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Statistical Analysis Plan

Heron Therapeutics, Inc.

HTX-011-C2016-208

A Phase 2, Randomized, Controlled, Multicenter Evaluation of the Efficacy and Safety of Locally Administered HTX-011, HTX-002, or HTX-009 for Postoperative Analgesia Following Bunionectomy

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ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
ASA	American Society of Anesthesiologists
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 pressure
ECG	electrocardiogr m
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
NRS	numeric rating scale
PACU	post anesthesia care unit
PGA	Patient Global Assessment
PI	pain intensity
PK	pharmacokinetic
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure

Abbreviation	Definition
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-C2016-208 titled "A Phase 2, Randomized, Controlled, Multicenter Evaluation of the Efficacy and Safety of Locally Administered HTX-011, HTX-002, or HTX-009 for Postoperative Analgesia Following Bunionectomy". 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 1.1	24 Mar 2016	Original protocol submitted to FDA on 01 April 2016; initial IRB submission on 25 March 2016
Protocol Version 2.0	09 May 2016	Added X-ray evaluation of bone healing and other clarifications
Protocol Version 3.0	08 June 2016	Injectable bupivacaine HCL added (HTX-002)
Protocol Version 4.0	24 June 2016	To evalu te lower doses of HTX-011-56; add new administration method: Local administration via instillation
Protocol Version 5.0	28 September 2016	Add Parts 5, 6 and 7
Protocol Version 6.0	20 December 2016	Add Part 8, add follow-up phone call at Day 60
Protocol Version 7.0	23 January 2017	Add Part 9

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

This SAP was based on protocol version 7.0, issued 23 January 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 the SAP 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.

The present Phase 2 study is designed to evaluate the safety, efficacy, and duration of analgesia following administration of HTX-011, HTX-002, or HTX-009 by three different techniques and various doses. There are 9 parts to this study. Part 1 will evaluate two HTX-011 formulations (HTX-011-49, HTX-011-56) administered in a single dose of 200 mg to the surgical site by closed or open wound infiltration following simple unilateral bunionectomy. Part 2 will evaluate the efficacy and safety of HTX-002 administered in a single 200 mg dose to the surgical site by closed or open wound infiltration following simple unilateral bunionectomy. Part 3 will evaluate HTX-011-56 administered in a single dose of 120 mg to the surgical site by closed or open wound infiltration, or local administration via instillation following simple unilateral bunionectomy. Part 4 will evaluate HTX-011-56 administered in a single dose of 60 mg to the surgical site by closed or open wound infiltration following simple unilateral

bunionectomy. Part 5 will evaluate HTX-002 administered in a single dose of 120 mg to the surgical site by closed or open wound infiltration following simple unilateral bunionectomy. Part 6 will evaluate HTX-011-56 administered in a single dose of 30 mg to the surgical site by closed wound infiltration following simple unilateral bunionectomy. Part 7 will evaluate HTX-009 administered in a single dose of 3.61 mg to the surgical site by closed or open wound infiltration following simple unilateral bunionectomy.

Subjects enrolled in Part 8 will receive 60 mg HTX-002 or Marcaine via closed wound or open wound infiltration, and subjects enrolled in Part 9 will receive 60 mg or 120 mg HTX-011-56 administered locally via instillation following simple unilateral bunionectomy.

Saline placebo groups will be included in each part to match part-specific administration methods and fluid volume.

Efficacy assessments are intended to characterize the analgesic effect-time curve and the magnitude of analgesic effect of HTX-011-49, HTX-011-56, HTX-002, or HTX-009 administered via 3 techniques, in comparison with bupivacaine HCl (Marcaine™) and normal saline. In addition, the study will further characterize the safety and PK profiles of bupivacaine and/or meloxicam in HTX-011, HTX-002, HTX-009, and bupivacaine HCl.

2 STUDY OBJECTIVES

The primary objective is to evaluate the efficacy and duration of analgesia following administration of HTX-011, HTX-002, and HTX-009 formulations by 3 different techniques and multiple doses.

The secondary objectives to be evalua ed are as follows:

- To determine the optimum study drug dose and administration technique.
- To determine the safety and tolerability of HTX-011, HTX-002, and HTX-009 formulations as evaluated by adverse events (AEs), serious AEs (SAEs), vital signs, clinical laboratory tests, electrocardiograms (ECGs), and indicators of surgical healing.
- To evaluate the PK profiles of bupivacaine and meloxicam in HTX-011, the PK profile of bupivacaine in HTX-002, and the PK profile of meloxicam in HTX-009 over 120 hours after study drug administration (details provided in a separate SAP).
- To evaluate the analgesic effects of HTX-011, HTX-002, and HTX-009 over various time intervals using a series of secondary efficacy endpoints for pain intensity (such as the patient's global assessment 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 formulations on wound healing at 48 hours, 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 various time intervals.

3 STUDY DESIGN

3.1 Overall Study Design

This is a Phase 2, 9-part, multicenter, randomized, controlled evaluation of the efficacy and safety of the intraoperative administration via closed or open wound infiltration or administration via local instillation of HTX-011-49, HTX-011-56, HTX-002, or HTX-009 in adult subjects undergoing simple unilateral bunionectomy. Marcaine is a local anesthetic commonly administered for acute analgesic effect and is therefore employed in this study as an active control, and normal saline is employed as a negative control, for efficacy and safety evaluations. Treatment cohorts will be enrolled for a planned total of 430 subjects (Table 2). In Part 1 (Cohorts A through F), approximately 90 subjects will receive HTX-011-49, HTX-011-56, bupivacaine HCl (Marcaine), or normal saline. In Part 2 (Cohorts G through J), approximately 60 subjects will receive HTX-002 or normal saline. In Part 3 (Cohorts K through N), approximately 60 subjects will receive HTX-011-56 or normal saline. In Part 4 (Cohorts O, P, and R), 45 subjects will receive HTX-011-56 or normal saline. In Part 5 (Cohorts S, T and U), 45 subjects will receive HTX-002 or normal saline. In Part 6 (Cohorts X and Y), 20 subjects will receive HTX-011-56 or normal saline. In Part 7 (cohorts Z1 to Z4), 40 subjects will receive HTX-009 or normal saline. In Part 8 (cohorts Z5 to Z9) 35 subjects will receive HTX-002 or Marcaine, and in Part 9 (cohorts A1 to A3) 35 subjects will receive HTX-011-56 or normal saline.

Table 2 Study Cohorts

Part 1

Cohort A (15 subjects) 200 mg HTX-011-49 via open wound infiltration
Cohort B (15 subjects) 200 mg HTX 011-49 via closed wound infiltration
Cohort C (15 subjects) 200 mg HTX-011-56 via open wound infiltration
Cohort D (15 subjects) 200 mg HTX-011-56 via closed wound infiltration
Cohort E (15 subjects) 50 mg bupivacaine (Marcaine) via a closed wound infiltration
Cohort F (15 subjects) normal saline via a closed wound infiltration

Part 2

Cohort G (15 subjects) 200 mg HTX-002 via closed wound infiltration
Cohort H (15 subjects) 200 mg HTX-002 via open wound infiltration
Cohort I (15 subjects) 6.84 mL of normal saline via a closed wound infiltration
Cohort J (15 subjects) 6.84 mL of normal saline via open wound infiltration

Part 3

Cohort K (15 subjects) 120 mg HTX-011-56 via closed wound infiltration
Cohort L (15 subjects) 120 mg HTX-011-56 via open wound infiltration
Cohort M (15 subjects) 120 mg HTX-011-56 local administration via instillation
Cohort N (15 subjects) 4.1 mL of normal saline via open wound infiltration

Part 4

Cohort O (15 subjects) 60 mg HTX-011-56 via closed wound infiltration
Cohort P (15 subjects) 60 mg HTX-011-56 via open wound infiltration
Cohort R (15 subjects) 2 mL of normal saline via open wound infiltration

Part 5

Cohort S (15 subjects) 120 mg HTX-002 via closed wound infiltration
Cohort T (15 subjects) 120 mg HTX-002 via open wound infiltration
Cohort U (15 subjects) 4.1 mL of normal saline via open wound infiltration

Part 6

Cohort X (15 subjects) 30 mg HTX-011-56 via closed wound infiltration
Cohort Y (5 subjects) 1.00 mL of normal saline via closed wound infiltration

Part 7

Cohort Z1 (15 subjects) 3.61 mg HTX-009 via closed wound infiltration
Cohort Z2 (15 subjects) 3.61 mg HTX-009 via open wound infiltration
Cohort Z3 (5 subjects) 4.1 mL normal saline via closed wound infiltration
Cohort Z4 (5 subjects) 4.1 mL normal saline via open wound infiltration

Part 8

Cohort Z5 (10 subjects) 60 mg HTX-002 via closed wound infiltration
Cohort Z6 (10 subjects) 60 mg HTX-002 via open wound infiltration
Cohort Z7 (5 subjects) 50 mg bupivacaine (Marcaine) via closed wound infiltration
Cohort Z8 (5 subjects) 50 mg bupivacaine (Marcaine) via open wound infiltration
Cohort Z9 (5 subjects) 2.05 mL normal saline via open wound infiltration

Part 9

Cohort A1 (15 subjects) 120 mg HTX-011-56 via instillation
Cohort A2 (15 subjects) 60 mg HTX-011-56 via instillation
Cohort A3 (5 subjects) 4.1 mL of normal saline via open wound infiltration

Male and female subjects ≥ 18 years of age undergoing elective bunionectomy will be screened for participation within 28 days of the scheduled surgery. After signing the informed consent form, subjects will be assessed for American Society of Anesthesiologists (ASA) classification, medical history, prior/concomitant medications, vital sign measurements, physical examination, clinical laboratory tests, drug and alcohol screen tests, 12-lead ECG, and serum pregnancy test. Post-operative nausea and vomiting (PONV) risk factors will be assessed, and subjects will be trained on providing pain assessments.

On the day of surgery (Day 0), each subject will be reassessed first for continued participation in the study. Subjects will undergo a primary, unilateral, first metatarsal bunionectomy procedure under regional anesthesia. Upon completion of the bunionectomy, a single dose of study drug will be administered by local open or closed wound infiltration or local instillation.

Following the completion of surgery and immediate postoperative recovery, 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 in the PACU for 72 hours after completion of the administration of study medication (T0) prior to discharge from the study center. Each subject will return to the study center 96 hours elapsed time after T0 to complete additional assessments. After completion of the 96-hour assessments, subjects will be scheduled to return on Days 10 and 28 for specific study assessments.

3.2 Treatment and Schedule of Assessments

Efficacy assessments will include pain intensity (PI) scoring using a numeric rating scale (NRS), use of rescue medication, and Patient Global Assessment (PGA) of pain control. Safety assessments will include AEs, nausea assessments, concomitant medications, physical examinations, neurologic assessments (including those for potential bupivacaine toxicity), vital sign measurements, clinical laboratory tests, ECGs, and wound healing assessments of the surgical intervention area. The planned schedule of study procedures is outlined in Table 3, Table 4, and Table 5.

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, including weight and height	X
Serum Pregnancy Test (female subjects of child bearing potential only)	X
Urine Drug Screen	X
Alcohol Breath Test	X
Clinical Laboratory Tests (Hematology and Chemistry)[a]	X
Vital Signs[b]	X
12-lead ECG	X
Pain Training	X
Prior and Concomitant Medication[c]	X
Serious Adverse Event Monitoring[d]	X

[a] Results will determine subject eligibility for the study.
[b] Resting vital signs: blood pressure, pulse, respiration rate, oral temperature and SpO_2. Resting tests must be obtained after resting (seated/reclined) for ≥ 5 minutes
[c] Concomitant medications taken within 30 days before dosing will be recorded on the eCRF.
[d] SAEs will be reported if considered related to study participation.

Table 4 Day 0 Prior to Surgery and Surgery

Procedure	Day 0	
	Prior to Surgery	Surgery
Eligibility Assessment (Inclusion/Exclusion criteria)	X	
Demographics and Medical History	X	
Physical Examination[c]	X	
Urine Pregnancy Test (female subjects of childbearing potential)	X	
Alcohol Breath Test	X	
Clinical Laboratory Tests (Hematology and Chemistry)[a]	X[d]	
Vital Signs[b]	X	
12-lead Electrocardiogram	X	
Pain Assessment Training	X	
Photograph of Foot Undergoing Surgery		X[f]
Blood Draw for Pharmacokinetic Analysis	X[d]	
Neurologic Exam	X	
Bunionectomy Procedure		X
Study Drug Administration		X
Prior and Concomitant Medication	X	X
Adverse Event (AE) Monitoring[g]	X	X

[a] Used as 'baseline' reference and not to determine eligibili y
[b] Resting vital signs: blood pressure, pulse, re pirati n rate, oral temperature, and SpO_2. Resting tests must be obtained after resting (seated/reclined) for ≥ 5 minutes.
[c] Physical exam will include weight only but not height
[d] Blood samples must be collected prior first surgical i cision.
[e] If screening 12-lead ECG was done >7 days prio to Day 0.
[f] Immediately after surgery ends.
[g] AEs that occur before study drug administration will be reported only if considered related to study participation. After study drug administration, all AEs that occur through Day 28 post-treatment must be reported.

Table 5 Post Study Medication Administration

	Day 0 to 5																										
	Post Study Drug Administration Time Points (hours)																										
	0.5	**1**	**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**	**Days 10 and 28 (± 2)**	**60**	**ET**
Subject confined at the study center	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]					X (Day 10)		X
Clinical Laboratory Tests[a]																				X							X
Vital Signs (±15 min window)[b]		X		X			X		X	X (12h only)		X	X		X		X		X	X			X		X (Day 10)		X
12-lead ECG													X				X			X			X		X (Day 10)		X
Pain Intensity (±15 min window) *in a dependent position*							X		X	X	X	X	X	X	X	X	X	X	X	X							X[i]
Pain Intensity (±15 min window) in an elevated position *at rest*		X[f]		X																	X	X	X				X[i]
PGA of Pain Control													X				X			X			X				X[i]
Use of Rescue Medication	X	X[f]	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 Samples (±15 min window)	X[j]	X	X	X	X	X	X	X	X	X		X	X	X	X		X		X	X			X	X[h]			
Numerical Rating Scale for Nausea (±15 min window)									X				X				X			X							X[i]
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		X
Assessment of Wound Healing																	X[n]			X[n]					X		X
Photograph of foot undergoing surgery																	X[m]			X[m]			X[m]		X		X
Neurologic Assessment (±15 min window)										X (12h only)			X		X		X		X	X			X				X[k]
X-ray (surgical intervention site)																									X[l] (D28-42)		
Phone Call																										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		X

[a] Laboratory tests will include hematology and chemistry.
[b] Resting vital signs: blood pressure, pulse, respiration rate, oral temperature and SpO_2. Resting tests must be obtained after resting (seated/supine) for ≥ 5 minutes.
[c] Physical examination will include weight only, but not height. Weight not required at 72 hour exam.
[d] AEs will be monitored after administration of study medication through completion of the study or resolution of AE, whichever comes first. SAEs will be monitored through Day 28 post-treatment. Toxicities thought to be associated with bupivacaine will be reported as AEs.
[e] Subjects may resume standard of care pain medication as advised by their surgeon after the T96 study visit.
[f] 1 hour assessments to be completed if subject is awake and alert.
[g] ±30 minutes window
[h] ±2 hours window
[i] Assessed only if early termination for subject is prior to T96.
[j] 15-minute window for sample collection not applicable to this timepoint.
[k] Assessed only if early termination for subject is prior to T72.
[l] Day 28 to Day 42 timeframe, as part of the routine surgical follow-up.
[m] If the institutional standard post-surgical recovery procedure does not warrant removal of the bandage at the specified timepoin then it is acceptable to forgo the photograph at that visit.
[n] If the institutional standard post-surgical recovery procedure does not facilitate this assessment to be conducted at 48 nd t 72 hours, then is acceptable to forgo this assessment at both these time points.

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 analgesic, opioid and non-opioid

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

6. Percentage of subjects who are pain free (NRS score = 0 or 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 for SPI_{0-24}, SPI_{0-48}, SPI_{0-72}, SPI_{0-96} and total opiate use through 24, 48, 72, and 96 hours post-study drug administration.

4.2 Safety Endpoints

The safety endpoints include:

- AEs and SAEs
- 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
- 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 st dy 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 th ough study completion or resolution of the AE, whichever comes first.

Any medical condition or clinically significant laboratory abnormality with an onset date before the first 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 is measured on a scale of 0-10, with 0 indicating no nausea and 10 indicating the worst nausea imaginable. Assessments of nausea will be performed at 6, 24, 48, and 72 hours post study medication administration.

4.2.3 Vital Signs

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, 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 for all events.

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, phosphate, calcium, glucose, bicarbonate, lactate dehydrogenase

In addition, urine 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 the time of early termination, if applicable.

4.2.6 Wound Healing Assessments

The surgical wound will be assessed 48 and 72 hours post-treatment, and on Days 10 and 28 post-treatment, or early termination, if applicable. Results are recorded as Normal or Abnormal, with a verbatim description of any abnormalities. Specific indications of wound healing will be assessed and results for each indication recorded. A photograph of the surgical intervention area will be taken immediately after surgery, and at 48, 72, and 96 hours, and on Days 10 and 28 post-T0, and an X-ray assessment will be performed between Day 28 and Day 42 to evaluate the status of the cartilage and bone healing process.

4.2.7 Liver Function

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

4.2.8 Neurological Exams

Neurological exams will be performed on Day 0 prior to surgery, and at hours 12, 24, 36, 48, 60, 72, and 96 post-treatment (or early termination). Parameters assessed include mental status, motor, sensory, cerebellar/gait, and cranial nerve function.

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 analysis set will include all subjects who are randomized to receive study medication.

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

Safety Population: The safety analysis set will include all treated subjects and will be used for safety and tolerability asses ments.

6.1 Sample Size Determination

The sample size of approximately 430 subjects was selected empirically without a formal statistical assumption. This study comprises 34 treatment cohorts in 9 parts, with between 5 and 15 subjects per cohort.

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 Harmonistation (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).

Subject Disposition, Demographics, Protocol Deviations, and AE summary tables will be grouped as follows:

- Formulations
    1. Saline Placebo (1.00-6.84 mL)
    2. Marcaine 50 mg (10 mL)
    3. HTX-009 3.61 mg (4.1 mL)
    4. HTX-002 60-200 mg (2.05-6.84 mL)
    5. HTX-011-49 200 mg (6.84 mL)
    6. HTX-011-56 30-200 mg (1.00-6.84 mL)
    7. Total (not included on AE tables)

In addition, all summary tables except Protocol Deviations will be grouped as follows:

- HTX-011-49:
    1. Saline Placebo (1.00-6.84 mL)
    2. Marcaine 50 mg (10 mL)
    3. HTX-011-49 200 mg (6.84 mL) Closed Wound
    4. HTX-011-49 200 mg (6.84 mL) Open Wound
    5. HTX-011-49 200 mg (6.84 mL) Total
- HTX-002:
    1. HTX-002 60 mg (2.05 mL) Closed Wound
    2. HTX-002 60 mg (2.05 mL) Open Wound
    3. HTX-002 60 mg (2.05 mL) Total
    4. HTX-002 120 mg (4.1 mL) Closed Wound
    5. HTX-002 120 mg (4.1 mL) Open Wound
    6. HTX-002 120 mg (4.1 mL) Total
    7. HTX-002 200 mg (6.84 mL) Closed Wound
    8. HTX-002 200 mg (6.84 mL) Open Wound
    9. HTX-002 200 mg (6.84 mL) Total

- HTX-009:
    1. HTX-009 3.61 mg (4.1 mL) Closed Wound
    2. HTX-009 3.61 mg (4.1 mL) Open Wound
    3. HTX-009 3.61 mg (4.1 mL) Total
- HTX-011-56 200 mg:
    1. Saline Placebo (1.00-6.84 mL)
    2. Marcaine 50 mg (10 mL)
    3. HTX-011-56 200 mg (6.84 mL) Closed Wound
    4. HTX-011-56 200 mg (6.84 mL) Open Wound
    5. HTX-011-56 200 mg (6.84 mL) Total
- HTX-011-56 120 mg
    1. Saline Placebo (1.00-6.84 mL)
    2. Marcaine 50 mg (10 mL)
    3. HTX-011-56 120 mg (4.1 mL) Closed Wound
    4. HTX-011-56 120 mg (4.1 mL) Open Wound
    5. HTX-011-56 120 mg (4.1 mL) Instillation
    6. HTX-011-56 120 mg (4.1 mL) Total
- HTX-011-56 30-60 mg:
    1. Saline Placebo (1.00-6.84 mL)
    2. Marcaine 50 mg (10 mL)
    3. HTX-011-56 30 mg (1.00 mL) Closed Wound
    4. HTX-011-56 60 mg (2.05 mL) Closed Wound
    5. HTX-011-56 60 mg (2.05 mL) Open Wound
    6. HTX-011-56 60 mg (2.05 mL) Instillation
    7. HTX-011-56 60 mg (2.05 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 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 mor 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 2 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 4 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 analysis set 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 1 post dose, 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 b 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 eason 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 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. 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 1, 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 sep rate 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

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 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. Parts 1 through 9 will be analyzed as described in a separate comparisons document. 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:

- Pooled 200 mg HTX-011-56 (Cohorts C and D)
- Pooled 120 mg HTX-011-56 (Cohorts K, L, M, and A1)
- Pooled 60 mg HTX-011-56 (Cohorts O, P, and A2)
- 30 mg HTX-011-56 (Cohort X)

- Pooled 200 mg HTX-002 (Cohorts G and H)
- Pooled 120 mg HTX-002 (Cohorts S and T)
- Pooled 60 mg HTX-002 (Cohorts Z5 and Z6)
- Saline Placebo (Cohorts F, I, J, N, R, U, Y, Z3, Z4, Z9, and A3)
- 50 mg Marcaine (Cohorts E, Z7, and Z8)

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 data as described in Section 7.8.

SPI

PI will be assessed by the subject for their current pain according to an 11-point NRS (0-10) where 0 equates to no pain and 10 equates to the worst pain imaginable. PI scores will be measured 2 ways: in a dependent position and in an elevated position at rest. PI scores will be assessed in a dependent position (i.e., subject sitting on the bed with the surgically attended foot resting at least partially on the floor) at the foll wing time points: 4, 6, 8, 10, 12, 14, 18, 24, 30, 36, 42, 48, 54, 60, 72 hours post study drug administration (i.e., post-T0). PI scores will be measured in an elevated position at rest at he following time points: 1, 2, 78, 84, and 96 (±2) hours post-T0. The assessments at 78 and 84 hours will be performed by subjects on an outpatient basis. All PI assessments scheduled between 24:00 and 06:00 must be collected, even if a subject is asleep at the time of the assessment. A ±15-minute window is allowed for the collection of each PI assessment. PI w ll also be assessed within 5 minutes prior to administration of each dose of rescue analgesia, and, at the time of early discontinuation 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_{0-24} 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 PI score at hour i.

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_{0-24}, 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 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 windowed last observation carried forward (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_{-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 tre tment group who reported a PI score no greater than 1 will be characterized as "pain-free". Comparisons of percentage pain-free will be performed at 24 hours post-treatment, 48 hours post-treatment, and 72 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 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, 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.

7.7.2.3 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 exact 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 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 ime 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 of the study, then the subject will be considered censored for analysis purposes at 96 hours. Time to administration of first opioid rescue medication will be analyzed in the same manner as time to first administration of any rescue medication. Kaplan-Meier curves will be presented for 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 those 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
MORPHINE	IV	4	1
MORPHINE	PO	4	0.33
OXYCODONE	IV	4	1
OXYCODONE	PO	6	0.5
TRAMADOL	PO	6	0.04
HYDROCODONE	PO	6	0.4

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

[redacted]

7.8 Data Imputation and Adjustment

7.8.1 Pain Intensity 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 p int 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:

PI scores recorded or imputed during the analgesic window (duration of effect) of any taken rescue medication will not be used for WLOCF analysis; instead alternate values will be calculated. The adjustment rules are as follows: All subjects are expected to assess their post-operative pain intensity 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. The analgesic windows for specified opioid rescue analgesics are listed in Table 6 Analgesic Windows and Morphine Milligram EquivalenciesNon-opioid analgesics 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 integrated 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

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 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. AEs will be coded using the MedDRA dictionary (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 for of the number of TEAEs, the number of subjects with at least 1 TEAE, the number of serious treatment-emergent SAEs, the number of subjects with serious treatment-emergent AEs, the number of subjects with study 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 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 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 according to total incidence (alphabetically for ties) in the highest HTX-011 dose group
- Opioid-related TEAEs (defined by the Sponsor) 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 defined by the Sponsor are AEs that code to any of the following PTs: Nausea, Vomiting, Constipation, Pruritus, Somnolence, R spiratory 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) will be analyzed using ANOVA as described in Section 7.7.1. Groups to be compared are listed in the separate comparisons document. 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

7.9.4 Physical Examinations

Physical exam findings will be presented in a data listing.

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 Wound Healing Assessm nts

The count and percentage of subjects with abnormal healing of the wound site at each time point will be summarized without form l 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 subject listing will be provided for photographs taken at time points 48, 72, and 96 hours, and on Days 10 and 28 post-T0 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.

7.9.7 X-ray Assessment

X-rays will be performed between Day 28 and Day 42, and results reported in a subject listing. Parameters include date of scan, and an assessment of whether or not appropriate healing occurred. Inappropriate healing is characterized as mal-union, non-union, or improper healing.

7.9.8 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. 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	≥ 3 ULN
AST	≥ 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

7.9.9 Neurological Exam

Mental status, motor, sensory, cerebellar/gait, and cranial ner e function 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 in lude the count and percentage of subjects within each category. The subject listing will also include a verbatim description of any abnormalities.

8 INTERIM ANALYSIS

Interim analyses are planned after Part 1 completes the 72 hour evaluation to support formulation and technique decisions; after Part 2 completes the 72 hour evaluation to support fixed combination dosing decisions; nd after Part 3 completes the 72 hour evaluation to support dose ranging decisions and inform design of potential future studies looking at the contribution of the individual components.

9 CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

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

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

Linear combinations of cohorts will not be tested, only pairwise comparisons from ANOVA.

Analysis of time to first opioid was added.

Analysis of percentage of subjects with no opioid use was added.

In Part 1, Cohort codes A and B were switched to B and A (C and D were switched to D and C) in the randomization file and caused inconsistent cohort codes between the analysis plan and the protocol.

Hour 24 added to analysis of percentage of subjects who were pain-free.

Time-to-event analysis will use the Wilcoxon test, rather than the log-rank test, to analyze between group differences.

A mistake was made in the randomization file description in Part 1 for Cohort E (50 mg bupivacaine via a closed wound infiltration), the randomization file showed open wound infiltration instead. Twelve of the 15 subjects randomized to receive bupivacaine via closed wound infiltration actually received drug via open wound infiltration, this cohort will be analyzed as open wound infiltration.

9.1 Changes within the Statistical Analysis Plan

Changes to the SAP between Version 1.0 and Version 2.0 are detailed in Table 9.

Table 9 Description of SAP Changes

SAP Revision Chronology:	
04NOV2016	MedDRA version updated to 19.1 and ATC version updated to September, 2016.
24JAN2017	Table layouts and efficacy figu s were updated to reflect added cohorts.
26JAN2017	The description of the WLOCF method of imputation was expanded to include rules for missing date/time.
31JAN2017	Tramadol and hydrocodone were added to the MME table.
09FEB2017	Nausea was changed from an efficacy outcome to a safety outcome.
23FEB2017	Screening table added, -019, -056 and -049 changed to -19, -56 and -49.
01MAR2017	Window timing for ibuprofen and acetaminophen added to text.

10 REFERENCES

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Statistical principles for clinical trials (E9). International Conference on Harmonization; 1998.

Chan ISF and Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. *Biometrics*. 1999;(55):1202-1209.

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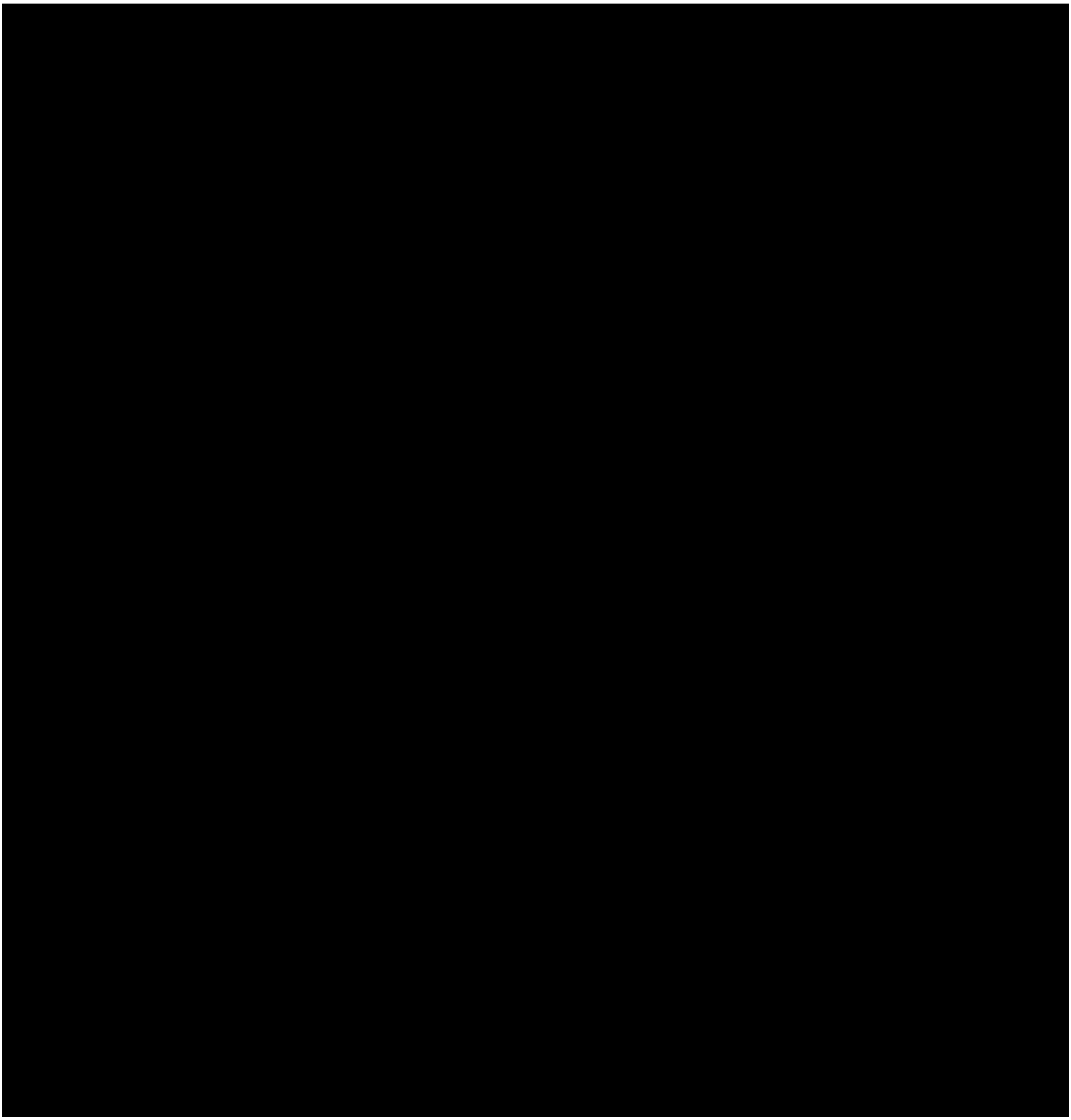

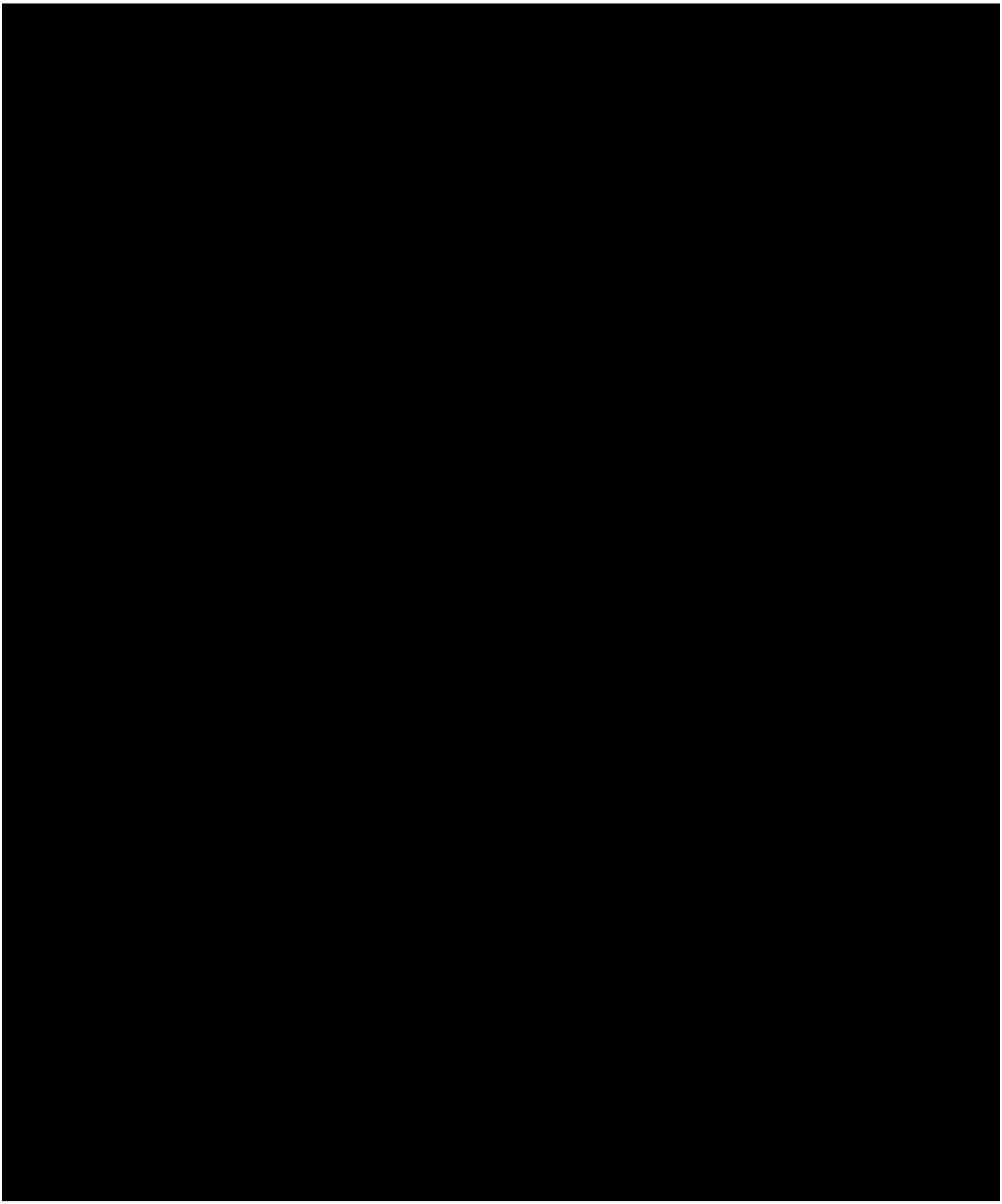

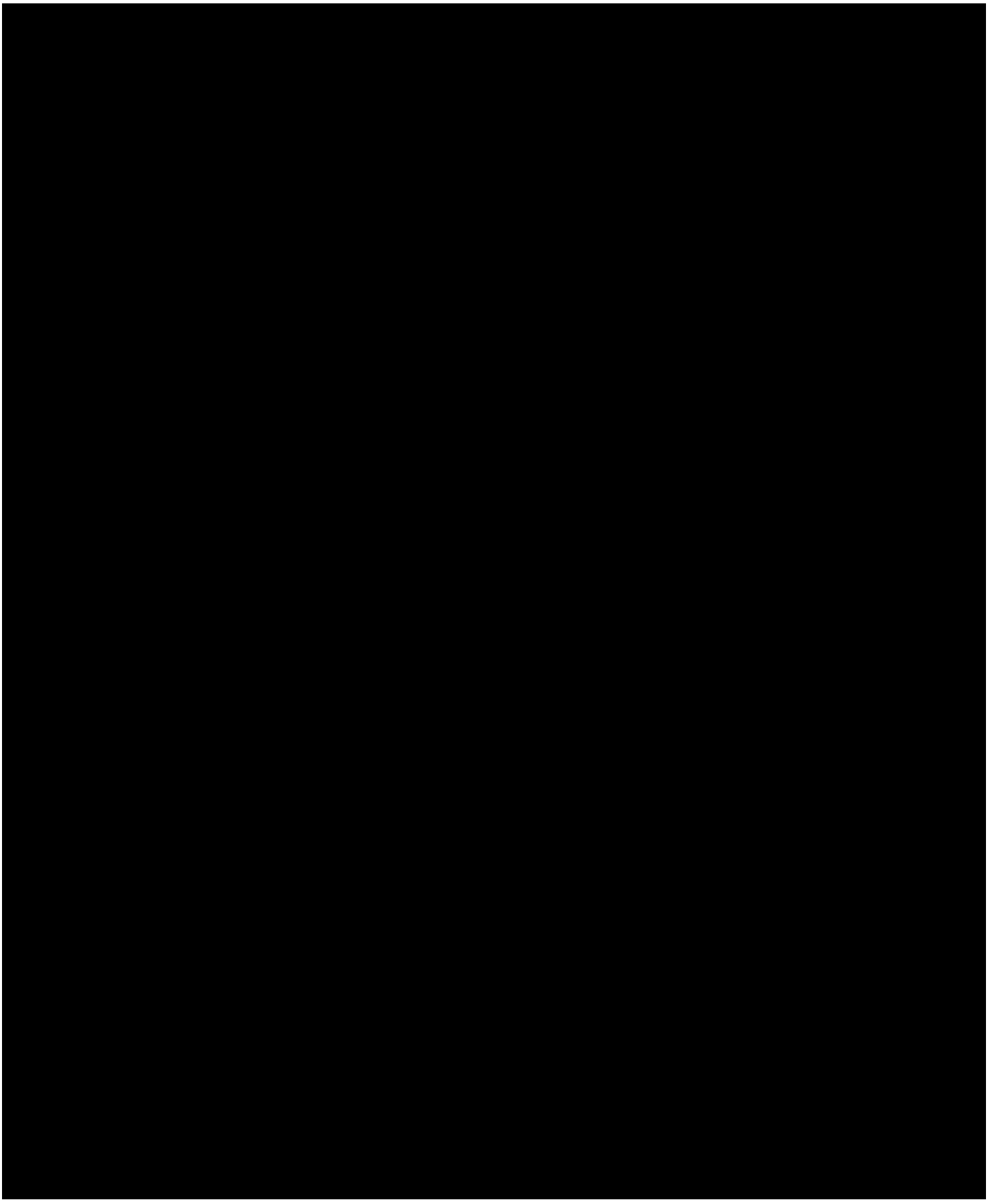

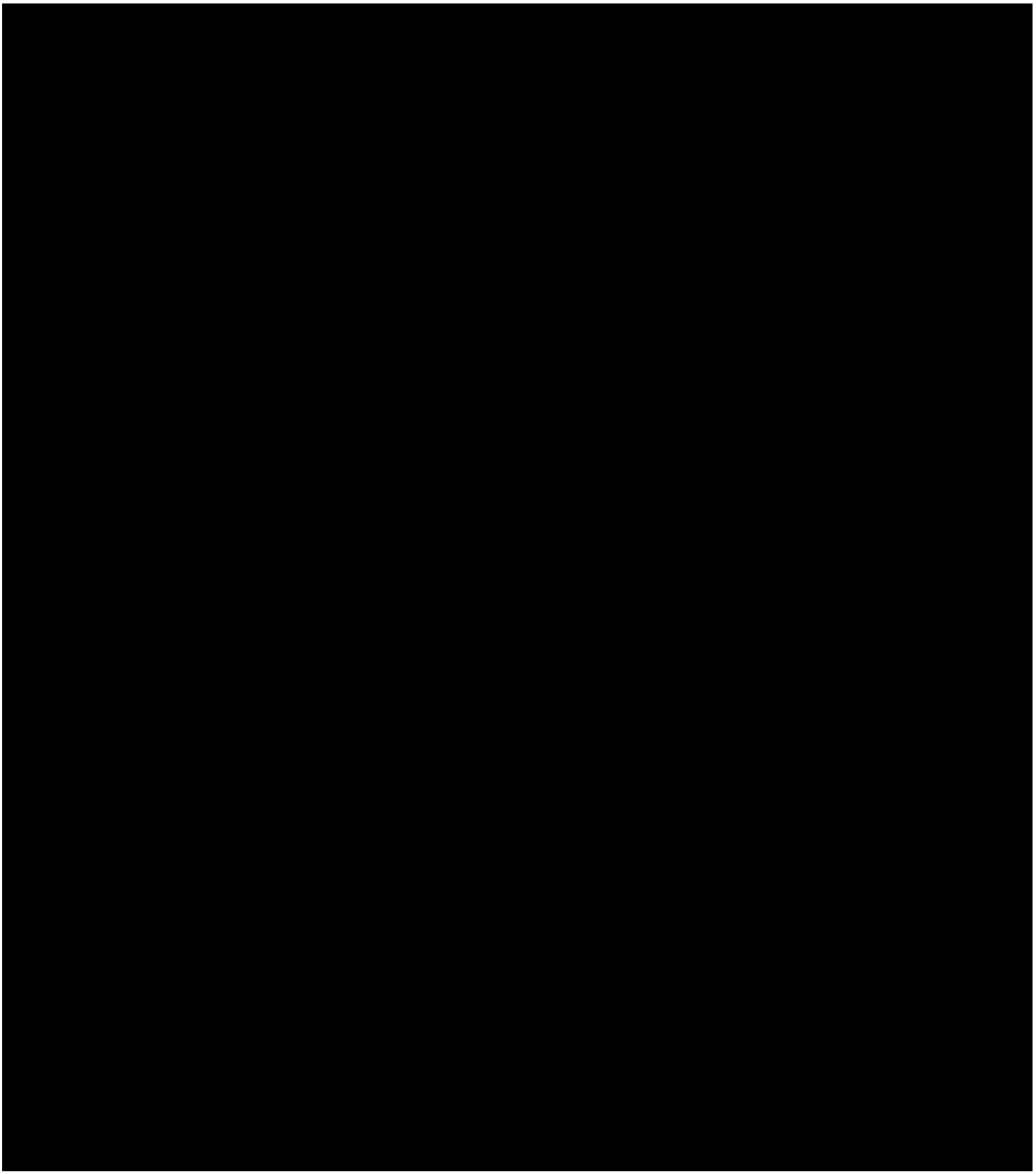

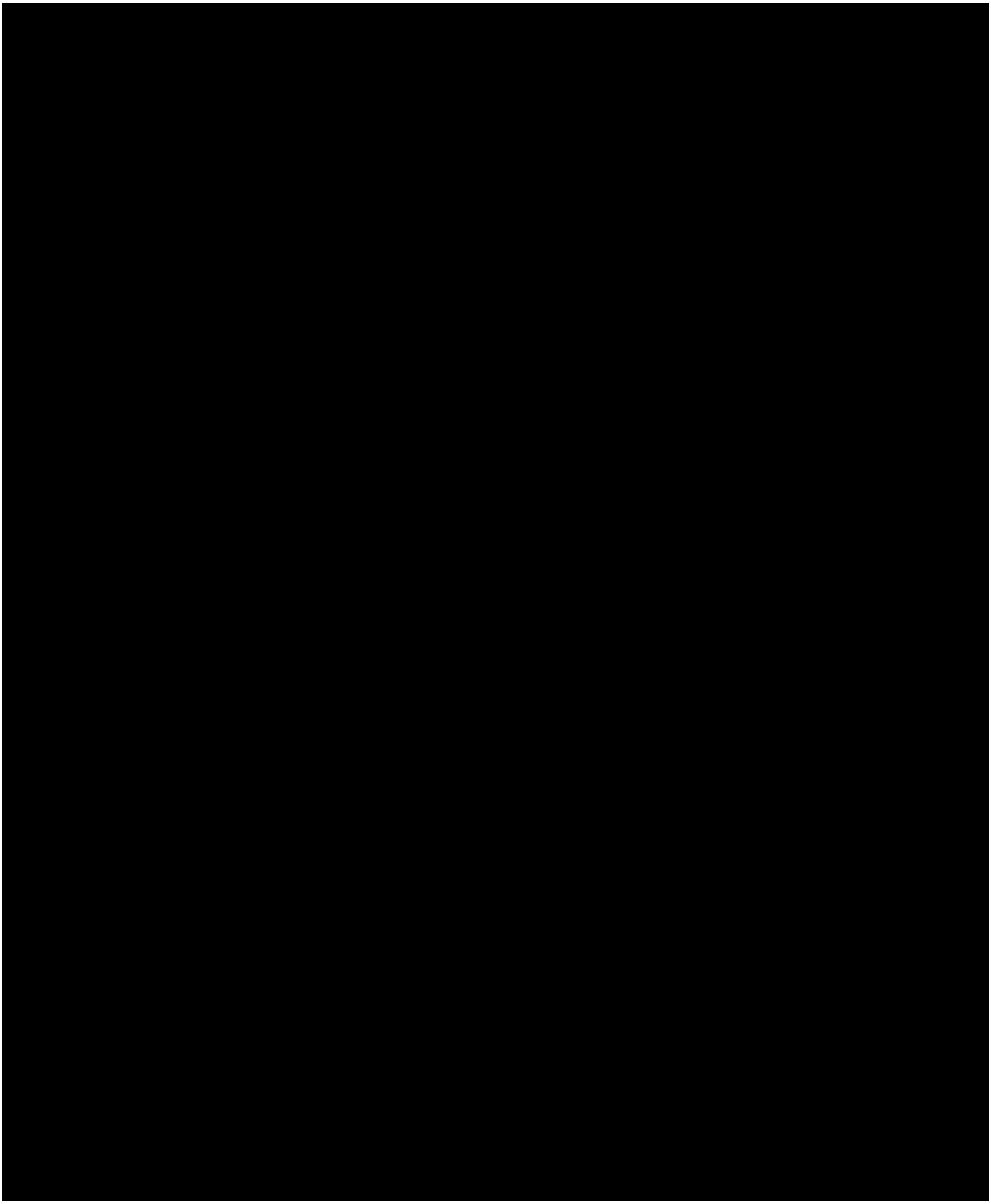

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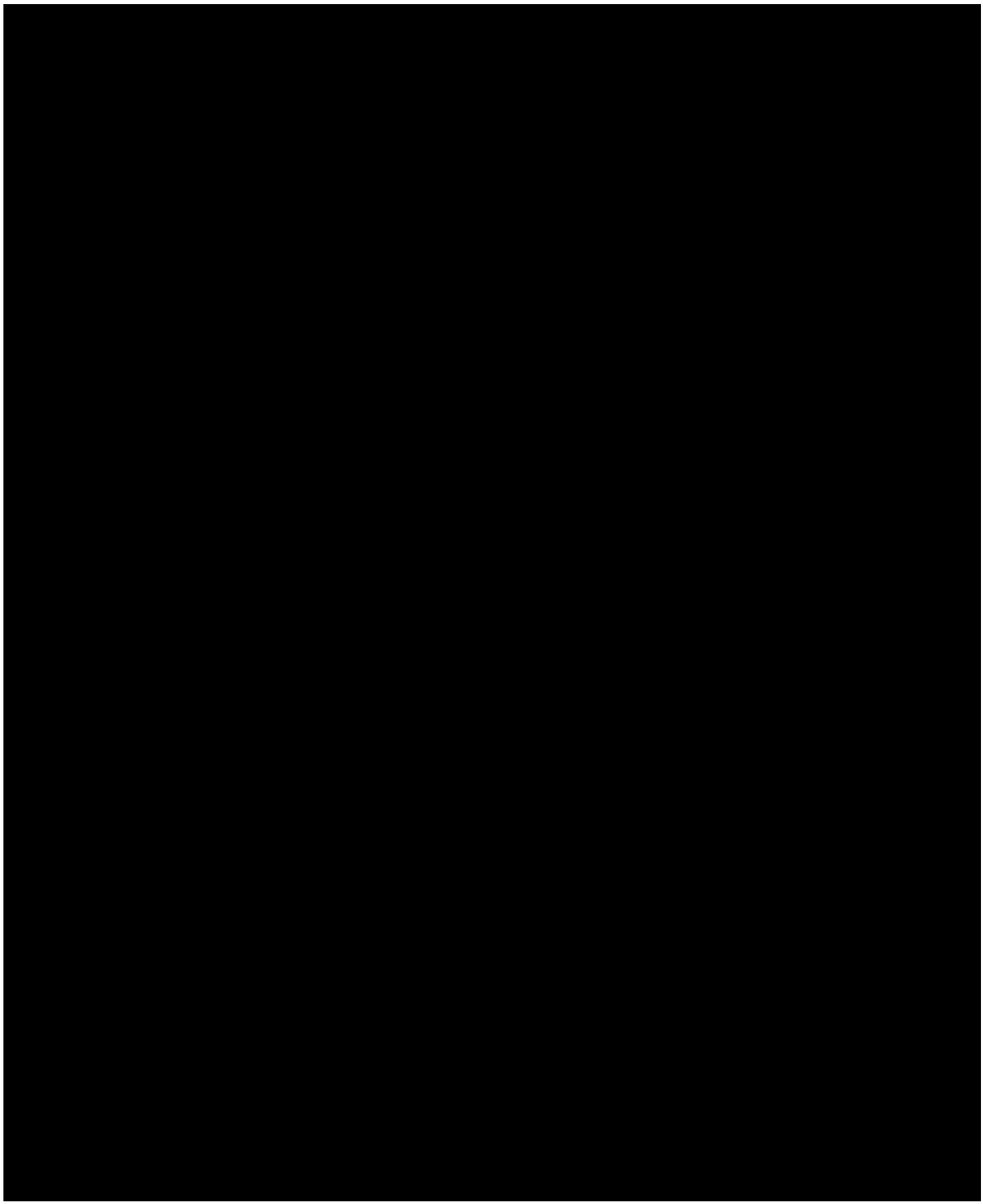

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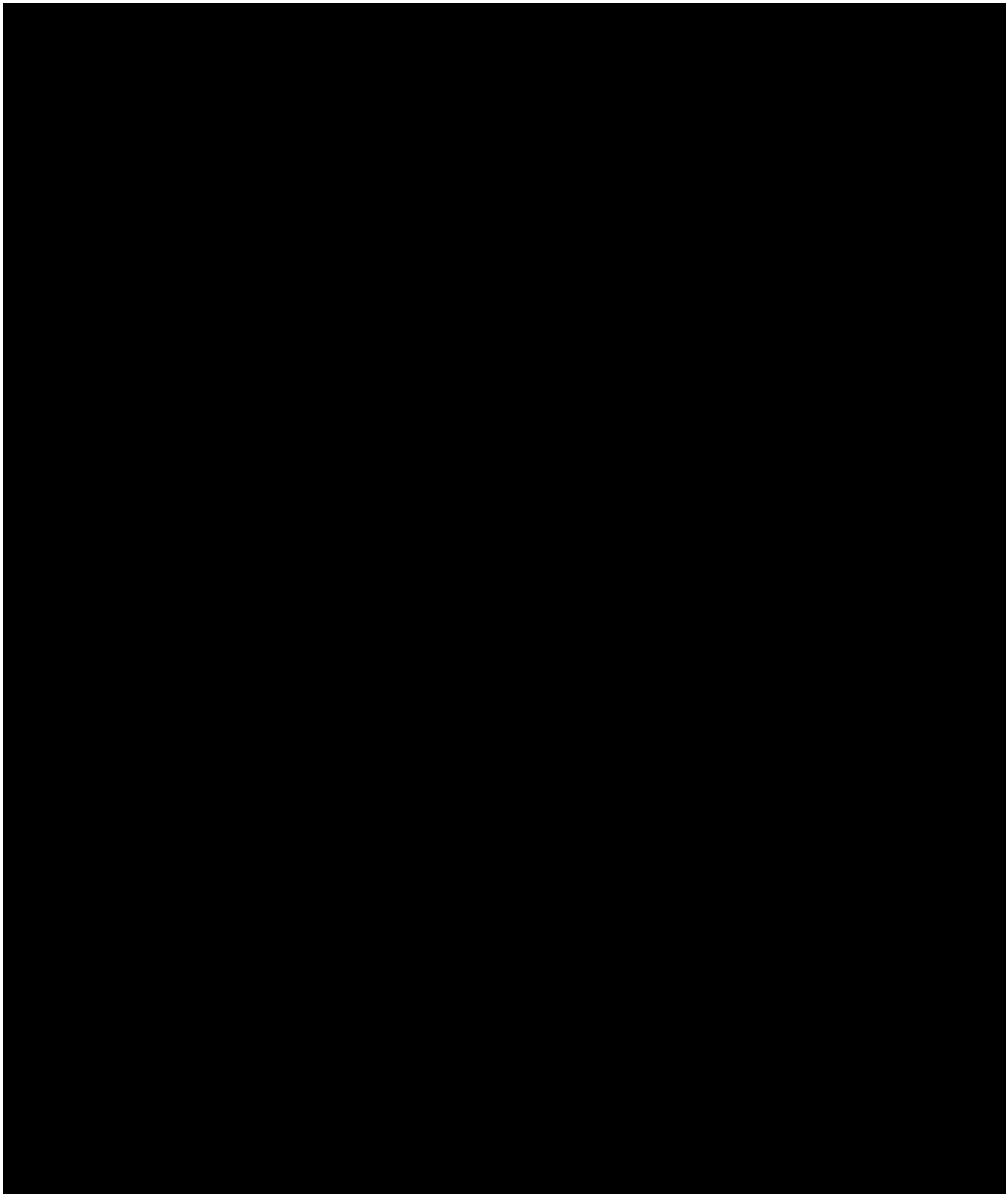

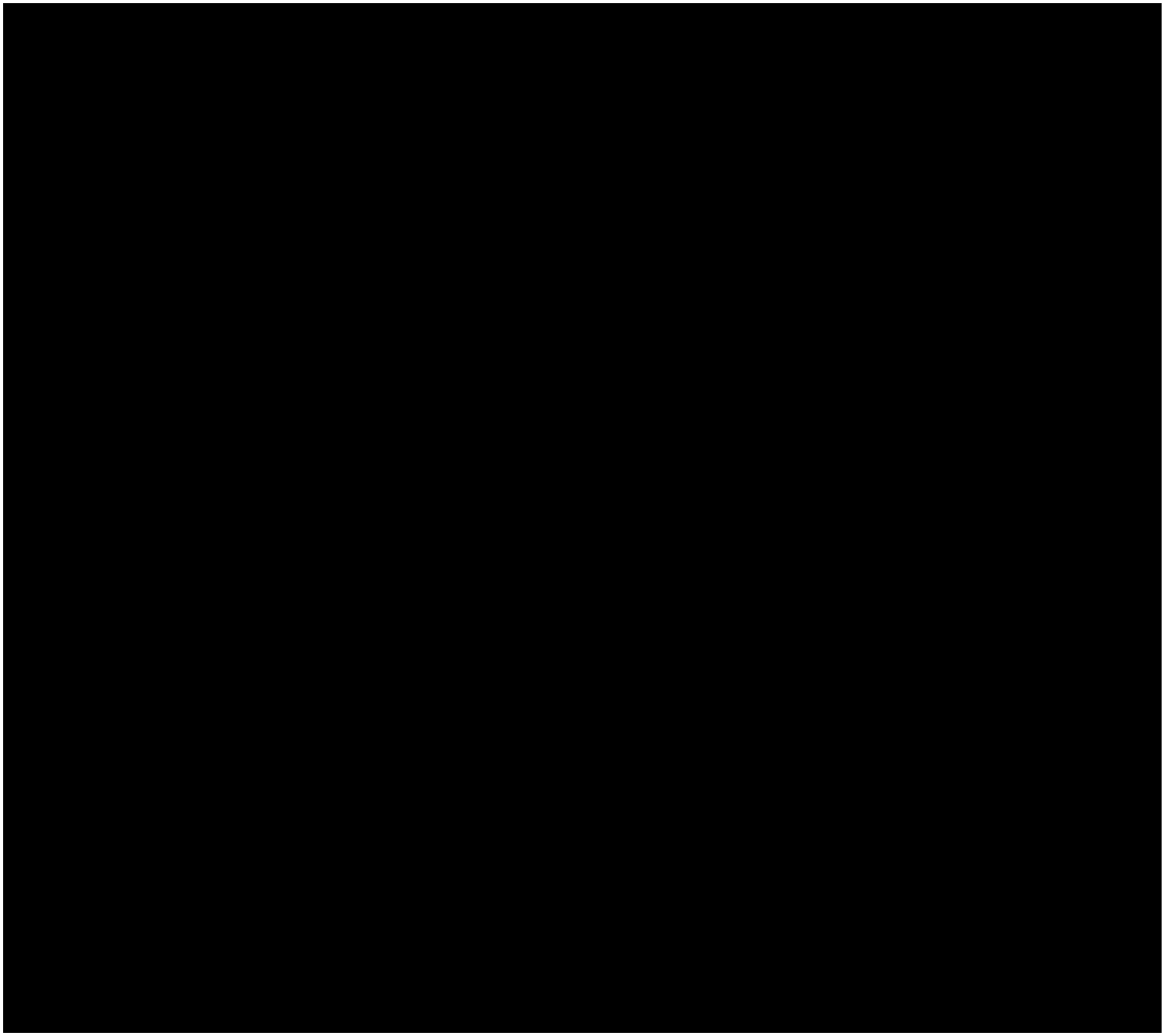

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Subject Data Listings