Document Type:	Statistical Analysis Plan
Official Title:	A Phase 2, Randomized, Controlled Evaluation of the Efficacy and Safety of HTX-011 or HTX-002 for Post-Operative Analgesia Following Abdominoplasty Surgery
NCT Number:	NCT02689258
Document Date:	23-Aug-2017

Statistical Analysis Plan

Heron Therapeutics, Inc.

HTX-011-C2015-203

A Phase 2, Randomized, Controlled Evaluation of the Efficacy and Safety of HTX-011 or HTX-002 for Post-Operative Analgesia Following Abdominoplasty Surgery

Protocol Version: 12 06 February 2017

Sponsor: **Heron Therapeutics, Inc.**
4242 Campus Point Court, Suite 200
San Diego, CA 92121

Version: **2 0**

Date of Creation: **25 July 2017**

Last Updated: **23 August 2017**

Signature Page

APPROVED BY:

[redacted]

[redacted]
Date

VP, Clinical Research
Heron Therapeutics

[redacted]

[redacted]
Date

Director, Biostatistics and Programming
Heron Therapeutics

[redacted]

[redacted]
Date

Biostatistician II
Agility Clinical, Inc.

[redacted]

[redacted]
Date

Principal Biostatistician
Agility Clinical, Inc.

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ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
BMI	body mass index
BPM	beats per minute
CRF	case report form
CSR	clinical study report
DBP	diastolic blood pressur
ECG	electrocardiogram
HIV	human immunodeficiency virus
ITT	Intent-to-Treat
IV	intravenous
LOCF	last observ tion carried forward
LSMD	least squares mean difference
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intend-to-Treat
PGA	Patient Global Assessment
PI	pain intensity
PK	pharmacokinetic
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SOC	System Organ Class

Abbreviation	Definition
SPI	summed pain intensity
SpO_2	peripheral oxygen saturation
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VAS	Visual Analog Scale
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-C2015-203 titled "A Phase 2, Randomized, Controlled Evaluation of the Efficacy and Safety of HTX-011 or HTX-002 for Post-Operative Analgesia Following Abdominoplasty Surgery". 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	04 Dec 2015	Original protocol submitted to FDA
Protocol Version 2	08 Jan 2016	Original protocol submitted to IRB and submitted to sites for study initiation visits on 13 January 2016
Protocol Version 3	21 Jan 2016	Protocol revised to address FDA reviewer comments.
Protocol Version 4	30 Mar 2016	Added HTX-011 56 formulation doses; removed HIV, hepatitis B and hepatitis C testing for inclusion criteria; added option of offering subjects acetaminophen 1000 mg for PI scores that are ≤ 4
Protocol Version 5	29 Apr 2016	Added the option to the protocol that additional subjects may be enrolled to further confirm the tolerability profile of a given Cohort.
Protocol Version 6	08 Jun 2016	Added more optional cohorts in Part B. Study drug administration instructions were clarified and a PK blood draw was added to determine bupivacaine levels if there was an AE associated with neurologic or cardiac symptoms.
Protocol Version 7	08 Aug 2016	Added hourly ECGs from 1 hour to 6 hours post surgery in Part B, and clarified combined infiltration and instillation dosing technique for mini-abdominoplasty.
Protocol Version 8	28 Sep 2016	Study drug administration instructions added for combination infiltration and instillation in subjects undergoing complete abdominoplasty.
Protocol Version 9	30 Nov 2016	Part C added to evaluate HTX-011-56 compared with bupivacaine HCl in subjects undergoing complete abdominoplasty without liposuction. Optional Part D added to evaluate HTX-011-56 compared with normal saline in subjects undergoing complete abdominoplasty with liposuction.
Protocol version 10	10 Jan 2017	Optional parts E through H added.
Protocol Version 11	18 Jan 2017	Optional Parts E through H updated, optional Part I added.
Protocol Version 12	06 Feb 2017	Added option of administering HTX-011-56 via instillation, injection, or a combination of injection and instillation, in Parts D through I; added bupivacaine HCl cohort to optional Part E; removed HTX-56 200mg and bupivacaine HCl cohorts from optional Part I; revised sample sizes for Parts B, E, and I.

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

This SAP was based on protocol version 12, issued 06 February 2017 and was prepared prior to database lock to provide full details to be included in the clinical study report (CSR). Revisions can be made to this SAP while the study is ongoing, but it must be finalized before the database is locked. Any changes between the statistical section 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.

This is a Phase 2, randomized, controlled evaluation of the efficacy and safety of up to four dose levels of two HTX-011 formulations and one dose level of HTX-002 in subjects following abdominoplasty surgery. The study will also evaluate different local administration techniques (injection, instillation, and a combination of the 2 techniques) on the analgesic efficacy of HTX-011. Efficacy assessments are intended to characterize the analgesic effect time curve and the magnitude of analgesic effect of HTX-011 in comparison with saline or HTX-002 or bupivacaine HCl. In addition, the study will further characterize the safety and PK profiles of bupivacaine and meloxicam in the HTX-011 formulations and the PK profile of bupivacaine in the HTX-002 formulation.

2 STUDY OBJECTIVES

The primary objective is to evaluate the efficacy and duration of analgesia following administration of HTX-011 or HTX-002 formulations.

The secondary objectives are as follows:

- To determine the safety and tolerability of HTX-011 and HTX-002 formulations.
- To determine the optimum study drug administration technique.
- To evaluate the PK profiles of bupivacaine and meloxicam in HTX-011 formulations and the PK profile of bupivacaine in HTX-002 over 120 hours after study drug administration (a separate SAP).
- To evaluate the analgesic effects of HTX-011 and HTX-002 formulations over various intervals using a series of secondary efficacy endpoints for pain intensity.
- To assess the effects of HTX-011 and HTX-002 formulations on wound healing at 48 hours, 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 remain pain free over time.

3 STUDY DESIGN

3.1 Overall Study Design

This is a Phase 2, randomized, multicenter, observer-blind, controlled evaluation of the efficacy and safety of HTX-011 and HTX-002 for post-operative analgesia following abdominoplasty surgery in approximately 275 adult subjects undergoing abdominoplasty. The total duration of this study for each

subject will be a maximum of 88 days that comprise a 28-day screening period, 72 hours in-house treatment period, and 25 days post-treatment period involving 4 post-treatment visits to the clinic. Subjects will also receive a phone call from the study site on Day 60. Subjects at least 18 years of age requiring abdominoplasty 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 American Society of Anesthesiologists classification, medical history and prior/concomitant medications, vital sign measurements, physical examination, clinical laboratory tests, drug and alcohol screen tests, neurologic exam, 12-lead electrocardiogram (ECG), and serum pregnancy test (as appropriate). Post-operative nausea and vomiting (PONV) risk factors will be assessed, and subjects will be trained on providing pain assessments.

Part A of the study is the dose-escalation phase of the study. Subjects enrolling into Part A will be randomized (2:1; active:saline) into each cohort to receive any one of HTX-011-49, HTX-011-56, or normal saline. For study Part A, the surgical procedure will be restricted to a mini-abdominoplasty, i.e., it will exclude liposuction and/or repositioning of the umbilicus. The primary objective of Part A will be to evaluate the efficacy and duration of analgesia following administration of two HTX-011 formulations (HTX-011-49 and HTX-011-56) in a range of doses. An optimal formulation/dose will be selected from Part A, and the identified formulation/dose will be utilized for subjects who will be enrolled into Part B. Part B will evaluate HTX-011 compared with HTX-002 or saline. The surgical procedure allowed will be broadened to accommodate an abdominoplasty that can include liposuction and/or repositioning of the umbilicus. Part C will include subjects undergoing complete abdominoplasty without liposuction. Approximately 30 subjects will be randomized to 1 of 2 cohorts in a 1:1 ratio (active HTX-011-56:Bupivacaine HCl). Part I will include subje ts undergoing complete abdominoplasty without liposuction. Approximately 35 subjects will be randomized to 1 of 2 cohorts in a 6:1 ratio (active:saline).

On the day of surgery (Day 0), after having been reassessed for eligibility, subjects will undergo abdominoplasty under a standardized general anesthesia regimen. No epidural or spinal anesthesia will be allowed; nor will any local anesthetic infiltration other than the administration of the IP or control be permitted. No prophylactic antiemetic, local anesthetics, or analgesic medications are allowed other than those used with general anesthesia. A single dose of study drug (HTX-011-49, HTX-011-56, HTX-002, Bupivacaine HCl, or saline placebo, according to a randomization schedule) will be administered intra-operatively by local infiltration, instillation, or combined infiltration and instillation. Start and stop time of dosing will be recorded. Dosing stop time will be considered Time 0.

Following the completion of surgery and immediate postoperative recovery stay, subjects will be transferred to the post-anesthesia care unit and, when appropriate, to the clinic floor. Subjects will stay in the post-anesthesia care unit for 72 hours after completion of the administration of study medication (i.e., T0), prior to discharge from the study center. Each subject will return to the study center 96 hours elapsed time (T96) after T0 to complete additional assessments. After completion of the 96-hour assessments, subjects will be scheduled to return to the study center on Days 10 and 28 for study specific assessments; each subject will be asked to return to the study center specifically for a PK blood sample draw at 120 hours (T120) post-T0. Subjects will also receive a phone call from the study site on Day 60 to collect follow-up information on post operative pain and whether any pain medications were used.

3.2 Treatment and Schedule of Assessments

Efficacy assessments will include pain intensity (PI) scoring using the Visual Analog Scale (VAS), use of rescue medication, and Patient Global Assessment (PGA) of pain control. Blood samples will be obtained

to assess meloxicam and bupivacaine pharmacokinetics out to 120 hours post-administration of study drug. Safety assessments will include adverse events (AEs), concomitant medications, physical examinations, neurologic assessments (including neurological/cardiovascular assessments for potential bupivacaine toxicity), vital sign measurements, clinical laboratory tests, ECGs, nausea assessments (using a VAS for nausea), and wound healing assessments and photographs of the surgical invention area. Dosing and formulation cohorts are outlined in Table 2, and the planned schedule of study procedures is outline in Table 3, Table 4, Table 5 and Table 6.

Table 2: Cohorts for Each Part

Part A: (mini-abdominoplasty)

Cohort A: 200 mg (6.84 mL) HTX-011-49 via injection administration / 6.84 mL saline (2:1)
Cohort E: 200 mg (6.84 mL) HTX-011-56 via injection administration / 6.84 mL saline (2:1)
Cohort F: 400 mg (13.68 mL) HTX-011-56 via injection administration / 13.68 mL saline (2:1)
Cohort G: 600 mg (20.52 mL) HTX-011-56 via injection administration / 20.52 mL saline (2:1)
Cohort H: Saline solution injection

Part B

Cohort D: 13.68 mL saline solution via injection administration
Cohort I: 400 mg (13.68 mL) HTX-011-56 via instillation and i jection combination administration (mini-abdominoplasty)
Cohort J: 400 mg (13.68 mL) HTX-002 via instillation and injection combination administration (mini-abdominoplasty)
Cohort K: 13.68 mL saline solution via injection adm nistration (mini-abdominoplasty)
Cohort L: 400 mg (13.68 mL) HTX-011-56 via instillati and injection combination administration for complete abdominoplasty
Cohort M: 13.68 mL saline solution via injection dministration for complete abdominoplasty

Part C

Cohort N: 400 mg (13.68 mL) HTX-011-56 via instillation for complete abdominoplasty without liposuction
Cohort O: 40 mL 0.25% Bupivacaine H l via injection for complete abdominoplasty without liposuction

Part I

Cohort U1: 300 mg HTX-011-56 via instillation and injection combination for complete abdominoplasty without liposuction
Cohort U2: 10.26 mL saline solution via injection for complete abdominoplasty without liposuction

Table 3: Screening

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

[a] Laboratory tests will include hematology and chemistry. 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 test must be obtained after resting (seated/reclined) for ≥ 5 minutes.
[c] Concomitant medications taken within 14 days before dosing will be recorded on the eCRF.
[d] SAEs will be reported if considered related to study participation.
[e] PE will include weight, height, and BMI.

Table 4: Day 0 Prior to Surgery and Surgery

	Day 0	
	Prior to Surgery	**Surgery**
Eligibility Assessment	X	
Demographics and Medical History	X	
Physical Examination [c]	X	
Urine Pregnancy Test (female subjects of child bearing potential only)	X	
Urine Drug Screen	X	
Alcohol Breath Test	X	
Clinical Laboratory Tests [a]	X [d]	
Vital Signs [b]	X	
12-lead ECG	X [e]	
Subject Pain Training	X	
Blood Draw for PK	X [d]	
Neurologic Exam	X	
Abdominoplasty Procedure		X
Study Drug Administration		X
Prior and Concomitant Medication	X	X
Serious Adverse Event Monitoring [f]	X	X
Post-surgical Photograph of Abdominal Wound		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.
[e] If screening 12-lead ECG was done > 7 days prior to Day 0.
[f] 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 must be reported.

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

			Day 0 to 5																						
			Post Study Drug Administration Time Points (hrs)																						
	0.5	1[f]	1.5	2	2.5	3	4	5	6	8, 10, 12	14	18	24	30	36	42	48	54	60	72	78	84	96[h]	120[h]
Confinement	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Physical Examination [c]																				X[g]				
Clinical Laboratory Tests [a]																				X				
Vital Signs [b]		X		X			X		X	X (hr 12 only)		X	X		X		X		X	X			X	
12-lead ECG		X[i]		X[i]		X[i]	X[i]	X[i]	X[i]				X				X			X			X	
Pain Intensity (PI) At Rest		X		X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pain Intensity (PI) on Movement							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[e]			X[e]	
PK Blood Draws (± 15 min 1 hr through 36 hr, ± 1 hr 48-72 hrs, ± 4 hrs 96 + 120 hrs)	X	X	X	X	X	X	X	X	X	X		X	X	X	X		X		X	X			X	X
Nausea Assessment									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	X
Assessment of Wound Healing																	X			X				
Abdominal Photographs																	X			X				
Neurologic Exam and Assessment													X				X			X				
Adverse Event 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	X

[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 28 study visit. SAEs will be monitored from screening 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.
[h] ± 4 hours, except for vital signs, which will be measured at ± 2 hours.
[i] Parts B, C, D, E, F, G, H, and I.

Table 6: Post Study Medication Administration (Follow-Up)

	Post Study Drug Administration Time Points			Early Termination
	Day 10 (± 2 days)	Day 28 (± 2 days)	Day 60 (± 7 days)	
Physical Examination	X[c]			X[e]
Clinical Laboratory Tests [a]				X
Vital Signs [b]	X			X
12-lead ECG	X			X
Pain Intensity (PI)				X[e]
PGA of Pain Control				X[e]
Nausea Assessment				X[e]
Concomitant Medications	X	X		X
Assessment of Wound Healing	X	X		X
Abdominal Photographs	X	X		X
Neurologic Exam and Assessment				X[f]
Adverse Event Monitoring [d]	X	X		X
Phone Call [g]			X	

[a] Laboratory tests will include hematology and chemist y.
[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 (se ted/supine) for ≥ 5 minutes.
[c] Physical examination will include weight only, bu not height or BMI. Weight not required at 72 hour exam.
[d] AEs will be monitored after administrat on of study medication through the Day 10 study visit. SAEs will be monitored through Day 28.
[e] PI, PGA, and nausea assessments are nly required at the Early Termination Visit if the subject discontinues before T96.
[f] Neurologic examination and assessment is only required at the Early Termination Visit if the subject discontinues before T72.
[g] Subjects will receive a phone call from the study site on Day 60 (±7 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) 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) score 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 consumption over 24, 48, 72, and 96 hours post-treatment, by each analgesia, opioid and non-opioid

5. Percentage of subjects who have not taken opioid rescue medication over time by time point and comparisons at 24, 48, 72 and 96 hours

6. Percentage of subjects who are pain free (VAS score≤ 1) over time by time point and comparisons at 24, 48, 72 and 96 hours after study drug administration.

[redacted]

4.2 Safety Endpoints

The safety endpoints include:

- AEs and serious AEs (SAE)s
- Opioid related AEs
- Nausea assessment
- Wound assessments of the surgical intervention area
- Vital signs abnormal values
- Neurological examinations
- Shift of clinical laboratory tests, including routine blood chemistry, liver function tests, and hematology
- Shift in ECG findings
- 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 causal 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 report 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 the VAS for Nausea. Assessment of nausea will be completed by subjects at the following time points: 6, 24, 48, nd 72 hours within a ± 15 minute window and at the time of early discontinuation, if it should occur and only if a subject is discontinued prior to T96.

4.2.3 Vital Signs

Vital signs will be obtained after resting (seated/s pine) 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, 12, 18 24, 36 48, 60, 72, and 96 hours and at the Day 10 visit, and at the time of early termination, with actual times recorded.

4.2.4 Laboratory Parameters

The clinical laboratory and oth r 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, phosphate, calcium, glucose, bicarbonate, lactate dehydrogenase

In addition, urine drug screening and breath 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 ECG

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 (if screening ECG was done > 7 days prior to

Day 0), at 24, 48, 72, 96 hours post-treatment, and at the Day 10 visit, and at the time of early termination, if applicable.

For subjects enrolled in Parts B through I, additional ECGs will be performed post-T0 time point at 1, 2, 3, 4, 5, and 6 hours. Data from the 12-lead ECG will be used to exclude a subject from participation in the study at screening or Day 0 if (s)he has a clinically significant abnormal ECG.

ECG intervals, notably QTc, will be analyzed in the context of time matching to peak PK values. The vendor (Biomedical Systems) will provide a separate SAP in ECG and PK exposure for Part B, C and I subjects.

4.2.6 Wound Healing Assessments

The surgical wound will be assessed 48 and 72 hours post-treatment, on Days 10 and 28 post-treatment and at time of early termination (if applicable). Results are recorded as Normal or Abnormal, with a verbatim description of any abnormalities. Specific indications of wound healing (wet[ness], dehiscence, erythema, presence of drainage, type of drainage, bruising, and swelling) will be assessed and results for each indication recorded. A photograph of the surgical in ervention area will be taken immediately after surgery, and at 72 hours, Days 10 and 28 and at time of early termination (if applicable).

4.2.7 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 Base 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 the sponsor for appropriate action and resolution.

6 POPULATIONS DEFINED

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

Efficacy Dataset: The efficacy dataset will include all subjects who are randomized to receive study medication and have recorded at least one scheduled post dosing PI score. This dataset is noted as the modified Intend-to-Treat (mITT) set.

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

6.1 Sample Size Determination

Sample sizes for this study were 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 conformance with guidelines specified by the ICH guideline *Statistical Principals for Clinical Trials* (E9) (1999).

Summary tables will be organized by surgical procedure, with mini-abdominoplasty summarized separately from complete abdominoplasty (without liposuction). Part A, Part B Step 1, and Part B Step 2 will be summarized together (mini abdominoplasty). Part B Step 3, and Parts C and I will be summarized together (complete abdominoplasty). Disposition, demographics, protocol deviation, and AE summary tables will be grouped as follows:

- Mini Abdominoplasty (only for disposition, demographics, protocol deviations, and AE tables)
    1. Saline Placebo 6 84 20.52 mL)
    2. HTX-002 400 mg (13.68 mL)
    3. HTX-011-49 200 mg (6.84 mL)
    4. HTX-011-56 200 mg (6.84 mL)
    5. HTX-011-56 400 mg (13.68 mL)
    6. HTX-011-56 600 mg (20.52 mL)
    7. HTX-011-56 Total
    8. Total (not included on AE tables)
- Mini Abdominoplasty (all tables except protocol deviations)
    1. Saline Placebo (6.84-20.52 mL)
    2. HTX-002 400 mg Combination (13.68 mL)

3. HTX-011-49 200 mg Injection (6.84 mL)
4. HTX-011-56 200 mg Injection (6.84 mL)
5. HTX-011-56 400 mg Injection (13.68 mL)
6. HTX-011-56 400 mg Combination (13.68 mL)
7. HTX-011-56 400 mg Total (13.68 mL)
8. HTX-011-56 600 mg Injection (20.52 mL)

- Complete Abdominoplasty (all tables)
  1. Saline Placebo (10.26-13.68 mL)
  2. Bupivacaine HCl 100 mg (40 mL)
  3. HTX-011-56 300 mg (10.26 mL) Combination
  4. HTX-011-56 400 mg (13.68 mL) Combination
  5. HTX-011-56 400 mg (13.68 mL) Installation
  6. HTX-011-56 400 mg (13.68 mL) Total
  7. Total (only included on disposition, demographics, and protocol deviation tables)

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 sample 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). Rounding conventions are described below.

- 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 7.8.1), no imputation will be conducted 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 which occurs prior to the time of completed application of study drug would be associated with a negative time calculation, while a study event which occurs after time of completed application of study drug would be a positive time calculation.

7.2 Analysis Datasets

ITT Analysis Population: The ITT dataset will include all subjects who are randomized.

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

Safety Population: The safety set will include all treated subjects 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 protocol violations in the Safety Population will be determined and appropriately

categorized prior to database lock. The count and percentage of subjects by category will be presented for the groups described in Section 7.1. A listing of subjects who were excluded from the efficacy analysis will be provided.

7.4 Demographic and 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. A listing of PONV risk factors for each subject (obtained at Screening) will be provided.

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. Frequency counts and percentages to summarize subjects reporting m dical history by SOC and PT will be presented. Subjects reporting more than one 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 1, 2016). Prior medications are defined as medications with a stop date occurring before Day 0 (surgery date). Concomitant medications are defined as medications that are ongoing on Day 0 or with a start date occurring on or after Day 0. Medications with start and stop dates which bracket Day 0, 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.

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 concomitant medications within 72 hours (T0-T72) 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

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 reported in hours. 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, Part B Step 1 and Part B Step 2 will be analyzed separately from Part B Step 3, Part C, and Part I. For treatment comparisons using pooled data, data from treatment groups will be combined prior to conducting the statistical comparison.

All efficacy figures will be structured according to the following groups:

Mini Abdominoplasty-

- HTX-011-56 200 mg (Cohort E)
- Pooled HTX-011-56 400mg (Cohorts F and I)
- HTX-011-56 600 mg (Cohort G)
- HTX-002 400 mg (Cohort J)
- Saline Placebo (Cohorts D, H, and K)

Complete Abdominoplasty-

- Saline Placebo (Cohorts M and U2)
- Bupivacaine 100 mg (Cohort O)
- HTX-011-56 300 mg (U1)
- Pooled HTX-011-56 400 mg (Cohorts L and N)

7.7.1 Primary Efficacy Endpoint Analysis Methods

The primary analysis set is the mITT Population. The primary efficacy endpoint is the $SPI_{0\text{-}24}$, with last observation carried forward (LOCF) imputation of missing data 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. The following comparisons will be made for all efficacy endpoints:

Mini Abdominoplasty-

- HTX-011-49 200 mg (6.84 mL) injection vs. Saline Placebo (6.84-20.52 mL)
- HTX-011-56 200 mg (6.84 mL) injection vs. Saline Placebo (6.84-20.52 mL)
- HTX-011-56 400 mg (13.68 mL) injection vs. Saline Placebo (6.84-20.52 mL)
- HTX-011-56 400 mg (13.68 mL) injection vs. HTX-002 400 mg (13.68 mL)
- HTX-011-56 400 mg (13.68 mL) combo vs. Saline Placebo (6.84-20.52 mL)

- HTX-011-56 400 mg (13.68 mL) combo vs. HTX-002 400 mg (13.68 mL)
- HTX-011-56 400 mg (13.68 mL) pooled vs. Saline Placebo (6.84-20.52 mL)
- HTX-011-56 400 mg (13.68 mL) pooled vs. HTX-002 400 mg (13.68 mL)
- HTX-011-56 600 mg (20.56 mL) injection vs. Saline Placebo (6.84-20.52 mL)

Complete Abdominoplasty-

- HTX-011-56 300 mg (10.26 mL) Instillation vs. Saline Placebo (10.26-13.68 mL)
- HTX-011-56 300 mg (10.26 mL) Instillation vs. Bupivacaine HCl 100 mg (40 mL)
- HTX-011-56 400 mg (13.68 mL) combo vs. Saline Placebo (10.26-13.68 mL)
- HTX-011-56 400 mg (13.68 mL) combo vs. Bupivacaine HCl 100 mg (40 mL)
- HTX-011-56 400 mg (13.68 mL) Instillation vs Saline Placebo (10.26-13.68 mL)
- HTX-011-56 400 mg (13.68 mL) Instillation vs Bupivacaine HCl 100 mg (40 mL)
- HTX-011-56 400 mg (13.68 mL) pooled vs. Saline Placebo (10.26-13.68 mL)
- HTX-011-56 400 mg (13.68 mL) pooled vs. Bupivacaine HCl 100 mg (40 mL)

SPI:

PI will be assessed by the subject for their current pain according to VAS where 0 equates to no pain and 10 equates to the worst pain imaginable. PI scores will be measured in two ways: on movement and at rest. There will be a ± 15 minute window allowed for the collection of each PI assessment. 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 performed by subjects at home using a patient diary.

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. A PI assessment will first be obtained at rest. A second PI assessment will be obtained after the subject sits up. 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. This is referenced as the per protocol method. PI will also be assessed within 5 minutes prior to administration of rescue analgesia, and at the time of early termination in the event it occurs, and only if the subject is discontinued prior to T96. 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, $SPI_{0\text{-}24}$ will be calculated as below:

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

Where PI_i denoted the pain intensity score at hour i.

At movement PI scores from hours 4-72 will be used for analysis, the at rest PI scores for these time points will only be listed. The 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. 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 alternative 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 Methods

7.7.2.1 Sum of Pain Intensity

SPI over various other time intervals (SPI_{0-48}, SPI_{0-72}, SPI_{0-96}, SPI_{0-6}, SPI_{0-12}, $SPI1_{2-24}$, SPI_{24-48}, SPI_{48-72}, and SPI_{72-96}) will be analyzed by 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 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, SE, 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.

7.7.2.2 Pain Intensity

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, SE, 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 VAS score less than or equal to 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 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, p-values, and exact unconditional 95% CIs for the difference between the groups based on the score statistic (Chan and Zhang, 1999) will be provided for summaries.

The percentage of subjects 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.

7.7.2.3 Patient Global Assessment

Pain control is 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 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, percentage 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.

7.7.2.4 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 exact u conditional 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 their 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 their 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 of the study, 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 phase of the study, then the subject will be considered censored at 96 hours. Kaplan-Meier curves will be presented for groups as described in Section 7.7, plotted as 1-S(t). Time to administration of first opioid rescue medication will be analyzed in the same manner as time to first administration of any rescue medication.

The count and percentage of subjects in the following categories will be summarized in tables:

1. Those who received only opioid rescue medications
2. Those who received only non-opioid rescue medications

3. Subjects who received both types of rescue medication but were administered opioid analgesics first

4. Subjects who received both types of rescue medication but were administered non-opioid analgesics 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 conversion include, but are not limited to, the medications in Table 7 (complete table will be provided in the CSR):

Table 7: Analgesic Windows and Morphine Milligram Equivalencies

Medication	Route	Window (Hours)	MME Factor
CODEINE	PO	6	0.05
DILAUDID	PO	4	1.33
HYDROCODONE	PO	6	0.4
MORPHINE	IV	4	1
MORPHINE	PO	4	0.33
MORPHINE	IM	4	1
OXYCODONE	IV	4	1
OXYCODONE	PO	6	0.5
TRAMADOL	ORAL	6	0.04

Average daily use and total use of rescue m dications will be calculated for each of the following periods: 0 to 24, 0 to 48, 0 to 72, and 0 to 96 hours post study medication administration. Subjects who did not use the specific rescue medication during a peri d 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 summarized separately by type of rescue medication (acetaminophen, morphine or oxycodone), and combined opioid use. Between groups comparisons of total opioid use will be performed for each time period using ANOVA, as described in Section 7.7.1. Results reported will include sample size, mean (SD), LSMD, 95% CI for LSMD, and p-value.

[redacted]

[redacted]

7.8 Data Imputation and Adjustment

7.8.1 Pain Intensity Assessments

Any missing PI score 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. For wLOCF imputation, PI scores recorded or imputed by LOCF 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 for wLOCF are as follows:

All subjects are expected to assess their post-operative PI according to the pain intensity schedule; this PI is referenced to as the scheduled PIs. 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. Acetaminophen has an assigned window of 6 hours, and the analgesic windows for specified rescue opioid analgesics are listed in Table 7. When the assessment of a scheduled PI is after the start time recorded for the 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 window (replace 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 worst PI score, it is not replaced. 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 date/time information is missing for a PI score, scheduled hours from dose end time will determine timing. 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 Integrated Rank Difference will be analyzed using two 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 on 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 are 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

AEs 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 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 application 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. AEs 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 study drug-related TEAEs, TEAE by severity and serious TEAE by severity, 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

- Study drug-related TEAEs by SOC in internationally agreed order and PT 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 according to total incidence (alphabetically for ties) in the highest HTX-011 dose group

Opioid related AEs are AEs that code to any of the following PTs: Nausea, Vomiting, Constipation, Pruritus, Somnolence, Respiratory depression, or Urinary retention. 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 VAS 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 ANOVA as described in Section 7.7.1. Results reported will include sample size, mean (SD), 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 change from baseline to the lowest post-baseline value, and the change from baseline to the highest post-baseline value will be included on summary tables, and will incorporate data from both scheduled and unscheduled visits. The data listing of laboratory values will flag values below and above the normal 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 8) 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 8: 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 Physical Examinations

Physical exam data will be presented in a data listing.

7.9.6 Electrocardiograms

The count and percentage of subjects with abnormal ECG findings at each time point will be summarized without formal statistical testing. Shift tables (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 clinically significant abnormal after baseline. Subject in Parts B, C, and I will have additional ECGs performed at 1, 2, 3, 4, 5, and 6 hours after administration of study medication.

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. Assessments of symptoms associated with wound healing include wet(ness), dehiscence, erythema, presence of drainage, type of drainage, bruising, and swelling. Findings from wound healing assessments will be listed per subject, per time point, and will include descriptions of any abnormalities found. A per subject listing will be provided for photographs taken at time points 48, 72, and 96 hours, and at Days 10 and 28 to visually document wound healing. Records include date and time of photograph, whether or not photographs were uploaded, location of the surgical site, and reason why photographs were not taken, if applicable.

7.9.8 Liver Function

Results from liver function tests performed at any post-baseline scheduled and unscheduled visits that meet the criteria presented in Table 9 will be summarized with counts and percentages, and subjects with abnormal liver function tes re ults will be presented in a separate listing.

Table 9: Criteria for Abnormal Liver Function

Test	Criteria for Abnormality
ALT (SGPT)	$\geq$ 3 ULN
AST (SGOT)	$\geq$ 3 ULN
Total Bilirubin	$\geq$ 2 ULN
ALP	$\geq$ 1.5 ULN
ALP	$\geq$ 2 ULN
ALT and AST	$\geq$ 3 ULN
ALT and Total Bilirubin	ALT $\geq$ 3 ULN and Total Bilirubin $\geq$1.5 ULN
AST and Total Bilirubin	AST $\geq$ 3 ULN and Total Bilirubin $\geq$ 1.5 ULN
Hy's Law	(ALT or AST $\geq$ 3 ULN) and ALP <2 ULN and Total Bilirubin $\geq$ 2 ULN

7.9.9 Neurological Exam

Mental status, motor, sensory, cerebellar/gait, and cranial nerve functioning will be assessed as Normal, Abnormal or Not Done. Abnormal results will be noted as NCS or CS. Change in overall neurological assessment from the previous assessment will be characterized as Better, Same or Unchanged, Worse, or

Not Done. Results will be summarized without formal statistical tests for each parameter and assessment time point, and will include the count and percentage of subjects within each category. The subject listing will also include a verbatim description of any abnormalities.

8 INTERIM ANALYSIS

An evaluation of the data from Part A will be used to determine the optimal HTX-011 formulation(s) and dose(s) for Part B.

9 CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

[redacted]

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} will also be analyzed using ANOVA, one set with LOCF and another with wLOCF imputation, as an exploratory analysis.

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

One subject who underwent complete abdominoplasty was un-intentionally randomized to receive HTX-002 (intended for mini-abdominoplasty pr cedure) and will be included only in data listings.

9.1 Changes in the SAP from Version 1.0 to Version 2.0

Part D was removed, and Part I was added.

A summary table and by-subj ct listing for Day 60 phone call responses were added.

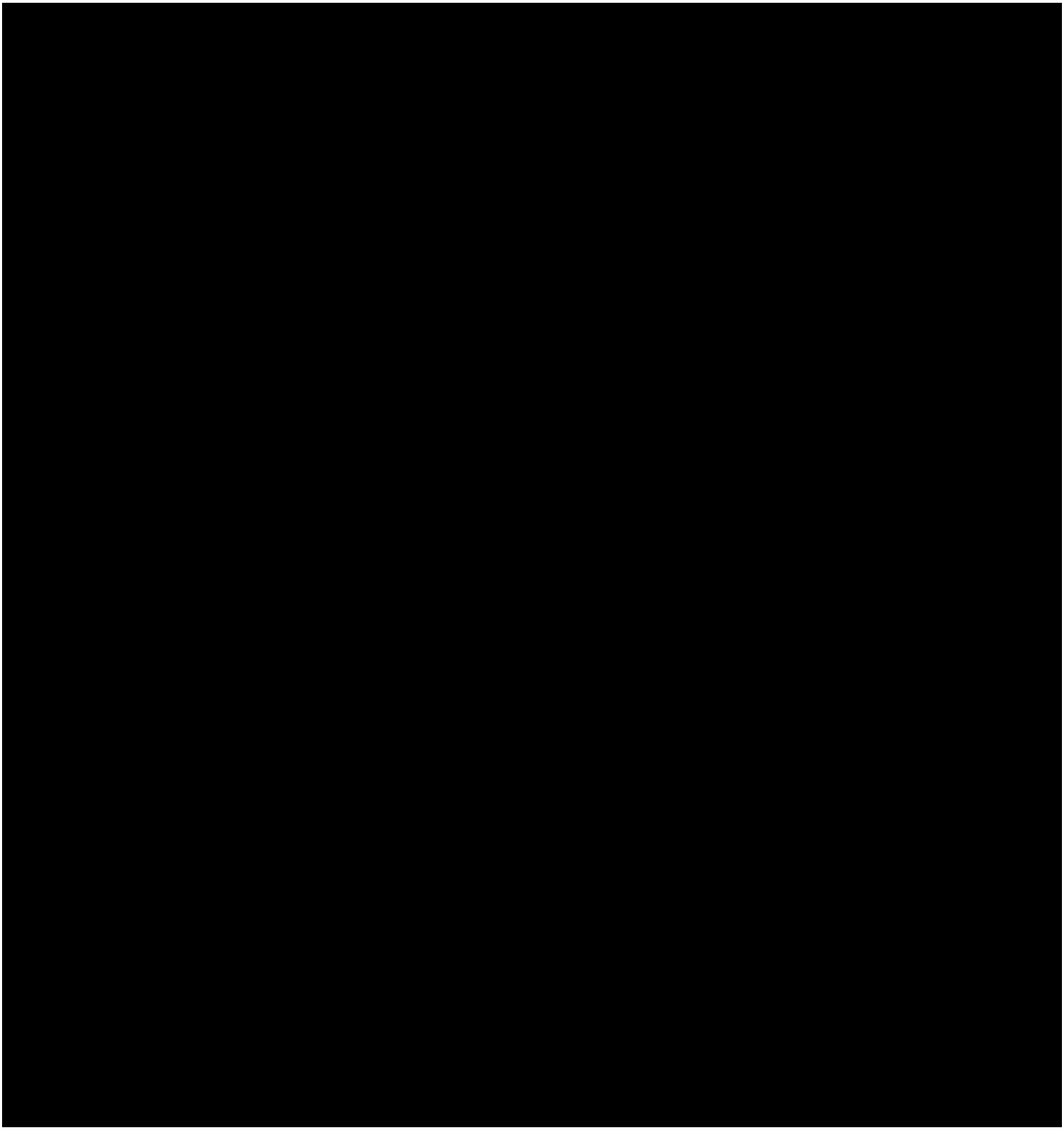
10 REFERENCES

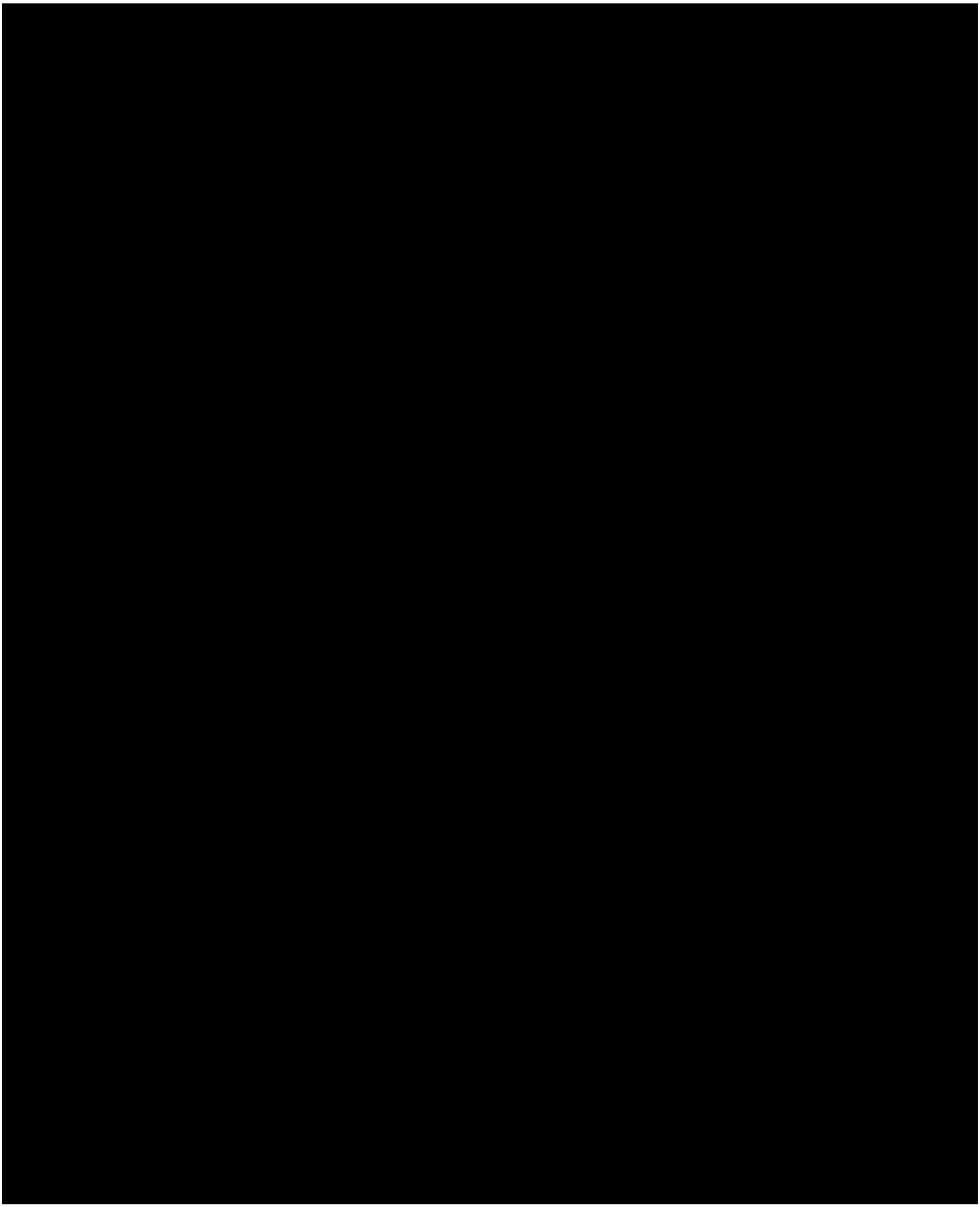
Chan, I. S. F. and Zhang, Z. (1999), "Test-Based Exact Confidence Intervals for the Difference of Two Binomial Proportions," *Biometrics*, 55, 1202–1209.

David G. Silverman, MD, Theresa Z. O'Connor, MPH, and Sorin J. Brull, MD (1993), "Integrated Assessment of Pain Scores and Rescue Morphine Use During Studies of Analgesic Efficacy," Anesth Analg 1993;77:168-70.

LIST OF TABLES, FIGURES AND DATA LISTINGS

List of Tables





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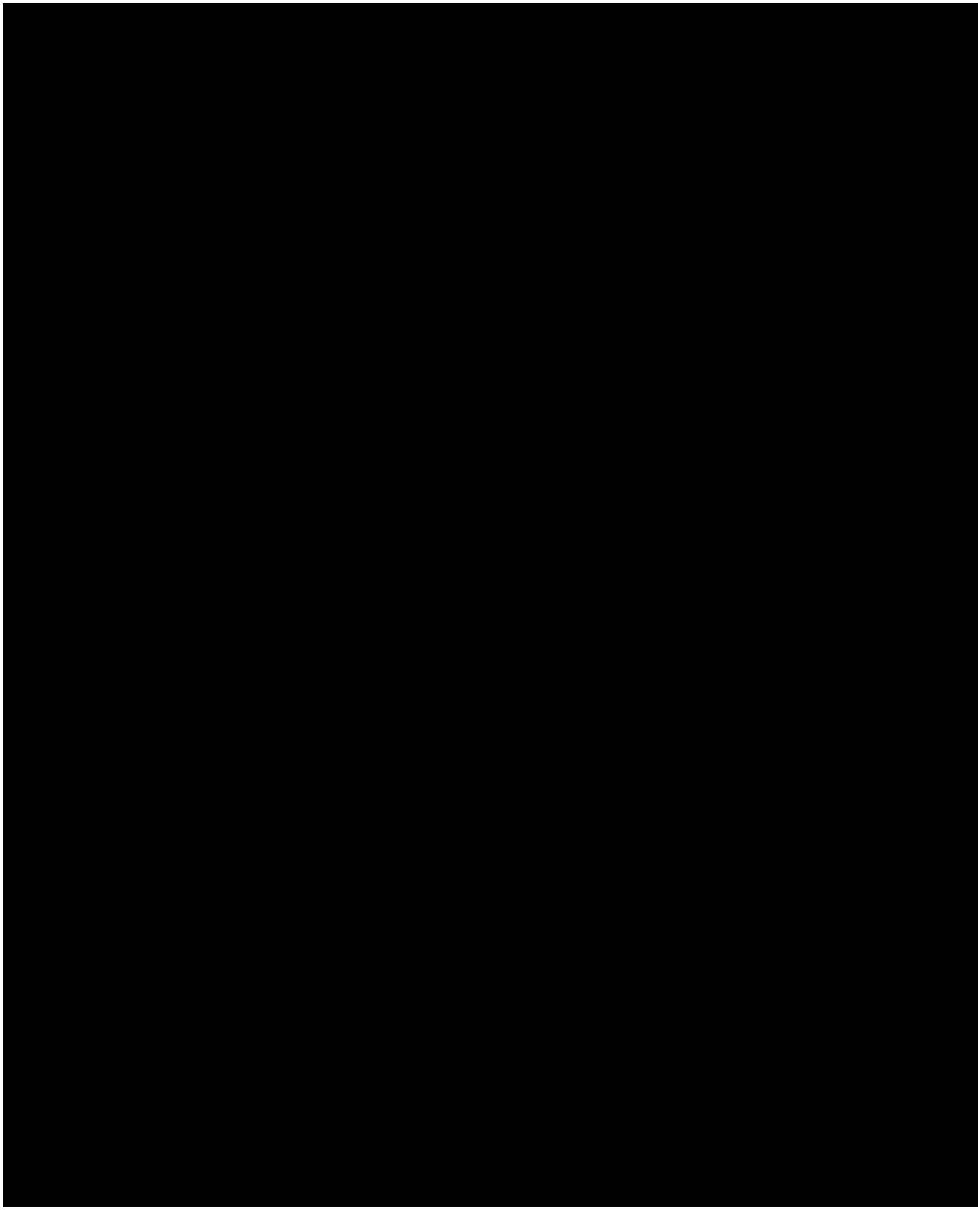

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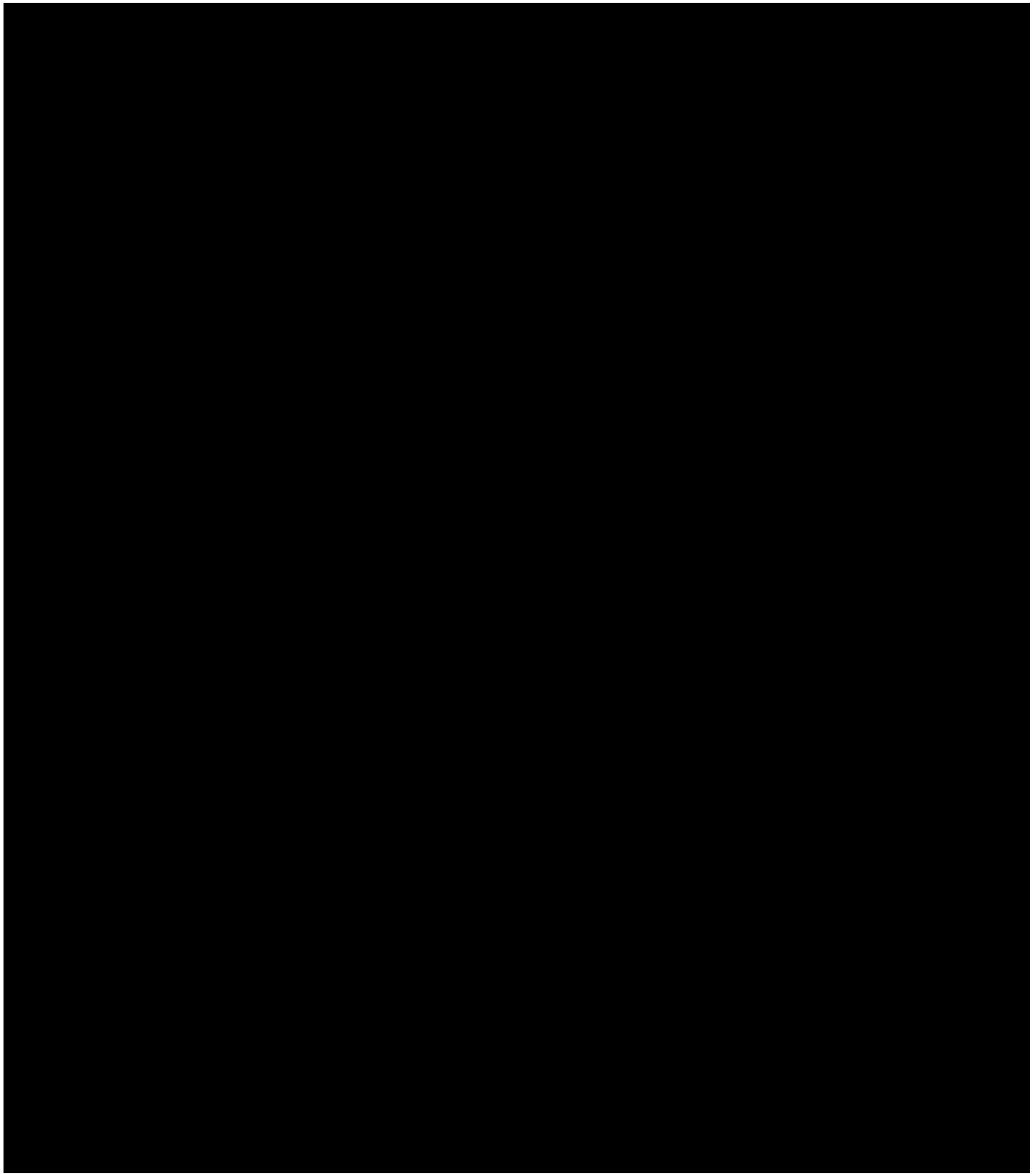
List of Figures



Subject Data Listings