 mg + Concurrent MMA	45
2	HTX-011 300 mg/ 9 mg + Alternating MMA	380
	HTX-011 300 mg/ 9 mg + Concurrent MMA	

All efficacy analyses will be performed on the Safety Population and summarized using descriptive statistics by Part, by MMA regimen, and overall (**Error! Reference source not found.**). In addition, Part 1 Total, Part 2 Total, and an Overall Parts 1 and 2 Total will be summarized. Statistical hypothesis testing will not be performed on any efficacy results.

Table 3. Layout of Summary

	Part 1			Part 2			Overall (Part 1 and Part 2)		
Endpoint	Cohort 1 HTX-011 + Alternating MMA	Cohort 2 HTX-011 + Concurrent MMA	Total	HTX-011 + Alternating MMA	HTX-011 + Concurrent MMA	Total	HTX-011 + Alternating MMA	HTX-011 + Concurrent MMA	Total

8.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects who do not receive a postoperative opioid prescription through the Day 15 visit.

8.1.1. Primary Analysis

Subjects who do not receive a postoperative opioid prescription through the Day 15 visit include those who do not receive an opioid prescription at discharge and do not receive a

postdicharge opioid prescription through the Day 15 visit. Descriptive statistics will be presented by Part, MMA regimen, and overall. Bar charts by Part, MMA regimen, and overall will also be provided.

8.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Proportion of subjects who do not receive an opioid prescription at discharge.
- Proportion of subjects who do not receive a postdischarge opioid prescription through the Day 15 visit.
- Pain intensity scores at the time of discharge.
- Number of oxycodone pills taken between discharge and the Day 15
- Mean TSQM-9 score

8.2.1. Analyses

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

The proportion of subjects who do not receive an opioid prescription at discharge will be summarized using descriptive statistics by Part, MMA regimen, and overall.

In addition, among subjects who received an opioid prescription at discharge, the reason for receiving the opioid prescription (NRS-R $\geq$ 6; or subject received postoperative, predischarge opioid; both; other) will be summarized.

Proportion of subjects who do not receive a postdischarge opioid prescription through Day 15 visit

The proportion of subjects who do not receive a postdischarge opioid prescription at discharge will be summarized using descriptive statistics by Part, MMA regimen, and overall.

In addition, proportion of subjects who did not receive an opioid prescription at discharge and remain not having an opioid prescription through Day 15 will also be summarized using descriptive statistics by Part, MMA regimen, and overall.

Pain intensity scores at the time of discharge

The NRS-A (Part 1 only) and NRS-R at the time of discharge will be summarized by Part, MMA regimen, and overall using descriptive statistics.

Part 1 only: Number of oxycodone pills taken between discharge and the Day 15 visit

The number of oxycodone pills, other opioid pills and all opioid pills taken between discharge and the Day 15 visit will be summarized by by Part, MMA regimen, and overall using descriptive statistics.

TSQM-9 scores

Subjects will be asked to evaluate their satisfaction with their assigned post operative MMA regimen at the Day 15 visit using the TSQM-9.

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:

([Sum(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 for each TSQM-9 domain (i.e. Effectiveness, Convenience, and Global Satistifaction) and overall composite score will be summarized using descriptive statistics (i.e. Mean, SD, Median, Min and Max) by Part, MMA regimen, and overall. In addition, each question will also be summarized using descriptive statistics by Part, MMA regimen, and overall.

8.3. Other Efficacy Analyses

Additional exploratory efficacy analyses include:

- Proportion of subjects who were opioid-free through Day 15 visit
- Proportion of subjects who were opioid-free from discharge through Day 15 visit
- Proportion of subjects with site- or subject-initiated postdischarge contacts through Day 15 Visit among subjects who who did not receive an opioid prescription at discharge
- Proportion of subjects with site- or subject-initiated postdischarge contacts through Day 15 Visit among subjects who received an opioid prescription at discharge
- Proportion of subjects who received a site-initiated postdischarge contact through the Day 15 Visit
- Proportion of subjects who received a site-initiated postdischarge contact that involved discussion of pain related to surgery through Day 15 visit
- Proportion of subjects who received a site-initiated postdischarge contact that resulted in an opioid prescription through Day 15 Visit
- Proportion of subjects who received a site-initiated postdischarge contact that involved discussion of pain related to surgery and resulted in an opioid prescription through Day 15 visit
- Proportion of subjects who contacted the site postdischarge through Day 15 visit
- Proportion of subjects who contacted the site postdischarge and discussed pain related to surgery through Day 15 visit
- Proportion of subjects who contacted the site postdischarge that resulted in an opioid prescription through Day 15 visit
- Proportion of subjects who contacted the site postdischarge and discussed pain related to surgery that resulted in an opioid prescription through Day 15 visit
- Proportion of subjects with site- or subject-initiated postdischarge contacts through Day 15 Visit who took their assigned MMA regimen as instructed (Yes/No).

These endpoints will be summarized using descriptive statistics of frequencies and proportions.

Part 1 Only: Took opioid postdischarge vs NRS pain intensity scores at discharge and postoperative opioid rescue medication prior to discharge

The proportion of subjects meeting the following criteria will be summarized for subjects who took opioids postdischarge versus those who did not take opioids postdischarge for 1) overall, 2) among subjects who received opioid prescription at discharge, and 3) among subjects who did not receive opioid prescription at discharge.

- NRS-R at discharge
  ≥ 6
  < 6

  ≥ 7
  < 7

- NRS-A at discharge
  ≥ 6
  < 6

  ≥ 7
  < 7

More specifically, the following summaries will be provided, as follows:

Received opioid rescue medication prior to discharge overall
Did not received opioid rescue medication prior to discharge overall

NRS-R ≥ 6 or received opioid rescue medication
NRS-R < 6 and did not receive opioid rescue medication

NRS-R ≥ 6 and received opioid rescue medication
NRS-R < 6 or did not receive opioid rescue medication

NRS-R ≥ 7 or received opioid rescue medication
NRS-R < 7 and did not receive opioid rescue medication

NRS-R ≥ 7 and received opioid rescue medication
NRS-R < 7 or did not receive opioid rescue medication

NRS-A ≥ 6 or received opioid rescue medication
NRS-A < 6 and did not receive opioid rescue medication

NRS-A ≥ 6 and received opioid rescue medication
NRS-A < 6 or did not receive opioid rescue medication

NRS-A ≥ 7 or received opioid rescue medication
NRS-A < 7 and did not receive opioid rescue medication

NRS-A ≥ 7 and received opioid rescue medication
NRS-A < 7 or did not receive opioid rescue medication

9. SAFETY ANALYSIS

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

All safety data will be summarized by Cohort,by Part and, overall (see Section 8, Table 3).

9.1. Adverse Events

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

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

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

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

AEs will be coded using MedDRA version 22.0. TEAEs and TESAEs will be presented in AE tables, according to the SOC and PT. Any AEs that occur and resolve prior to Study Day 1 or are ongoing but do not worsen on or after Study Day 1 will be considered pretreatment AEs and will appear in the AE listing but not in TEAE tables.

9.1.1. Incidence of Treatment Emergent Adverse Events

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

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

- Number of TEAEs
- Number of subjects with at least 1 TEAE
- Number of subjects with at least 1 TEAE possibly related to study drug
- Number of subjects with at least 1 TEAE possibly related to MMA regimen
- Number of subjects with at least 1 severe TEAE
- Number of subjects with at least 1 TEAE leading to study withdrawal
- 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 at least 1 TESAE possibly related to MMA
- Number of subjects with fatal TEAEs

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

9.1.2. Relationship of Adverse Events to Study Drug

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

9.1.3. Relationship of Adverse Events to MMA Regimen

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

9.1.4. Severity of Adverse Event

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

9.1.5. 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. 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 be listed.

9.1.6. Adverse Events Leading to Study Withdrawal

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

9.1.7. Death

Any subject deaths during this study will be 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. Clinical Laboratory Evaluations

9.2.1. Part 1

Laboratory assessments will be performed by a central laboratory (hematology and serum chemistry, Part 1 only) 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.

For Part 1, 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 and Day 15), highest postdose value, lowest postdose value, and last postdose value.

Part 1 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, in Part 1, will contribute to tables of shifts from Baseline and in tables showing changes from Baseline to highest value, lowest value, and last value. Unscheduled laboratory results will not be windowed for the purposes of assigning a nominal visit.

Listings of laboratory values will include flags for values outside the central laboratory normal ranges that indicate how far out of the normal range an abnormal value is. For example, a value that is ≥ 3 times the upper limit of normal (ULN) but below 4 times the upper limit of normal will have a "3H" flag. Flag multipliers will show values that are 1, 2, 3, 4, 5, and 10 times relative to the ULN if high. Values that are below the lower limit of normal (LLN) will be flagged simply with "L".

Listings of abnormal values for hematology and chemistry will be presented separately in addition to listings of all laboratory values.

9.2.1.1. Hematology

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

9.2.1.2. 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. Subjects with laboratory values meeting liver function ranges will also be presented in data listing.

- ALT or AST:
    - > 1 x ULN
    - ≥ 2 x ULN
    - ≥ 3 x ULN
    - ≥ 4 x ULN
    - ≥ 5 x ULN
- Total bilirubin ≥ 2 x ULN
- ALP:
    - ≥ 1.5 x ULN
    - ≥ 2 x ULN
- ALT ≥ 3 x ULN and AST ≥ 3 x ULN
- ALT ≥ 3 x ULN and total bilirubin ≥ 2 x ULN
- AST ≥ 3 x ULN and total bilirubin ≥ 2 x ULN
- Potential Hy's Law: (ALT or AST ≥ 3 x ULN) and ALP < 2 x ULN and total bilirubin ≥ 2 x ULN

9.2.1.3. Urine Pregnancy Test and Urine Drug Screen

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

9.2.2. Part 2

Laboratory data collected at screening and unscheduled visits will be included in listings in Part 2. Unscheduled laboratory results for Part 2 will mainly be captured for the purposes of identifying AEs.

9.3. 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 assessed at Screening, preoperatively on Day 1, at Discharge, and at the Day 15 visit.

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

Table 4. Out-of-Range Vital Signs Values

Vital Sign	Low	High
HR	≤50 bpm, 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.

9.4. Electrocardiogram

12-lead ECG (triplicate) will be performed at screening and ECG data will be listed.

9.5. Physical Examination

Physical examinations will be performed at Screening and physical examination data will be listed.

10. INTERIM ANALYSIS

10.1. Interim Analysis

No formal interim analysis is planned. Preliminary summary-level efficacy and safety data from Part 1 were reviewed by the Sponsor to inform selection of the following for Part 2: MMA regimen(s), criteria for prescribing an opioid at discharge, and details of the allowed opioid prescriptions.

10.2. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will not be involved with the conduct of this study. The Sponsor will review tables and listings of accumulating data approximately monthly to check enrollment, adherence to follow-up schedule, and ongoing safety results.

11. REFERENCES

IQVIA (2018). User Manual for the Treatment Satisfaction Questionnaire for Medication (TSQM)**:** 1-40.

PROMIS (2019). PROMIS® Scoring Manuals. Retrieved from http://www.healthmeasures.net/promis-scoring-manuals

Swartzman LC, Gwadry FG, Shapiro AP, Teasell RW. The factor structure of the Coping Strategies Questionnaire (1994). Pain; 57:311-6

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, there is no need to impute an incomplete AE start date, as the AE is not treatment emergent and the event should be in the medical history.

Concomitant Medications

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

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

APPENDIX 2. DOCUMENT REVISION HISTORY

Version	Date	Notes/Revisions
1	12 April 2019	Initial version, based on protocol version 1.0 (22 March 2019)
2	16 December 2019	Second version, based on protocol version 3.0 (12 September 2019) • Updated study objective and study design per protocol version 3.0 • Removed summary for MMA accountability • Added summary for baseline pain phenotyping questionnaire • Updated summaries for efficacy and safety data to be by Cohort, by Part and overall

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Approval	[redacted] 17-Dec-2019 23:44:45 GMT+0000

Approval	[redacted] 25-Dec-2019 00:29:12 GMT+0000

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