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Statistical Analysis Plan

Heron Therapeutics, Inc.

HTX-011-C2015-202

A Phase 2, Randomized, Pilot Study to Investigate the Safety, Efficacy, Pharmacokinetics and Bioavailability of HTX-011, HTX-002, or HTX-009 Administered Via Injection and/or Topical Application Fol owing Unilateral Open Inguinal Herniorrhaphy

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TABLE OF CONTENTS

List of Tables

ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
BMI	body mass index
BPM	beats per minute
CI	confidence interval
CRF	case report form
CS	clinically significant
CSR	clinical study report
DBP	diastolic blood pressure
ECG	electrocardiogram
ICH	International Conference on Harmonisation
IP	investigational product
ITT	Intent-to-Treat
IV	intravenous
LOCF	last observation carried forward
LSMD	least-squares mean difference
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intend-to-Treat
MME	morphine milligram equivalency
NCS	not clinically significant
NRS	numeric rating scale
PACU	post anesthesia care unit
PGA	Patient Global Assessment
PI	pain intensity

Abbreviation	Definition
PK	pharmacokinetic
PONV	postoperative nausea and vomiting
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SEM	standard error of the mean
SOC	system organ class
SPI	summed pain intensity
SpO_2	peripheral oxygen saturation
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO	World Health Organization
WLOCF	windowed last observation carried forward

1 INTRODUCTION

This statistical analysis plan (SAP) describes the planned statistical analysis and reporting of the clinical study HTX-011-C2015-202 titled "A Phase 2, Randomized, Pilot Study to Investigate the Safety, Efficacy, Pharmacokinetics and Bioavailability of HTX-011, HTX-002, or HTX-009 Administered Via Injection and/or Topical Application Following Unilateral Open Inguinal Herniorrhaphy". This SAP does not include the planned analysis and reporting of the pharmacokinetic (PK) assessments in the study; these will be presented in a separate document.

Table 1: Protocol Revision History

Protocol Revision Chronology:		
Protocol Version 1	13 May 2015	Original protocol submitted to FDA
Protocol Version 2	23 Jun 2015	Updates predominantly administrative
Protocol Version 3	13 Aug 2015	HTX-011-49 to replace HTX-011-19 if available, additional PK time point (120 hours)
Protocol Version 4	03 Sep 2015	Removal of Mesh and HTX-011-49
Protocol Version 5	23 Nov 2015	Reintroduction of Mesh
Protocol Version 6	22 Dec 2015	Addition of HTX-011-49 and clarification of dosing
Protocol Version 7	28 Feb 2016	Addition of HTX-011-56 and separation of study into Part A and Part B
Protocol Version 8	08 Jun 2016	Addition of two HTX-002 injection cohorts and two HTX-011-56 topical cohorts as Part C
Protocol Version 9	08 Jul 2016	Addition of two HTX-002-013 topical cohorts and Marcaine to Part C
Protocol Version 10	07 O t 2016	Addition of three HTX-011-56 cohorts, with/without fentanyl injection as Part D, and 2 cohorts of HTX-009 or saline placebo as Part E
Protocol Version 11	28 Dec 2016	Addition of Part F; saline placebo or 400 mg HTX-56 via instillation, with 50 µg fentanyl IV. Terminology changed from "Topical" to "Instillation".
Protocol Version 12	31 Jan 2017	Addition of 3 Part G cohorts; saline + fentanyl, 75 mg Marcaine without epinephrine + fentanyl, and 300 mg HTX-011-56 + fentanyl.

Note: This SAP may not be revised with every amendment of the study protocol.

This SAP was based on protocol version 12, issued 31 January 2017, and was prepared prior to database lock to provide full details to be presented in the clinical study report (CSR). Revisions can be made to this SAP while the study is ongoing, but the SAP must be finalized before the database is locked. Any changes between the statistical methods provided in the clinical study protocol and this SAP will be explained herein; any changes or deviations from this SAP relative to the final analysis will be fully documented in the CSR, including the rationale.

The present Phase 2 study is designed to evaluate the efficacy and duration of analgesia following administration of HTX-011, HTX-002, or HTX-009. There are 7 parts to this study. Part A will evaluate 2 administration techniques and 2 dose levels of the HTX-011-19 formulation applied into the surgical site following unilateral open inguinal herniorrhaphy. Upon the completion of Part A, one of the two administration techniques will be chosen for Part B. Part B will evaluate the efficacy and safety of the HTX-011-49 and HTX-011-56 formulations at 2 dose levels via administration of the preferred technique as determined in Part A. Part C will evaluate the efficacy and duration of analgesia following administration of HTX-011-56 and HTX-002, at 2 dose levels, with two administration techniques in comparison to normal saline and Marcaine™. Part D will evaluate the efficacy and duration of analgesia following administration of 400 mg HTX-011-56 with or without fentanyl at the end of surgery via combination administration. Part E will evaluate the efficacy and duration of analgesia following administration of HTX-009 or saline placebo. Part F will evaluate the efficacy and duration of analgesia following administration of 400 mg HTX-011-56 with fentanyl at the end of surgery via instillation administration, and Part G will evaluate the efficacy and duration of analgesia following administration of 300 mg HTX-011-56 with fentanyl IV or Marcaine (without epinephrine) with fentanyl IV at the end of surgery via injection administration before wound closure.

Saline placebo groups are included in each part to match part-specific administration methods.

Efficacy assessments are intended to characterize the analgesic time action curve and the magnitude of analgesic effect of multiple dosing techniques and formulations of HTX-011, HTX-002, and HTX-009. In addition, the study will further characterize the safety and PK profiles of all formulations of HTX-011, HTX-002, and HTX-009.

2 STUDY OBJECTIVES

The primary objective for Part A is to evaluate the efficacy and duration of analgesia following administration of one of two doses of HTX-011-19 by two different techniques.

The primary objective of Parts B th ough G will be to evaluate the efficacy and duration of analgesia following administration of HTX-011-49, HTX-011-56, HTX-002, HTX-009, bupivacaine (Marcaine), or normal saline.

The secondary objectives to be evaluated in Parts A through G are as follows:

- To determine in Part A the optimal administration technique of study drug
- To determine the safety and tolerability of HTX-011, HTX-002, and HTX-009 as evaluated through physical examination, vital signs, clinical laboratory tests, electrocardiograms (ECGs), and incidence of adverse events (AEs) and serious AEs (SAEs)
- To evaluate the PK profiles of bupivacaine and/or meloxicam in HTX-011, HTX-002, and HTX-009 over 120 hours
- To evaluate the analgesic effects of HTX-011, HTX-002, and HTX-009 over various intervals using a series of secondary efficacy endpoints for pain intensity (such as the patient's global assessment [PGA] of pain control, time to administration of first dose of rescue analgesia, and total and average daily rescue consumption)

- To assess the effects of HTX-011, HTX-002, and HTX-009 on wound healing at 72 hours and on Days 10 and 28 post-treatment

- To evaluate nausea at 6, 24, 48, and 72 hours post-treatment

- To evaluate the percentage of subjects who are pain free over time

3 STUDY DESIGN

3.1 Overall Study Design

This is a Phase 2, multicenter, single-dose, randomized study in adult subjects undergoing unilateral open inguinal herniorrhaphy. The study will enroll up to approximately 453 subjects.

Male and female subjects at least 18 years of age requiring unilateral open inguinal herniorrhaphy will be screened for participation at the study sites in the United States within 28 days of the planned surgery. After signing the informed consent form, subjects will be assessed for medical history, postoperative nausea and vomiting (PONV) risk factors, physical examination, baseline clinical laboratory tests, drug and alcohol screen, 12 lead electrocardiogram (ECG), pregnancy testing, vital sign measurements. Additionally, they will undergo pain and placebo assessment training during the screening visit.

On the day of surgery (Day 0), after having been reassessed for eligibility, subjects will undergo a unilateral open inguinal herniorrhaphy und r general anesthesia. No epidural or spinal anesthesia will be allowed, nor will any local anesthetic infiltration, other than the administration of the investigational product (IP), be permitted. No prophyl ctic antiemetic, local anesthetics, or analgesic medications are allowed at any time. A single dose of study drug (either HTX-011, HTX-002, HTX-009, Marcaine, or saline, according to a randomization schedule) will be administered. Start and stop time of dosing will be recorded. Dosing stop time will be co sidered Time 0.

Following the completion of surgery and immediate postoperative recovery stay, subjects will be transferred to the post-anesthesia care unit (PACU). Staff members in the PACU will be blinded to study treatment administered. Subjects will stay at the PACU for approximately 72 hours after the administration of study medication and will return to the study center 96 and 120 hours after the administration of study medication to complete additional assessments. Subjects will be scheduled to return on Day 10 for additional efficacy and safety assessments and Day 28 for an assessment of wound healing and collection of AEs and concomitant medications. Part A of the study will determine the optimal technique of administration of study drug. Efficacy assessments will include pain intensity scoring, use of rescue medication, PGA of pain control, assessments of nausea, and use of analgesia rescue medicine. Safety assessments will include monitoring of AEs, physical examinations, vital sign measurements, clinical laboratory tests, ECGs, and wound healing assessments and photographs of the surgical site. Blood samples will be obtained to assess meloxicam and bupivacaine pharmacokinetics. Subjects will also receive a phone call from the study site on Day 60 to collect follow-up information on postoperative pain and pain medications.

3.2 Treatment and Schedule of Assessments

Efficacy assessments will include pain intensity scoring using a numeric rating scale (NRS), use of rescue medication, and the PGA of pain control. Safety assessments will include monitoring of AEs, vital sign measurements, clinical laboratory tests, ECGs, nausea assessments, and wound healing assessments. Blood samples will be obtained to assess meloxicam and bupivacaine pharmacokinetics. Dosing and formulation cohorts are outlined in Table 2, and the planned schedule of study procedures is outlined in Table 3, Table 4, and Table 5.

Table 2: Cohorts for each Part

Part A
Cohort A (18 subjects) 200 mg (3.42 mL) HTX-011-19 injection
Cohort B (18 subjects) 400 mg (6.84 mL) HTX-011-19 injection
Cohort C (18 subjects) 200 mg (3.42 mL) HTX-011-19 instillation
Cohort D (18 subjects) 400 mg (6.84 mL) HTX-011-19 instillation
Cohort E (18 subjects) 400 mg (6.84 mL) HTX-011-19 injection and instil ation combination
Cohort F (18 subjects) 6.84 mL saline placebo injection
Part B
Cohort M (15 subjects) 200 mg (6.84 mL) HTX-011-49 injection
Cohort N (15 subjects) 400 mg (13.68 mL) HTX-011-49 injection
Cohort O (15 subjects) 200 mg (6.84 mL) HTX-011-56 injection
Cohort P (15 subjects) 400 mg (13.68 mL) HTX-011-56 injec ion
Cohort Q (15 subjects) 6.84 mL saline placebo injection
Cohort R (15 subjects) 13.68 mL saline placebo injecti n
Part C
Cohort S (15 subjects) 200 mg (6.84 mL) HTX-011-56 instillation
Cohort T (15 subjects) 400 mg (13.68 mL) HTX-011 56 instillation
Cohort U (15 subjects) 200 mg (6.84 mL) HTX-002 injection
Cohort V (15 subjects) 400 mg (13.68 mL HTX-002 injection
Cohort X (15 subjects) 6.84 mL saline placebo injection
Cohort Y (15 subjects) 13.68 mL saline placebo injection
Cohort Z (15 subjects) 75 mg (30 mL) Marcaine injection
Cohort W1 (15 subjects) 200 mg (6.84 mL) HTX-002 instillation
Cohort W2 (15 subjects) 400 mg (13.68 mL) HTX-002 instillation
Part D
Cohort A1 (15 subjects) 400 mg (13.68 mL) HTX-011-56 injection and instillation combination + fentanyl 50 µg IV
Cohort A2 (15 subjects) 400 mg (13.68 mL) HTX-011-56 injection and instillation combination + fentanyl 150 µg IV
Cohort A3 (15 subjects) 400 mg (13.68 mL) HTX-011-56 injection and instillation combination
Part E
Cohort B1 (15 subjects) 12 mg (13.68 mL) HTX-009 injection and instillation combination
Cohort B2 (5 subjects) 13.68 mL saline placebo injection and instillation combination
Part F
Cohort C1 (15 subjects) 13.68 mL saline placebo instillation + fentanyl 50 µg IV
Cohort C2 (5 subjects) 400 mg (13.68 mL) HTX-011-56 instillation + fentanyl 50 µg IV
Part G
Cohort D1 (15 subjects) 300 mg (10.26 mL) of HTX-011-56 via instillation and fentanyl 50 µg IV before wound closure

Cohort D2 (15 subjects) 75 mg (30 mL) of 0.25% Marcaine w/o epinephrine via injection and fentanyl 50 µg IV before wound closure
Cohort D3 (5 subjects) 10.26 mL of normal saline via injection and fentanyl 50 µg IV before wound closure

Table 3: Screening

Procedure	Day -28 to Day -1
	Screening
Informed Consent	X
Eligibility Assessment	X
Demographics and Medical History	X
Assessment of PONV Risk Factors	X
ASA Classification Assessment	X
Physical Examination	X
Pregnancy Test (female subjects of child bearing potential only)	X[serum]
Urine Drug Screen	X
Alcohol Breath Test	X
Clinical Laboratory Tests [a]	X
Vital Signs [b]	X
BMI Determination	X
12-lead ECG	X
Pain Training	X
Prior and Concomitant Medication [c]	X
Serious Adverse Event Monitoring [d]	X

[a] Laboratory tests will include hematology and chemistry screenings in all subjects. Results will determine subject eligibility for the study.

[b] Resting vital signs (VS) will be collected at screening. Resting VS include: resting blood pressure, resting pulse, respiratory rate, oral temperature and SpO2. Resting tests must be obtained after resting (seated/reclined) for ≥ 5 minutes.

[c] ConMeds taken within 30 days before dosing will be recorded.

[d] SAEs will be reported if considered related to study participation.

Table 4: Prior to Surgery and Surgery (Day 0)

	Day 0	
	Prior to Surgery	**Surgery**
Eligibility Assessment	X	
Demographics and Medical History	X	
Physical Examination [c]	X	
Pregnancy Test (female subjects of child bearing potential only)	X[urine]	
Urine Drug Screen	X	
Alcohol Breath Test	X	
Clinical Laboratory Tests [a]	X [d]	
Vital Signs [b]	X	
12-lead ECG	X	
Pain Training	X	
Blood Draw for PK	X [d]	
Neurologic Exam	X	
Surgery Procedure		X
Study Drug Administration		X
Prior and Concomitant Medication [f]	X	
Serious Adverse Event Monitoring[g]	X	X

[a] Laboratory tests will include hematology and chemistry and will be used as baseline reference and not for determining subject eligibility.
[b] Resting vital signs (VS) will be collected at screening and check-in only, all other assessments will include resting VS only. Resting VS include: resting blood pressure, resting pulse, respiratory rate, oral temperature and SpO2. Resting tests must be obtained after resting (seated/reclined) for ≥ 5 minutes. VS will have a ± 15 minute window.
[c] Physical examination will include weight only but not height or BMI.
[d] Baseline laboratory samples can be collected prior to surgery.
[f] ConMeds taken within 30 days before dosing will be recorded
[g] SAEs that occur before study drug administration will be reported only if considered related to study participation. After study drug administration, all SAEs that occur through Day 28 post-treatment must be reported.

Table 5: Post Study Medication Administration (Days 0-5)

	Day 0 to 5																						D10 (±2d)	D28 (±2d)	D60 (±8d)
	Post Study Drug Administration Time Points (hrs)																								
	0.5	1[f]	1 5	2	3	4	6	8, 10, 12	14	18	24	30	36	42	48[g]	54[g]	60[g]	72[g]	78[g]	84[g]	96[g]	120			
Confinement	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Physical Examination																		X[g]					X[c]		
Clinical Laboratory Tests [a]																		X							
Vital Signs [b]		X		X		X	X	X (12hr only)		X	X		X		X		X	X			X		X		
12-lead ECG											X				X			X			X		X		
Pain Intensity (PI)		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
PGA of Pain Control											X				X			X			X				
Use of Rescue Medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[e]	X[e]	
PK Blood Draws (±15 min)	X	X	X	X	X	X	X	X		X	X	X	X		X		X	X			X	X[g]			
Numerical Rating Scale for Nausea							X				X				X			X							
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Assessment of Wound Healing																		X					X	X	
Photos	X														X			X			X		X	X	
Bupivacaine Toxicity and Neurological Assessment											X				X			X							
AE Monitoring [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Phone Call [h]																									X

Abbreviations: AE, adverse event; D, day; ECG, electrocardiogram; hr(s), hour(s); min, minutes; PK, pharmacokinetics.

[a] Laboratory tests will include hematology and chemistry.

[b] Resting VS only. Resting VS include: resting blood pressure, resting pulse, respiratory rate, oral temperature and SpO2. Resting tests must be obtained after resting (seated/supine) for ≥ 5 minutes.

[c] Physical examination will include weight only, but not height or BMI. Weight not required at 72 hour exam.

[d] AEs will be monitored after administration of study medication through the Day 10 study visit. SAEs will be monitored through Day 28.

[e] Subjects may resume standard of care pain medication as advised by their surgeon after the 72 hour study visit.
[f] 1 hour assessments to be completed if subject is awake and alert.
[g] ± 30 minutes for 72hr Physical Exam, ± 60 minutes for the 48, 54, 60 and 72 hr assessments, and ± 4 hours for the 96 and 120 hr assessments
[h] Subjects will receive a phone call from the study site on Day 60 (±8 days). Subjects will be asked if they have any current pain related to the operation. Subjects will also be asked to think about the previous 24 hours and to rate their pain intensity related to the operation using the NRS and to report any medication(s) taken to treat the pain (name, dose, and route).

4 STUDY ENDPOINTS

4.1 Efficacy Endpoints

The primary efficacy endpoint is the summed pain intensity (SPI) scores over the first 24 hours (SPI_{0-24}).

Secondary efficacy endpoints include the following:

1. SPI over various other time intervals (SPI_{0-6}, SPI_{0-12}, SPI_{12-24}, SPI_{24-48}, SPI_{0-48}, SPI_{48-72}, SPI_{0-72}, SPI_{72-96}, SPI_{0-96})
2. The PGA of pain control at 24, 48, 72, and 96 hours
3. Time to first use of rescue medication (any, and opioid)
4. Total and average daily rescue analgesia consumpt on over 24, 48, 72, and 96 hours post-treatment, by each analgesic, opioid and non-opioid
5. Percentage of subjects who have not taken opioid rescue medication over time
6. Percentage of subjects that are pain-free (NRS score $\leq$ 1) over time by time point and comparisons at 24, 72, and 96 hours after study drug administration.

Exploratory endpoints include the following

1. Area under the curve (AUC) for PI scores collected over various time intervals (AUC_{0-24}, AUC_{0-48}, AUC_{0-72}, AUC_{0-96}, AUC_{0-6}, AUC_{0-12} AUC_{12-24}, AUC_{24-48}, AUC_{48-72}, and AUC_{72-96})
2. Integrated Rank Difference fo SPI_{0-24}, SPI_{0-48}, SPI_{0-72}, SPI_{0-96}, and total opioid use through 24, 48, 72, and 96 hours post-study drug administration.

4.2 Safety Endpoints

The safety endpoints include:

- AEs and SAEs
- Sponsor defined opioid-related AEs
- Mean nausea assessments at 6, 24, 48, and 72 hours
- Vital signs abnormal values
- Assessments of the surgical intervention area
- Neurological examinations
- Shift of clinical laboratory tests, including routine blood chemistry, liver function tests, and hematology

- Shift in ECG findings
- Symptoms related to bupivacaine toxicity
- Use of concomitant medications

4.2.1 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.

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 medication, whether or not considered causally associated with the use of the study medication. Any abnormal laboratory value deemed clinically significant by the investigator, regardless of cau al relationship, must be reported as an AE.

All AEs, whether volunteered, elicited, or noted on physical examination and regardless of causality or seriousness, will be assessed and recorded in the case rep rt form (CRF) beginning after the administration of study medication through study completion or resolution of the AE, whichever comes first.

Any medical condition or clinically significant laboratory abnormality with an onset date before the date of study drug administration is usually considered to be pre-existing, should be recorded as medical history, but should not be documented in the CRF as an AE. Any AE (i.e., a new event or an exacerbation of a pre-existing condition) with an onset date after study drug administration up to and including the designated follow-up safety visit should be recorded as an AE on the CRF. All AEs must be recorded on the AE CRF regardless of the severity or relationship to study drug.

4.2.2 Nausea Assessments

Nausea will be assessed during the study using an NRS scale. Assessments of nausea will be completed by subjects at the following time points: 6, 24, 48, and 72 hours, and at the time of early termination if it should occur, and only if the subject is discontinued prior to T96.

4.2.3 Vital Signs

Resting vital signs will be obtained after resting (seated/supine) for at least 5 minutes, and will include resting blood pressure, resting pulse, respiratory rate, oral temperature, and peripheral oxygen saturation (SpO_2). After the administration of study medication, subjects will have resting vital signs measured and recorded at the following times: 1, 2, 4, 6, 8, 10, 12, 18, 24, 36, 48, 60, 72, and 96 hours and at the Day 10 visit, or at early termination, with actual times recorded.

4.2.4 Laboratory Parameters

The clinical laboratory and other tests relating to safety to be performed during the study are described below.

- Hematology parameters include: red blood cells, hematocrit, hemoglobin, platelets, white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, basophils.

- Serum chemistry parameters include aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, gamma glutamyl transferase, albumin, total protein, creatinine, uric acid, urea, sodium, potassium, magnesium, chloride, phosphorus, calcium, glucose, bicarbonate, lactate dehydrogenase.

In addition, serological testing will be performed for hepatitis B and hepatitis A, drug screening and salivary testing for alcohol will be performed. For women of childbearing potential, a serum pregnancy test will be performed at screening, and a urine pregnancy test will be performed on the day of admission prior to surgery.

4.2.5 Electrocardiograms

A 12-lead ECG will be performed after the subject has been supine for at least 5 minutes and will be completed for all subjects at screening, at check-in on Day 0, at 24, 48, 72, 96 hours post-treatment, and at the Day 10 visit, or at time of early discontinuation, if applicable.

4.2.6 Wound Healing Assessments

The surgical wound will be assessed 72 hours post-treatment, 10 days post-treatment and 28 days post-treatment. Results are recorded as Normal or Abnormal with verbatim descriptions of abnormalities.

4.2.7 Bupivacaine Toxicity

Subjects will be assessed for symptoms (peri ral tingling, strange taste, muscle twitching, ringing in ears, seizure, bradycardia, and cardiac arrest) related to bupivacaine toxicity at 24, 48, and 72 hours post-treatment.

4.2.8 Liver Function

Subjects will be assessed for post-treatment abnormalities in liver function tests ALT, ALP, AST, and total bilirubin.

4.2.9 Neurological Exams

Neurological exams will be performed on Day 0 prior to surgery, and at hours 24, 48, and 72 post-treatment (or early termination). Parameters assessed include mental status, motor, sensory, cerebellar/gait, and cranial nerve functioning.

5 DATA QUALITY ASSURANCE

Report summaries will be generated using validated SAS® software, version 9.4 or higher, on a PC or server-based platform. Additional validated software may be used to generate analyses, as needed.

All SAS programs that create outputs or supporting analysis datasets will be validated by a second statistical programmer or biostatistician. At a minimum, validation of programs will consist of a review of the program log, review of output or dataset format and structure, and independent confirmatory programming to verify output results or dataset content. Additionally, all outputs will undergo a review by a senior level team member before finalization.

The content of the source data will be reviewed on an ongoing basis by project statistical programmers and statisticians. Data will be checked for missing values, invalid records, and extreme outliers through defensive programming applications, analysis-based edit checks, and other programmatic testing procedures. All findings will be forwarded to sponsor for appropriate action and resolution.

6 POPULATIONS DEFINED

Intent-to-Treat (ITT) Population: The ITT population will include all subjects who are randomized to receive study medication.

Efficacy Population: The efficacy population will include all subjects who are randomized to receive study medication and have at least one postdose, scheduled PI score. This population is noted as the modified Intent-to-Treat (mITT) population.

Safety Population: The safety population will include all treated subjects and will be used for safety and tolerability assessments.

6.1 Sample Size Determination

The sample size of approximately 453 subjects was selected empirically without a formal statistical assumption.

7 STATISTICAL METHODS AND DATA CONSIDERATIONS

7.1 General Considerations

Data will be analyzed by Agility Clinical biostatistics personnel. Statistical analyses will be reported with tables, figures and subject data listings, presented in rich text format, and using recommended International Conference on Harmonisation (ICH) numbering. Output specifications for all tables, listings and figures will be in conform nce with guidelines specified by the ICH guideline *Statistical Principals for Clinical Trials* (E9) (1999).

Unless otherwise specified, safety tables will be summarized separately for Part A and Parts B/C/D/E/F/G. Summary tables will be grouped as follows:

Part A

HTX-011-19 (all summary tables):

1. Saline Placebo (6.84 mL)
2. HTX-011-19 200 mg (3.42 mL) Injection
3. HTX-011-19 200 mg (3.42 mL) Instillation
4. HTX-011-19 200 mg (3.42 mL) Total
5. HTX-011-19 400 mg (6.84 mL) Injection

6. HTX-011-19 400 mg (6.84 mL) Instillation
7. HTX-011-19 400 mg (6.84 mL) Combination
8. HTX-011-19 400 mg (6.84 mL) Total
9. HTX-011-19 Total
10. Total

The last 2 Total groups will be included only on demographics, disposition, and protocol deviations. AE summary tables will not include the last Total group.

Parts B/C/D/E/F/G

Formulations (only for demographics, disposition, protocol deviations, and AE tables):

1. Saline Placebo (6.84-13.68 mL)
2. 75 mg (30 mL) Marcaine
3. HTX-009 12 mg (13.68 mL)
4. HTX-002 200-400 mg (6.84-13.68 mL)
5. HTX-011-49 200-400 mg (6.84-13 68 mL)
6. HTX-011-56 200-400 mg (6 84-13 68 mL)
7. Total (not included on AE tables)

Additionally, all Parts B/C/E summary tables except protocol deviations will be grouped as follows:

HTX-011-49:

1. Saline Placebo (6.84-13.68 mL)
2. Marcaine 75 mg (30 mL)
3. HTX-011-49 200 mg (6.84 mL)
4. HTX-011-49 400 mg (13.68 mL)

HTX-011 Components:

1. HTX-009 12 mg (13.68 mL) Combination
2. HTX-002 200 mg (6.84 mL) Injection
3. HTX-002 200 mg (6.84 mL) Instillation

4. HTX-002 200 mg (6.84 mL) Total
5. HTX-002 400 mg (13.68 mL) Injection
6. HTX-002 400 mg (13.68 mL) Instillation
7. HTX-002 400 mg (13.68 mL) Total

All Parts B/C/D/E summary tables except protocol deviations will be grouped as follows:

HTX-011-56:

1. Saline Placebo (6.84-13.68 mL)
2. Marcaine 75 mg (30 mL)
3. HTX-011-56 200 mg (6.84 mL) Injection
4. HTX-011-56 200 mg (6.84 mL) Instillation
5. HTX-011-56 200 mg (6.84 mL) Total
6. HTX-011-56 400 mg (13.68 mL) Injection
7. HTX-011-56 400 mg (13.68 mL) Instillation
8. HTX-011-56 400 mg (13.68 mL) Combination
9. HTX-011-56 400 mg (13.68 mL) Total

All Part D, F and G summary tables except protocol deviations will be grouped as follows:

HTX-011-56 + Fentanyl:

1. Saline Placebo (10.26-13.68 mL) + 50 µg Fentanyl IV
2. Marcaine 75 mg (30 mL) + 50 µg Fentanyl IV
3. HTX-011-56 300 mg (10.26 mL) + 50 µg Fentanyl IV
4. HTX-011-56 400 mg (13.68 mL) + 50 µg Fentanyl IV
5. HTX-011-56 400 mg (13.68 mL) + 150 µg Fentanyl IV
6. HTX-011-56 400 mg (13.68 mL) Total

In general, all data collected from all enrolled subjects will be presented in subject data listings. Listings will be ordered by site, subject number, and assessment or event date. The early termination visit is considered its own visit, where applicable.

In general, continuous variables will be summarized to indicate the population sample size (N), number of subjects with available data (n), mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized by the population size (N), number of subjects with available data (n), number of subjects in each category, and the percentage of subjects in each category. Unless otherwise noted, the denominator to determine the percentage of subjects in each category will be based on the number of subjects with available data. Select ordinal data may be summarized using both descriptive statistics and counts and percentages of subjects in each category, as appropriate.

Non-zero percentages will be rounded to one decimal place. Rounding conventions for presentation of summary statistics will be based on the precision of the variable of summarization, as it is collected in its rawest form (i.e., on the CRF or as provided within an external file) and are outlined as follows:

- The mean and median will be rounded to one more decimal place than the precision of the variable of summarization;
- Measures of variability (e.g., SD, standard error of the mean [SEM]) will be rounded to two more decimal places than the precision of the variable of summarization; and
- Minimum and maximum values will be presented using the same precision as the variable of summarization.

Other statistics (e.g., confidence intervals [CIs]) will be presented using the same general rules outlined above, or assessed for the most appropriate presentation based on the underlying data.

Unless otherwise specified, 95% CIs will be calculated for point estimates, and statistical significance testing will be two-sided and performed using α=0.05. P-values will be reported for all statistical tests, rounded to four decimal places. P values less than 0.0001 will be displayed as "<0.0001"; p-values greater than 0.9999 will be displayed as ">0.9999".

Unless indicated otherwise (see Section 7.8), no imputation will be done for missing data, and no adjustments will be made for conducting multiple hypothesis tests.

7.1.1 Standard Calculations

Where appropriate, the calculated study time of each assessment or event will be presented with the assessment or event time on subject data listings. Study time is calculated using hours and minutes in HH:MM format, where hour is between 0 and 23, and minute is between 0 and 59.

Study time will be calculated in reference to the time of completed application of study drug. Thus, a study event that occurs prior to the time of completed application of study drug would be associated with a negative time calculation, while a study event that occurs after time of completed application of study drug would be a positive time calculation.

7.2 Analysis Datasets

ITT Analysis Population: The ITT analysis set will include all subjects who are randomized to receive study medication.

Efficacy Population: The efficacy analysis set will include all subjects who were randomized to receive study medication and have at least 1 postdose, scheduled PI score. This analysis set is noted as the mITT set.

Safety Population: The safety analysis set will include all subjects who received study drug and will be used for safety and tolerability assessments.

For the ITT and mITT analyses, subjects are assigned to a treatment group based on the randomization schedule, regardless of the treatment actually received.

For the safety analysis, treatment group assignment will be based on the treatment actually received.

7.3 Disposition of Subjects and Protocol Violations

A summary table of subject disposition will include the number of subjects who were randomized and number in each analysis population. Counts and percentages of randomized subjects who did/did not complete the study will be presented as described in Section 7.1, with subjects who did not complete the study summarized by reason for discontinuation. A separate summary table will include the number of subjects who failed screening. The summary will include counts and percentages of subjects by reason for screen failure. All major protocol violations in the Safety Population will be determined and appropriately categorized prior to database lock. The count and percentage of subjects with any major protocol violations as well as the number and percentage of subjects with violations within each category will be presented for the Formulations groups described in Section 7.1. A listing of subjects who were excluded from the efficacy analysis will be provided.

7.4 Demographic and Other Baseline Characteristics

The demographic summary will include descriptive statistics for age, sex, ethnicity, and race, presented as described in Section 7.1, with saline placebo cohorts pooled. The baseline characteristics will include weight, height, and body mass index (BMI). Age will be summarized using descriptive statistics. Sex, ethnicity, and race will be summarized with the count and percentage of subjects in each parameter category.

Medical history will be summarized, with reported terms mapped to preferred term (PT) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.1. Subjects with multiple medical history events will be sorted by date of onset, date of resolution (if applicable), and SOC. Frequency counts and percentages to summarize subjects reporting medical history by SOC and PT will be presented. Subjects reporting > 1 event per SOC/PT will be counted only once. Medical history will also be provided in a subject listing.

7.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification index (version September 01, 2016). Prior medications are those that stop prior to the start of the study drug administration. Any medication that stops at or after the start of study drug administration is considered concomitant medication. If it cannot be determined whether a medication was stopped prior to the start of study drug administration due to partial or missing medication dates, it will be considered a concomitant medication. Concomitant medications will be included in summaries. Prior medications will be included in a subject data listing.

The number and percentage of subjects who take concomitant medications will be summarized by ATC class and PT. Subjects reporting use of more than one medication at each level of summarization (any medication received, ATC class, and PT) will be counted only once. ATC class terms will be displayed by descending order of incidence, as will PT within each ATC class. Concomitant medications will be summarized as described in Section 7.1 and provided in a subject listing. Prior medications will be provided in a separate listing. A listing of subjects who received prohibited opioid rescue medications will be provided, to include Subject ID, drug name, indication, dose, route of administration, frequency, date/time of administration, date/time of stopping medication, and treatment cohort.

7.6 Treatment Compliance and Extent of Exposure

Since study drug is administered intra-operatively, no formal summary of treatment compliance will be produced.

Summary statistics for duration of surgery will include times of surgery start and completion, with duration calculated as completion time minus start time, and r ported in minutes. Results will be presented as described in Section 7.1. A per subject listing of duration of surgery will include start and stop time of study drug administration.

7.7 Efficacy Analysis

The efficacy analysis will be performed using the mITT population. Part A will be analyzed separately. Parts B/C/D/E/F/ G will be analyzed together. For treatment comparisons using pooled data, data from treatment groups will be combined prior to conducting the statistical comparison. Unless otherwise specified, the planned comparisons to be performed will be described in a separate document.

Figures for efficacy endpoints will be provided separately for Part A and Parts B/C/D/E/F/G. All efficacy figures will be structured according to the following groups:

Part A

- Pooled 200 mg HTX-011-19 (Cohorts A and C)
- Pooled 400 mg HTX-011-19 (Cohorts B, D, and E)
- Saline Placebo (Cohort F)

Parts B/C/D/E

- Pooled 200 mg HTX-011-56 (Cohorts O and S)
- Pooled 400 mg HTX-011-56 (Cohorts A3, P, and T)
- 75 mg Marcaine (Cohort Z)
- Pooled 200 mg HTX-002 (Cohorts U and W1)
- Pooled 400 mg HTX-002 (Cohorts V and W2)
- 12 mg HTX-009 (Cohort B1)

- Saline Placebo (Cohorts B2, Q, R, X, and Y)

Parts D/F/G

- 400 mg HTX-011-56 + 50 µg or 150 µg Fentanyl (Cohorts A1, A2, and C2)
- 300 mg HTX-011-56 + 50 µg Fentanyl (Cohort D1)
- 75 mg Marcaine + 50 µg Fentanyl (Cohort D2)
- Saline Placebo + 50 µg Fentanyl (Cohorts C1 and D3)

7.7.1 Primary Efficacy Endpoint Analysis Methods

The primary analysis set is the mITT Population. The primary efficacy endpoint is the SPI_{0-24}, with last observation carried forward (LOCF) imputation of missing d ta as described in Section 7.8. A similar analysis will be conducted with missing data imputed by the windowed last observation carried forward (WLOCF) method described in Section 7.8.

SPI:

PI will be assessed by the subject for their current pain according to an 11-point NPRS (0-10) where 0 equates to no pain and 10 equates to the worst pain imaginable. PI scores will be measured two ways: on movement and at rest. PI scores will be assessed at the following time points: 1, 2, 4, 6, 8, 10, 12, 14, 18, 24, 30, 36, 42, 48, 54, 60, 72, 78, 84, and 96 hours post study drug administration. Assessments performed at 78 and 84 hours will be p rformed by subjects on an out subject basis. PI assessments scheduled between 24:00 and 06:00 must be collected, even if subjects are asleep at the time of the assessment.

Pain scores will be measured on movement (sitting up from a supine position) starting at Hour 4 and measured at 6, 8, 10, 12, 14, 18, 24, 30, 36, 42, 48, 54, 60, and 72 hours. Pain Scores will be measured at rest at 1, 2, 78, 84, and 96 hours after administration of study medication. The pain score will be measured after the patient has been supine for a minimum of 5 minutes and a resting pain score has been obtained. There will be a ± 15 minute window allowed for the collection of each PI assessment unless otherwise stated. This is referenced as the per protocol method.

PI will also be assessed within 5 minutes prior to administration of each dose of rescue analgesia and at time of early discontinuation (should it occur and only if the subject was discontinued prior to 96 hour).

The SPI endpoints will be derived by summing the PI score at the relevant time points weighted by the scheduled time duration since the prior PI assessment. For example, SPI_{0-24} will be calculated as below:

$$SPI_{0-24} = PI_1+PI_2+2*PI_4+2*PI_6+2*PI_8+2*PI_{10}+2*PI_{12}+2*PI_{14}+4*PI_{18}+6*PI_{24};$$

Where PI_i denoted the pain intensity score at hour i.

The SPI endpoints will be analyzed for Part A using analysis of covariance (ANCOVA) with treatment as an effect, and PI collection method (per protocol or not per protocol, as described above) as covariate. For Parts B/C/D/E/F/G, SPI endpoints will be analyzed using analysis of variance (ANOVA) with treatment as an effect. The differences between the specified planned group comparisons will be examined and nominal p-values will be reported without adjustment for multiplicity. For Parts B/C/D/E/F/G efficacy analysis, all saline placebo cohorts are pooled and treated as a single group (except for the saline + fentanyl cohorts). The number of subjects in each group, group mean, SD, least-squares mean point estimates of group differences (LSMD) and the associated 95% CI will be presented for each comparison, with the associated p-value. The null hypothesis to be tested for each comparison is that there is no difference between groups of interest, Treatment A and Treatment B:

$$H_0: \mu_A = \mu_B;$$

Where μ_A and μ_B represent the mean values for Treatment A and Treatment B, respectively. The alternate hypothesis to be tested is that the treatment group means differ

$$H_1: \mu_A \neq \mu_B;$$

7.7.2 Secondary Efficacy Endpoint Analysis Me hods

7.7.2.1 Sum of Pain Intensity

SPI over various other time intervals (SPI_{0-24}, SPI_{0-48}, SPI_{0-72}, SPI_{0-96}, SPI_{0-6}, SPI_{0-12}, SPI_{12-24}, SPI_{24-48}, SPI_{48-72}, and SPI_{72-96}) will be analyzed by ANCOVA/ANOVA and reported as described above in Section 7.7.1.

Tables of summary statistics of SPI scores for SPI_{0-24}, SPI_{0-48}, SPI_{0-72}, SPI_{0-96}, SPI_{0-6}, SPI_{0-12}, SPI_{12-24}, SPI_{24-48}, SPI_{48-72}, and $SPI_{72\ 96}$ will be pr vided as described in Section 7.1, with data imputed using LOCF as described in Section 7.8, and separately summarized with data imputed using WLOCF. Summary statistics include the number of subjects in each group, group means, SD, SEM, and 95% CI, median, minimum, and maximum values. Mean SPI_{0-6}, SPI_{0-12}, SPI_{0-24}, SPI_{0-48}, SPI_{0-72}, and SPI_{0-96} scores will be plotted against specified hours post-treatment as described in Section 7.7.

Summaries of PI scores at every collection time point (1, 2, 4, 6, 8, 10, 12, 14, 18, 24, 30, 36, 42, 48, 54, 60, 72, 78, 84, and 96 hours post-treatment) will be provided as described in Section 7.1, with data imputed using LOCF as described in Section 7.8 and separately summarized with data imputed using WLOCF. Summary statistics include the number of subjects in each group, group means, SD, SEM, 95% CI, median, maximum, and minimum values. Mean PI scores at will be plotted against every post-treatment collection time point for groups as described in Section 7.7.

The percentage of subjects in each treatment group who reported a PI score of 0 or 1 will be characterized as “pain-free”. Comparisons of percentage pain-free will be performed at 24 hours post-treatment, 48 hours post-treatment, 72 hours post-treatment, and 96 hours post-treatment for Part A using the Cochran-Mantel-Haenzel test, stratified by PI collection method. Comparisons of percentage pain-free will be performed at 24 hours post-treatment, 48 hours post-treatment, 72 hours post-treatment, and 96 hours post-treatment for Parts B/C/D/E/F/G using Fisher’s exact test. Data will be analyzed independently at each time point and will not be cumulative. Sample size, percentage pain-free, absolute percent-difference

between groups, and p-values will be provided for Part A and Parts B/C/D/E/F/G. In addition, exact unconditional 95% CIs for the difference between the groups based on the score statistic (Chan and Zhang, 1999) will be provided for the Parts B/C/D/E/F/G summaries.

The percentage of subjects who were pain-free will be plotted over time by time point at every collection time point (1, 2, 4, 6, 8, 10, 12, 14, 18, 24, 30, 36, 42, 48, 54, 60, 72, 78, 84, and 96 hours post-treatment) for groups as described in Section 7.7.

7.7.2.2 Patient Global Assessment

Pain control will be measured on a scale of 0-4, with 0 indicating poor pain control and 4 indicating excellent pain control. The proportion of subjects rating their pain control as 'Very Good' (3), or 'Excellent' (4) at 24 hours post-treatment, 48 hours post-treatment, 72 hours post-treatment, and 96 hours post-treatment will be compared between groups using Fisher's exact test. Missing subject data per time point will be imputed as rated below 'Very Good'. Data will be reported independently at each time point of interest and will not be cumulative. Group sample size, per entage of at least 'Very Good', absolute percent-difference between groups, and p-values from Fisher's exact test will be provided. In addition, exact unconditional 95% CIs for the difference between the groups based on the score statistic (Chan and Zhang, 1999) will be provided.

The percentage of subjects with at least very good pain control will be presented in bar charts at 24, 48, 72, and 96 hours post-treatment for groups as described in Section 7.7.

7.7.2.3 Rescue Medication

The cumulative percentage of subjects who have not received opioid rescue medication over 24 hours, 48 hours, 72 hours, and 96 hours post-treatment will be analyzed by treatment group in pairwise comparison using Fisher's exact test. Use of opioid rescue medication will be imputed for subjects terminating without reported opioid use. Group sample size, percentage opioid-free, absolute percent-difference between groups, p-values, and xact unconditional 95% CIs for the difference between the groups based on the score statistic (Chan and Zhang, 1999) will be provided for summaries.

Cumulative percentages will be plotted at 1, 2, 4, 6, 8, 10, 12, 14, 18, 24, 30, 36, 42, 48, 54, 60, 72, 78, 84, and 96 hours post-treatment for groups as described in Section 7.7.

Kaplan-Meier estimates of the median time to first administration of any rescue medication along with the 95% CIs will be presented for each group. The time to administration of the first dose of rescue medication will be compared between groups using the generalized Wilcoxon test, and the comparison will be summarized with hazard ratios along with the 95% CI, and the associated p-value from the Wilcoxon test. If a subject does not take rescue medication but prematurely discontinues from the study during the 96-hour treatment phase, then the subject will be censored at the time of the last post-treatment collection of vital signs, or the stop time of study drug administration, whichever occurs later. If a subject never takes rescue medication and completes the 96-hour treatment phase, then the subject will be considered censored for analysis purposes at 96 hours. Kaplan-Meier curves will be presented for Part A and Parts B/C/D/E/F/G groups as described in Section 7.7, plotted as 1-S(t).

The count and percentage of subjects who were administered only opioid rescue medications, and only non-opioid rescue medications will be summarized in tables, including counts and percentages of subjects

who received both types of analgesics but were administered opioid analgesics first, and received both but non-opioids first.

All opioid dosages and formulations will have the morphine milligram equivalency (MME) calculated, with oxycodone plus acetaminophen treated as oxycodone (Opioid Morphine Equivalent Conversion Factors, Centers for Disease Control and Prevention, Atlanta, GA, May 2014). Opioid conversions include, but are not limited to, the medications in Table 6 (complete table will be provided in the CSR):

Table 6: Analgesic Windows and Morphine Milligram Equivalencies

Medication	Route	Window (Hours)	MME Factor
CODEINE	PO	6	0.05
DILAUDID	PO	4	1.33
DILAUDID	IV	4	6.67
HYDROCODONE	PO	6	0 4
MORPHINE	IV	4	1
MORPHINE	PO	4	0 33
OXYCODONE	IV	4	1
OXYCODONE	PO	6	0 5
SUFENTANIL	PO	2	500
TRAMADOL	PO	6	0.04

Note: One record listed as hydrocodone (Percocet) was trea ed as hydrocodone.

Average daily use and total use will be calculated for each of the following periods: 0-24, 0-48, 0-72, and 0-96 hours post study medication administration. Subjects who did not use the specific rescue medication during a period will be assigned to "0". Thus, for the summary of oxycodone use, a subject who received only morphine would be counted as zero for that outcome.

Average daily use and total use data will be tabulated by treatment group with descriptive statistics to include SEM, and summarized separately by type of rescue medication (acetaminophen, morphine or oxycodone), and combined opioid use (morphine, oxycodone, sufentanil, tramadol, Percocet, and Dilaudid). Between groups comparisons of total opioid use for all opioids combined (morphine, oxycodone, sufentanil, tramadol, Percocet, and Dilaudid) will be performed for each time period using ANOVA, as described in Section 7.7.1. Results reported will include sample size, mean (SD), SEM, LSMD, 95% CI for LSMD, and p-value. The groups to be compared are listed in a separate document.

[redacted]

[redacted]

7.8 Data Imputation and Adjustment

7.8.1 PI Assessments

Any missing PI score for scheduled time points will be imputed using the standard LOCF method, unless the missing score occurs before values are available to carry over (such as the 1 hour post-treatment PI score). In such case, the missing score will be replaced by the worst score collected at any scheduled time point during the study. PI scores recorded or imputed during the analgesic window (duration of effect) of any taken rescue medication will not be used for analyses; instead alternate values will be calculated. The adjustment rules are as follows:

Subjects who require rescue analgesia during the first 96 hours (inclusive) after treatment are expected to report their pain intensity immediately before taking the rescue medication; this PI is referenced as the pre-rescue PI. The analgesic windows for specified rescue analgesics are listed in Table 6:

Analgesic Windows and Morphine Milligram Equivalencies. Non-opioid analgesic ibuprofen and acetaminophen are assigned a window of 6 hours. When the date/time of a scheduled PI is at or after the start time recorded for a rescue medication and within the analgesic window (inclusive) of the rescue medication, the scheduled PI score will be replaced by the pre-rescue PI score within the analgesic window (replaced with the worst pre-rescue PI if there were multiple rescue medications used within the analgesic window); if the scheduled PI score within the analgesic window is higher than the pre-rescue PI score, it will not be replaced. If the PI date/time is missing or time point is Hour 78 or 84 post T0, those time points will be imputed with the nominal date/time post T0. This method is referenced as the WLOCF method.

PI scores reported will be displayed in data listings, with LOCF-imputed scores, and WLOCF-adjusted PI scores flagged. Where timing information is missing for administration of rescue medication, the record will be excluded from the WLOCF analysis.

All SPI endpoints and PI outcomes except the PI/MME int grated rank difference will be analyzed using 2 sets of data: PI scores with missing values imputed by LOCF only and PI scores adjusted for the use of rescue medications using WLOCF.

7.8.2 Other Assessments

Any missing nausea assessment scores will be imputed using the LOCF method as described in Section 7.8. The scheduled nausea scores will be displayed in a data listing, with LOCF imputed records clearly indicated.

Missing data for the PGA of pain control will be imputed as a non-responder.

7.9 Safety Analysis

Baseline values will be taken from Day 0 prior to surgery, if available, or otherwise from the most recent values available prior to Day 0. Safety summaries will be presented as described in Section 7.1. Summaries of safety data will include all scheduled visits; unscheduled visits will be included only in safety data listings, unless otherwise specified.

7.9.1 Adverse Events

Adverse events will be classified as treatment-emergent adverse events (TEAEs) if the AE has an onset date/time greater than or equal to the start date/time of the administration of the intra-operative study drug. Events reported with a partial onset date (e.g., month and year are reported but the day is missing) will be considered to be treatment-emergent if it cannot be confirmed that the event onset was prior to administration of study drug based on the available date entries. Except where noted, summary tables for AEs will include only TEAEs. However, all AEs will be listed and pre-treatment AEs will be flagged. Adverse events will be coded using MedDRA (Version 19.1) and the duration of each AE reported on data listings. The following AE summaries will be tabulated and provided as tables/listings:

- An overall summary of the number of TEAEs, the number of subjects with at least one TEAE, the number of serious TEAEs, the number of subjects with serious TEAEs, the number of subjects with drug-related TEAEs, the number of subjects with severe TEAEs, the number of subjects with fatal TEAEs, and the number of subjects with TEAEs leading to premature discontinuation.

- TEAEs by SOC in internationally agreed order, PT in descending frequency according to total incidence (alphabetically for ties) in the highest HTX-011 dose group, and maximum severity
- TEAEs by PT in descending frequency according to the total incidence (alphabetically for ties) in the highest HTX-011 dose group
- TEAEs by SOC in internationally agreed order and PT in descending frequency according to total incidence (alphabetically for ties) in the highest HTX-011 dose group
- TEAEs leading to premature study discontinuation by SOC in internationally agreed order and PT in descending frequency according to total incidence (alphabetically for ties) in the highest HTX-011 dose group
- Study drug-related TEAEs by SOC in internationally agreed order and PT in descending frequency according to total incidence (alphabetically for ties) in the highest HTX-011 dose group
- Opioid-related TEAEs by SOC in internationally agreed order and PT in descending frequency according to total incidence (alphabetically for ties) in the highest HTX-011 dose group

Opioid-related AEs defined by the Sponsor are AEs that code to any of the following PTs: Nausea, Vomiting, Constipation, Pruritus, Somnolence, Respiratory depression, or Urinary retention throughout the study. For a given SOC and PT, a subject will be counted once even if the subject has experienced multiple episodes for that particular SOC and PT. AE tables will be organized as described in Section 7.1.

7.9.2 Nausea Assessments

Nausea is measured on a scale of 0-10, with 0 indicating no nausea and 10 indicating the worst nausea imaginable. Assessments of nausea at each time point (6, 24, 48, and 72 hours post-treatment, early termination) will be analyzed using ANCOVA/ANOVA as described in Section 7.7.1. Results reported will include sample size, mean (SD), SEM, LSMD, 95% CI for LSMD, and p-value. Mean nausea scores over time will be plotted for the groups described in Section 7.7.

7.9.3 Clinical Laboratory Tests

Observed values at each time point and change from baseline (Day 0) will be summarized without formal statistical testing. Shift tables (i.e., low-normal-high at baseline versus low-normal-high at follow-up in a 3-by-3 contingency table) will be provided to assess changes in laboratory values from Day 0 at baseline to each follow-up time point. The lowest post-baseline value, and the highest post-baseline value will be included in summary tables, and will incorporate data from both scheduled and unscheduled visits. The data listing of labs will flag values below and above the normal reference ranges.

7.9.4 Vital Sign Measurements

Observed values at each time point and change from baseline (Day 0) will be summarized without formal statistical testing. The count and percentage of subjects who meet the abnormal criteria (Table 7) at any post-baseline visit will be summarized, using data collected at scheduled and unscheduled visits. In addition, a table listing subjects with abnormal changes from baseline will be provided, over all scheduled and unscheduled visits.

Table 7: Criteria for Abnormal Vital Signs

Vital Sign	Low	High
Heart Rate	≤ 50 bpm and ≥ 15 bpm decrease from baseline	≥ 120 bpm and ≥ 15 bpm increase from baseline
SBP	≤ 90 mmHg and ≥ 20 mmHg decrease from baseline	≥ 160 mmHg and ≥ 20 mmHg increase from baseline
DBP	≤ 50 mmHg and ≥ 15 mmHg decrease from baseline	≥ 100 mmHg and ≥ 15 mmHg increase from baseline

7.9.5 Electrocardiograms

The count and percentage of subjects with abnormal ECG findings at each time point will be summarized without formal statistical testing. Shift tables (i.e., normal or abnormal-not clinically significant [NCS] at baseline versus normal, abnormal-NCS, or abnormal-clinically significant [CS] at follow-up) will be provided to assess changes in ECG status from Day 0 at baseline to each follow up time point. In addition, a table will be provided listing subjects with any change from normal or abnormal-NCS at baseline to CS abnormal after baseline.

7.9.6 Physical Examinations

Physical exam findings will be presented in a data listing.

7.9.7 Wound Healing Assessments

The count and percentage of subjects with abnormal healing of the wound site at each time point will be summarized without formal statistical testing.

7.9.8 Bupivacaine Toxicity

Assessments of symptoms associated with bupivacaine toxicity include perioral tingling, strange taste, muscle twitching, ringing in the ears, seizure, bradycardia, and cardiac arrest. Count and percentage of subjects with each symptom will be summarized. Listings by subject and by time/visit will be provided, with a verbatim description of any symptoms present, and a determination on the clinical significance of the symptom.

7.9.9 Liver Function

Results from liver function testing performed at any post-baseline scheduled and unscheduled visits that meet the criteria presented in Table 8 will be summarized with counts and percentages, and subjects with abnormal liver function test results will be presented in a separate listing:

Table 8: Criteria for Abnormal Liver Function

Test	Criteria for Abnormality
ALT (SGPT)	≥ 3 times the upper limit of normal (ULN)
AST (SGOT)	≥ 3 ULN
Total Bilirubin	≥ 2 ULN
ALP	≥ 1.5 ULN

ALP	≥ 2 ULN
ALT and AST	≥ 3 ULN
ALT and Total Bilirubin	ALT ≥ 3 ULN and total bilirubin ≥1.5 ULN
AST and Total Bilirubin	AST ≥ 3 ULN and total bilirubin ≥ 1.5 ULN
Hy's Law	(ALT or AST ≥ 3 ULN) and ALP <2 ULN and total bilirubin ≥ 2 ULN

7.9.10 Neurological Exam

Date of exam, reason not done, if applicable, and a verbatim description of any clinically significant abnormalities will be provided in data listings.

8 INTERIM ANALYSIS

An interim analysis will be conducted when Part A is complete in order to determine the optimal technique of administration of study drug for Part B and P rt C. Administrative interim analyses will be performed in order to determine additional formulations, dosage, or administration techniques to be investigated.

9 CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

SPI over 24 hours, SPI over 48 hours, SPI over 72 hours, and SPI over 96 hours will also be analyzed using a Wilcoxon Rank Sum test for integrated ass ssment of PI scores and rescue opioid use as an exploratory analysis.

AUCs of PI scores over time were added s an exploratory endpoint and will be analyzed using ANOVA, 1 set with LOCF imputation and another with WLOCF imputation.

The analysis of number of times rescue medication used during the treatment phase was removed as multiple kinds of rescue medications were allowed for rescue.

One subject who received HTX-011-49 by injection into surgical wound also received sufentanil from another trial. This subject was excluded from the mITT Population, and included in the Safety Population, effective 12MAY2016.

Reporting of PONV risk factors was removed as these data were not explicitly collected.

Method for time to first rescue medication analysis was changed to Wilcoxon test.

Method of PI score collection stratification factor was added to Part A PI score analyses.

Tabulation of subjects in each pain control category was replaced by a responder analysis for the percentage of subjects reporting 'Very Good' or 'Excellent' pain control.

Analysis of the proportion of subjects requiring rescue medication was changed to an analysis of the proportion of opioid-free subjects.

Additional collection of vital signs at time points 8 and 10 hours post-treatment included in listings.

Nausea was changed from an efficacy outcome to a safety outcome.

10 REFERENCES

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LIST OF TABLES, FIGURES AND DATA LISTINGS

List of Tables

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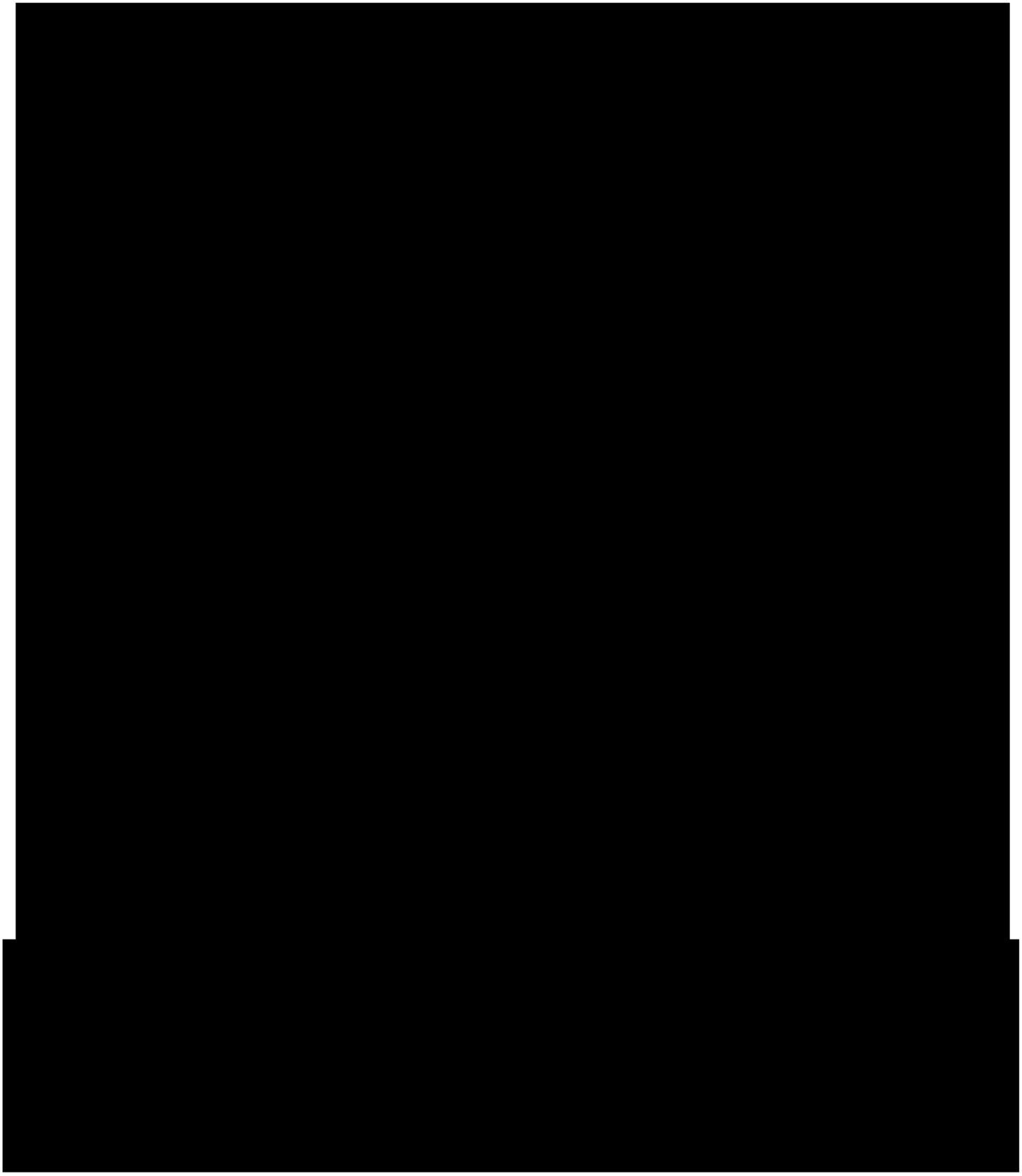
List of Figures



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Subject Data Listings

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