

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211988Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	211988
Priority or Standard	Priority
Submit Date(s)	Rolling Review Part 2, Clinical data submitted on October 30, 2018
Received Date(s)	Part 2, Clinical data received on October 30, 2018
PDUFA Goal Date	April 30, 2019
Division/Office	DAAAP/OND
Reviewer Name(s)	Renee Petit-Scott, M.D.
Review Completion Date	April 29, 2019
Established/Proper Name	Zynrelef™
(Proposed) Trade Name	Bupivacaine and Meloxicam extended-release solution
Applicant	Heron Therapeutics, Incorporated
Dosage Form(s)	Solution
Applicant Proposed Dosing Regimen(s)	400 mg bupivacaine and 12 mg meloxicam single-dose administration 200 mg bupivacaine and 9 mg meloxicam, 10 mL single-dose administration 60 mg bupivacaine and 1.8 mg meloxicam, 10 mL single-dose administration
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval of Zynrelef® 60 mg/1.8 mg for bunionectomy and 300 mg/9 mg for open inguinal hernia repair with mesh.
Recommended Indication(s)/Population(s) (if applicable)	Zynrelef® is indicated for application into bunionectomy and open inguinal hernia surgical sites to reduce postoperative pain for up to 72 hours.

Table of Contents

Table of Contents	2
Table of Tables.....	6
Table of Figures	9
Glossary	10
1. Executive Summary	12
1.1. Product Introduction.....	12
1.2. Conclusions on the Substantial Evidence of Effectiveness.....	13
1.3. Benefit-Risk Assessment	14
1.4. Patient Experience Data	27
2. Therapeutic Context.....	28
2.1. Analysis of Condition.....	28
2.2. Analysis of Current Treatment Options	28
3. Regulatory Background	30
3.1. U.S. Regulatory Actions and Marketing History	30
3.2. Summary of Presubmission/Submission Regulatory Activity	31
3.3. Foreign Regulatory Actions and Marketing History	33
4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety	33
4.1. Office of Scientific Investigations (OSI)	33
4.2. Product Quality	34
4.3. Clinical Microbiology.....	34
4.4. Nonclinical Pharmacology/Toxicology	34
4.5. Clinical Pharmacology	35
4.5.1. Mechanism of Action.....	35
4.5.2. Pharmacokinetics (PK)	37
4.6. Devices and Companion Diagnostic Issues	41
5. Sources of Clinical Data and Review Strategy	45
5.1. Table of Clinical Studies	45
5.2. Review Strategy	49

6.	Review of Relevant Individual Trials Used to Support Efficacy	50
6.1.	A Phase 2b, Randomized, Double Blind, Saline Placebo- and Active-Controlled, Multicenter Study of HTX-011 via Infiltration for Postoperative Analgesia in Subjects Undergoing Total Knee Arthroplasty (Study 209).....	50
6.1.1.	Study Design	50
6.1.2.	Study Results	57
6.2.	A Phase 3, Randomized, Double-Blind, Saline Placebo- and Active-Controlled, Multicenter Study of HTX-011 via Local Administration for Postoperative Analgesia and Decreased Opioid Use Following Unilateral Simple Bunionectomy (Study 301).....	71
6.2.1.	Study Design	71
6.2.2.	Study Results	78
6.3.	A Phase 3, Randomized, Double-Blind, Saline Placebo- and Active-Controlled, Multicenter Study of HTX-011 via Local Administration for Postoperative Analgesia and Decreased Opioid Use Following Unilateral Open Inguinal Herniorrhaphy (Study 302)	88
6.3.1.	Study Design	88
6.3.2.	Study Results	95
7.	Integrated Review of Effectiveness	105
7.1.	Assessment of Efficacy Across Trials	105
7.1.1.	Fixed Combination Product Classification	105
7.1.2.	Primary Endpoints	108
7.1.3.	Secondary and Other Endpoints	109
7.1.4.	Subpopulations	112
7.1.5.	Dose and Dose-Response	114
7.2.	Additional Efficacy Considerations.....	114
7.2.1.	Considerations on Benefit in the Postmarket Setting.....	114
7.3.	Integrated Assessment of Effectiveness	115
8.	Review of Safety	117
8.1.	Safety Review Approach	117
8.2.	Review of the Safety Database	119
8.2.1.	Overall Exposure	119
8.2.2.	Relevant characteristics of the safety population:	121
8.2.3.	Adequacy of the safety database:	121
8.3.	Adequacy of Applicant’s Clinical Safety Assessments	122

8.3.1. Issues Regarding Data Integrity and Submission Quality.....	122
8.3.2. Categorization of Adverse Events	122
8.3.3. Safety Assessments and Evaluations	125
8.4. Safety Results	126
8.4.1. Deaths.....	126
8.4.2. Serious Adverse Events (SAEs).....	126
8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects.....	130
8.4.4. Study Pregnancy	131
8.4.5. Treatment-Emergent Adverse Events (TEAEs).....	131
8.4.6. Laboratory Findings	143
8.4.7. Vital Signs.....	148
8.4.8. Electrocardiograms (ECGs)	150
8.4.9. QT	151
8.4.10. Immunogenicity.....	153
8.5. Analysis of Drug-Specific Safety Issues	153
8.5.1. Local Anesthetic Systemic Toxicity (LAST)	153
8.5.2. Meloxicam-Related Cardiovascular (CV) and Gastrointestinal (GI) Adverse Events 157	
8.5.3. Wound-Related Adverse Events	158
8.5.4. Opioid-Related Adverse Events	166
8.6. Safety Analyses by Demographic Subgroups	167
8.7. Recently Completed Clinical Trials	169
8.8. Additional Safety Explorations	171
8.8.1. Pregnancy and Lactation.....	171
8.8.2. Pediatrics and Assessment of Effects on Growth	172
8.8.3. Overdose.....	172
8.9. Safety in the Postmarket Setting	174
8.9.1. Safety Concerns Identified Through Postmarket Experience	174
8.9.2. Expectations on Safety in the Postmarket Setting.....	174
8.9.3. Additional Safety Issues From Other Disciplines	174
8.10. Integrated Assessment of Safety	174
8.10.1. Integrated Assessment of Safety of HTX-011 400 mg/12 mg.....	174

8.10.2. Integrated Assessment of Safety of Other HTX-011 Doses	176
9. Labeling Recommendations	181
9.1. Prescription Drug Labeling	181
10. Risk Evaluation and Mitigation Strategies (REMS)	182
11. Postmarketing Requirements and Commitments	182
12. Appendices	183
12.1. References	183
12.2. Financial Disclosure.....	183

Table of Tables

Table 1: Summary of FDA-Approved Local Anesthetics for Postsurgical Analgesia.....	29
Table 2: Summary of Pre-Submission and Submission Regulatory Activities	31
Table 3: Summary of Nonclinical Study Wound Findings	35
Table 4: Measured Meloxicam PK Parameters After Administration of HTX-011 400 mg/12 mg in Three Surgical Models	38
Table 5: Measured Bupivacaine PK Parameters After Administration of HTX-011 400 mg/12 mg in Three Surgical Models	40
Table 6: Planned Vial Fill Volumes and Commercial Kit Presentations for HTX-011 (bupivacaine 29.25 mg/mL and meloxicam 0.88 mg/mL).....	44
Table 7: Clinical Studies Supporting NDA 211988.....	46
Table 8: Schedule of Events, Study 209, Cohort 2	52
Table 9: Incidence of Important Protocol Deviations in Cohort 2 (ITT Population).....	60
Table 10: Demographic and Baseline Characteristics in Study 209, Cohort 2 (Safety Population)	61
Table 11: Results for Hierarchical Testing for the Primary and Key Secondary Endpoints, Study 209, Cohort 2 (wWOCF, ITT Population).....	63
Table 12: Mean AUC ₀₋₄₈ and AUC ₀₋₇₂ of NRS-R Pain Intensity Scores for HTX-011 Compared with Bupivacaine HCl, Study 209, Cohort 2 (wWOCF, ITT Population).....	65
Table 13: Proportion of Patients Pain-Free at Rest at Each Timepoint Using NRS-R, Study 209, Cohort 2 (wWOCF, ITT Population)	67
Table 14: Mean AUC of NRS-A Pain Intensity Scores by Interval for HTX-011 Compared with Saline Placebo, Study 209, Cohort 2 (wWOCF, ITT Population).....	68
Table 15: Mean AUC of NRS-A Pain Intensity Scores by Interval for HTX-011 Compared With Bupivacaine HCl, Study 209, Cohort 2 (wWOCF, ITT Population).....	68
Table 16: Total Postoperative Opioid Consumption From 0 Through 24, 48, and 72 Hours, Study 209, Cohort 2 (ITT Population)	69
Table 17: Schedule of Assessments, Study 301	73
Table 18: Incidence of Important Protocol Deviations, Study 301 (ITT Population).....	80
Table 19: Summary of Demographic and Baseline Characteristics, Study 301 (ITT Population) .	82
Table 20: Mean Total Postoperative Opioid Consumption in Morphine Equivalents, Study 301 (ITT Population)	85
Table 21: Incidence of Opioid-Related Treatment-Emergent Adverse Events (TEAE) by Preferred Term, Study 301 (Safety Population).....	85
Table 22: Proportion of Patients Who Are Opioid-Free Through Day 10 or 28, Study 301 (ITT Population)	86
Table 23: Schedule of Assessments, Study 302	91
Table 24: Incidence of Important Protocol Deviations, Study 302 (ITT Population).....	97
Table 25: Summary of Demographic and Baseline Characteristics, Study 302 (ITT Population) .	98

Table 26: Mean Total Postoperative Opioid Consumption in Morphine Equivalents, Study 302 (ITT Population)	101
Table 27: Incidence of Opioid-Related Treatment-Emergent Adverse Events (TEAE) by Preferred Term, Study 302 (Safety Population)	102
Table 28: Proportion of Patients Who Are Opioid-Free Through Day 10 or 28, Study 302 (ITT Population)	103
Table 29: Results for the Primary and Key Secondary Endpoints in Study 301 and Study 302 (ITT Populations)	108
Table 30: Summary of Rescue Medication Use Through 72 Hours – Study 301 and Study 302 (ITT Population)	110
Table 31: Proportion of Patients Who Were Opioid-Free Through Day 10 or Through Day 28 in Study 301 and Study 302 (ITT Population)	111
Table 32: Phase 3 and Phase 2b Study Safety Population	120
Table 33: Overall Disposition of Patients in Phase 2b and Phase 3 Studies (All Enrolled Patients)	121
Table 34: Safety Assessments and Evaluation Timepoints for Phase 2b and Phase 3 Studies Included in the Applicant’s Pooled Analysis	125
Table 35: Safety Assessments and Evaluation Timepoints for Phase 2b and Phase 3 Studies Not Included in the Applicant’s Pooled Analysis	126
Table 36: Overall Summary of TEAEs, Study 301 (Safety Population)	132
Table 37: Incidence of Most Common Treatment-Emergent Adverse Events by Preferred Term, Study 301 (Safety Population)	133
Table 38: Summary of Treatment-Emergent Adverse Events by Severity, Study 301 (Safety Population)	134
Table 39: Incidence of Potential LAST-Related Adverse Events, Study 301 (Safety Population)	135
Table 40: Incidence of Rapid and Delayed Onset of Potential LAST-Related Adverse Events, Study 301 (Safety Population)	136
Table 41: Overall Summary of Treatment-Emergent Adverse Events, Study 302 (Safety Population)	137
Table 42: Incidence of Treatment-Emergent Adverse Events for the Investigations System Order Class by Preferred Term, Study 302 (Safety Population)	138
Table 43: Incidence of Treatment-Emergent Adverse Events for the Injury, Poisoning, and Procedural Complications System Organ Class by Preferred Term, Study 302 (Safety Population)	139
Table 44: Incidence of Most Common Treatment-Emergent Adverse Events by Preferred Term, Study 302 (Safety Population)	140
Table 45: Summary of Treatment-Emergent Adverse Events by Severity, Study 302 (Safety Population)	141
Table 46: Incidence of Potential LAST-Related Treatment-Emergent Adverse Events, Study 302 (Safety Population)	142
Table 47: Incidence of Rapid and Delayed Onset of Potential LAST-Related Adverse Events, Study 302 (Safety Population)	143

Table 48: Mean Change from Baseline in WBC Count*, Study 301 and Study 302 (Safety Population)	144
Table 49: Criteria for Abnormal Liver Function, Study 301 and Study 302.....	145
Table 50: Incidence of Clinically Relevant Abnormalities in Liver Function Tests (Safety Population)	148
Table 51: Summary of Clinically Relevant Abnormalities in Vital Signs, Study 301 (Safety Population)	149
Table 52: Summary of Clinically Relevant Abnormalities in Vital Signs, Study 302 (Safety Population)	150
Table 53: The Largest Mean $\Delta\Delta\text{QTcF}$ and the 90% Cis by Time Post Dosing (FDA Analysis)	152
Table 54: Incidence of Potential LAST-Related Treatment-Emergent Adverse Events, Study 211 (Safety Population)	154
Table 55: Proportion of Patients With Rapid and Delayed Onset of Potential LAST-Related TEAEs, Study 211 (Safety Population).....	155
Table 56: Incidence of Potential LAST-Related Treatment-Emergent Adverse Events, Study 209, Cohort 2 (Safety Population)	156
Table 57: Local Inflammatory TEAEs, Study 209, Cohort 2 (Safety Population)	158
Table 58: Incidence of Local Inflammatory TEAEs for Study 301 (Safety Population)	160
Table 59: Summary of Wound Healing Assessment Results at Day 42, Study 301 (Safety Population)	162
Table 60: Summary of Bone Healing Results by Treatment Group for Study 208 (Safety Population)	163
Table 61: Summary of X-ray for Bone Healing Assessment Results for Study 301 (Safety Population)	163
Table 62: Overall Incidence of Local Inflammatory Treatment-Emergent Adverse Events for HTX-011-56, Bupivacaine HCl, and Saline Placebo – Complete Abdominoplasty, Study 203 (Safety Population)	164
Table 63: Summary of Abnormal Wound Healing Findings Post-Treatment by Treatment Group – Complete Abdominoplasty, Study 203 (Safety Population)	165
Table 64: Incidence of Local Inflammatory Treatment-Emergent Adverse Events, Study 302 (Safety Population)	166
Table 65: Summary of Treatment-Emergent Adverse Events in Phase 2b and Phase 3 Studies by Subgroup (Safety Population).....	168
Table 66: Overview of Studies Contributing to the 4-Month Safety Update.....	170
Table 67: CNS and CVS Symptoms of Bupivacaine and Other Local Anesthetic Toxicity.....	173

Table of Figures

Figure 1: Meloxicam Profile Comparison after HTX-011 400 mg/12 mg Administration	37
Figure 2: Bupivacaine Profile Comparison after HTX-011 400 mg/12 mg Administration	40
Figure 3: Proposed Drug Delivery Device	42
Figure 4: Patient Disposition, Cohort 2.....	59
Figure 5: Mean NRS-R Pain Intensity Scores Over Time for HTX-011 vs. Saline Placebo, Study 209, Cohort 2 (wWOCF, ITT Population).....	64
Figure 6: Hierarchical Test Procedure for Primary and Key Secondary Endpoints, Study 301	77
Figure 7: Patient Disposition, Study 301.....	79
Figure 8: Summary of Hierarchical Testing Results for the Primary and Key Secondary Efficacy Endpoints, Study 301	83
Figure 9: Mean NRS-A Pain Intensity Scores Over Time, Study 301 (wWOCF, ITT Population) ...	84
Figure 10: Patient Disposition, Study 302.....	96
Figure 11: Summary of Hierarchical Testing Results for the Primary and Key Secondary Efficacy Endpoints, Study 302	100
Figure 12: Mean NRS-A Pain Intensity Scores Over Time, Study 302 (wWOCF, ITT Population)	100
Figure 13: Contribution of HTX-011-56 Components to the Reduction in Mean AUC of Pain Intensity Scores Following Herniorrhaphy, Study 202 (wWOCF, Preliminary Data).....	106
Figure 14: Contribution of HTX-011-56 Components to the Reduction in Mean AUC of Pain Intensity Scores Following Bunionectomy, Study 208 (wWOCF, Preliminary Data).....	107
Figure 15: Total Post-Operative Opioid Consumption (MME) from 0 Through 72 Hours – Study 301 and Study 302 (ITT Population)	109
Figure 16: Subgroup Analysis for Mean AUC ₀₋₇₂ of the NRS-A Pain Intensity Scores for HTX-011 vs. Saline Placebo, Study 301 (wWOCF, ITT Population)	113
Figure 17: Subgroup Analysis for Mean AUC ₀₋₇₂ of the NRS-A Pain Intensity Scores for HTX-011 vs. Saline Placebo, Study 302 (wWOCF, ITT Population)	114
Figure 18: LAST Questionnaire, Phase 3 Studies.....	123
Figure 19: Boxed Warning, Mobic® Package Insert	124
Figure 20: eDISH Plot: Maximum Postdose ALT versus Total Bilirubin, Study 301 (Safety Population)	146
Figure 21: eDISH Plot: Maximum Postdose ALT versus Total Bilirubin, Study 302 (Safety Population)	147

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Heron Therapeutics, Inc. (Heron) describes their drug product, HTX-011 (also referred to as HTX-011-56 to distinguish from earlier formulations), as “...an extended-release, fixed-ratio combination product that contains two active pharmaceutical ingredients (APIs), bupivacaine hydrochloride (HCl) as the disease-active ingredient and low-dose meloxicam to enhance the effectiveness of bupivacaine, incorporated in a proprietary bioerodible polymer (referred to as AP135 and termed Biochronomer®)” (End-of-Phase 2 Meeting background materials submitted on April 14, 2017). Heron has submitted this New Drug Application for marketing approval of their product for the management of postsurgical pain up to 72 hours and reduction in opioid analgesic use. This product is not marketed anywhere in the world at the time of NDA submission. However, there is one product on the market that utilizes the Biochronomer® technology for drug delivery. Sustol® (granisetron) is marketed by Heron for the treatment of chemotherapy-induced nausea and vomiting. The adverse events associated with Sustol® administration are briefly discussed in this NDA review to help inform the risk profile regarding wound healing after administration of HTX-011.

Bupivacaine HCl (bupivacaine) is an amide local anesthetic, which reduces pain by blocking the generation and the conduction of nerve impulses, by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. Bupivacaine HCl is considered an immediate-release local anesthetic, with a mean duration of analgesic action of approximately six hours after surgical wound infiltration. There is currently one bupivacaine product on the market, liposomal bupivacaine, which is *advertised* as an extended-release formulation. Meloxicam is a non-steroidal anti-inflammatory (NSAID) medication approved for oral administration for the treatment of pain associated with osteoarthritis, rheumatoid arthritis, and juvenile rheumatoid arthritis. There are no approved injectable meloxicam products on the U.S. market.

Heron has described the mechanism by which bupivacaine HCl is delivered to the surgical site as follows:

 (b) (4)

(End-of-Phase 2 Meeting background materials submitted on April 14, 2017).

The proposed dosing is dependent on the size of the surgical site and the volume of HTX-011 required to coat the tissues. The label includes general guidelines for determination of proper

dosing, such that smaller surgical incisions, such as bunionectomy, would likely need less HTX-011. The maximum dose, HTX-011 400 mg/12 mg, is recommended for larger incisions, such as total knee arthroplasty and augmentation mammoplasty.

Throughout this NDA, the nomenclature for the bupivacaine and meloxicam dose in the final drug product is a fractional expression, with the bupivacaine dose in the numerator and the meloxicam dose in the denominator. Specifically, bupivacaine HCl 300 mg and meloxicam 9 mg is written as HTX-011 300 mg/9 mg. The clinical studies referenced in this NDA will be abbreviated by their three-digit number as follows:

- Study HTX-011-C2015-202 – Study 202
- Study HTX-011-C2015-203 – Study 203
- Study HTX-011-C2016-208 – Study 208
- Study HTX-011-209 – Study 209
- Study HTX-011-211 – Study 211
- Study HTX-011-301 – Study 301
- Study HTX-011 302 – Study 302

1.2. Conclusions on the Substantial Evidence of Effectiveness

The clinical development program conducted by the Applicant has demonstrated statistically significant and clinically meaningful decreases in pain scores with activity when compared to bupivacaine HCl and saline placebo wound infiltration for up to 72 hours post-operatively. The NDA submission contains adequate data to recommend approval of HTX-011 60 mg/1.8 mg for administration during unilateral bunionectomy and HTX-011 300 mg/9 mg during open inguinal hernia repair with mesh.

As described in Section 7. Integrated Review of Effectiveness, the Applicant demonstrated, in Studies 202 and 208, improved efficacy after administration of HTX-011 compared to administration of the individual drug products, bupivacaine and meloxicam, in the vehicle. These studies further demonstrate that bupivacaine is the disease-active component of the fixed-ratio combination product, supporting the Applicant's claim that meloxicam enhances the efficacy of bupivacaine. Refer to Section 7 for a detailed discussion of the classification of this fixed-combination product and the Proposed Rule requirements.

While the reduction in opioid analgesic use through 72 hours did reach statistical significance in the HTX-011 treatment groups in both Phase 3 studies (Study 301 and 302), it appears that early differences contribute to the statistical significance observed at the later timepoints. Specifically, the difference in opioid consumption is the largest through 24 hours and then less impressive from 24 to 48 hours and from 48 to 72 hours. Additionally, while there was a trend toward a lower incidence of opioid-related adverse events in patients treated with HTX-011 in the Phase 3 studies, this same trend was not observed in Study 209, Cohort 2, the additional study proposed by the Applicant (b) (4). Furthermore, the

administration of antiemetic medication appeared similar between the HTX-011 and bupivacaine HCl treatment groups in the Phase 3 study.

The adequate and well-controlled studies the Applicant is relying on to support the efficacy and safety of the to-be-marketed formulation include one Phase 2b study and two Phase 3 studies. These studies evaluated the intended commercial route of administration in two bony surgical models, bunionectomy and total knee arthroplasty (TKA), and a single soft tissue surgical model, open inguinal hernia repair with mesh. Additional studies evaluated earlier formulations, which generally included different doses of bupivacaine and/or meloxicam, in patients undergoing augmentation mammoplasty, mini- or complete abdominoplasty, open inguinal hernia repair with mesh, and bunionectomy. The Applicant has described their development program as an evaluation of “...*unique surgical procedures with different anatomic spaces, vascularities, and levels of pain in diverse patient populations*”.

(b) (4)

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Bupivacaine HCl was first approved in the United States in 1972 (NDA 016964) and has been widely used in the management of postsurgical pain, as well as other painful conditions, since that time. It is safe and effective for use via wound infiltration, peripheral nerve blockade, and neuraxial anesthesia in a variety of clinical settings and for a range of surgical procedures. Based on the well-known safety profile and demonstrated effectiveness, in combination with the on-going opioid epidemic, there is considerable interest in developing bupivacaine products with extended-release profiles in an effort to prolong the analgesic effect. Currently, there are no such products marketed. Heron has developed HTX-011, a formulation of bupivacaine and meloxicam in a Biochronomer® vehicle, in an attempt to extend the duration of action of bupivacaine such that post-operative opioid analgesic use and, therefore, opioid-related adverse events are reduced. The results of the HTX-011 drug development program do support an analgesic benefit over saline placebo and bupivacaine HCl wound infiltration for up to 72 hours post-operatively after bunionectomy (Study 301) and open unilateral inguinal hernia repair (IHR or herniorrhaphy) with mesh (Study 302). The primary and key secondary efficacy results from the Phase 3 studies are statistically significant (b) (4)

(b) (4)

When administered to patients undergoing open IHR with mesh or bunionectomy, the risks of HTX-011 include local anesthetic systemic toxicity (LAST), cardiovascular and gastrointestinal adverse events as described in the Mobic® label boxed warnings, and impaired healing of the surgical wound. In general, there did not appear to be any patients in the Phase 3 studies who experienced a clinically significant episode of LAST, requiring medical intervention. The reported mean maximum concentration, C_{max} , for bupivacaine after administration of HTX-011 60 mg/1.8 mg in patients undergoing bunionectomy was 33 ng/mL with a mean T_{max} of 3 hours. The mean C_{max} for bupivacaine after administration of HTX-011 300 mg/9 mg in patients undergoing open IHR with mesh was 271 ng/mL with a mean T_{max} of 18 hours. There was a single patient in Study 302 with a C_{max} greater than 1000 ng/mL (measured 1290 ng/mL at 24 hours, estimated 1310 ng/mL at 33 hours). This patient had a single potential LAST-related adverse event of syncope, moderate in severity, approximately five hours after study drug administration. The investigator felt the adverse event was unlikely related to study drug administration, which appears a reasonable conclusion given the reported adverse event time relative to C_{max} . The incidence of LAST-related adverse events appeared to be similar in the bupivacaine HCl treatment group compared to the HTX-011 treatment group. Therefore, despite the delivered dose of bupivacaine in HTX-011 300 mg/9 mg being higher than the maximum recommended dose of Marcaine™, there does not appear to be an increased risk for the development of LAST.

Regarding the need for the boxed warnings included in the Mobic® label, the risk for development of cardiovascular (CV) thrombotic and gastrointestinal (GI) bleeding, ulceration, or perforation events after a single administration of HTX-011 is low due to the lower systemic exposure compared to repeated oral meloxicam administration. Specifically, the Mobic® package insert states that C_{max} after oral administration of 7.5 mg was 1050 ng/mL. The mean area under the curve to infinity (AUC_{inf}) was calculated for Mobic® based on clearance values identified in the label and determined to be 85227 ng·h/mL for three days and 142045 ng·h/mL for five days. The highest C_{max} and AUC_{inf} after HTX-011 400 mg/12 mg administration, the highest proposed dose, during bilateral augmentation mammoplasty was 527 ng/mL and 41808 ng·h/mL, respectively. At the time of this clinical review, it seemed unlikely that the maximum proposed dose would gain marketing approval such that the highest recommended dose would be HTX-011 300 mg/9 mg, for use during open IHR with mesh. The measured PK parameters for that dose were reported as C_{max} 196 ng/mL and AUC_{inf} 21300 ng·h/mL, values much lower than those observed after oral Mobic® administration. Additionally, review of the observed adverse events across drug development did not identify a single case of a CV thrombotic event or a GI bleed, ulceration, or perforation. These results are reassuring and support safe use of HTX-011 for the indicated surgical procedures, however, it is not clear if there is a level of exposure that would negate the risk and eliminate the need for the boxed

warnings in the label.

The risk of impaired or delayed healing of the surgical wound after treatment with HTX-011 was extensively evaluated during review of this NDA. There was a measurable increase in wound-related adverse events, such as incision site cellulitis, infection, and impaired healing, after administration of HTX-011 60 mg/1.8 mg during bunionectomy compared to saline placebo and bupivacaine HCl. There are three reasons, however, why I recommend approval of HTX-011 despite this increase in wound-related adverse events. First, the majority of reported wound-related adverse events were mild in severity and resolved by Day 42, the end of the study. Second, the soft tissue wound changes did not result in more clinically significant bony changes, such as osteomyelitis or failure of the hardware, as assessed by post-operative x-rays. And third, smaller incisions and surgical spaces may not have been able to accommodate the entire volume of HTX-011 (2.1 mL), resulting in leakage of excess medication from the wound, and potentially poor approximation of the wound edges, local inflammation, and ultimately, delayed healing. There was a subset of patients who underwent complete abdominoplasty, received HTX-011 300 mg/9 mg via a combination of injection and instillation, and experienced a high incidence (20%) of wound dehiscence that persisted through the 28-day post-operative evaluation. It is possible that multiple injections of a viscous liquid disrupted the surgical plication of the posterior rectus sheath, resulting in the observed increase in wound dehiscence. Until additional safety information can be provided, this data lends additional support for limited postsurgical use. There did not appear to be an increase in wound-related adverse events reported during Study 302, IHR with mesh.

An additional, potential safety, consideration is whether lack of HTX-011 efficacy may result in increased post-operative opioid use. Bupivacaine is detected in the plasma through 120 hours post-operatively after open IHR, limiting the administration of additional local anesthetics during this time, which may potentially result in reliance on opioids for the management of post-operative pain. Additionally, because concomitant NSAID administration was not evaluated in the Phase 3 clinical studies (and was an exclusion criterion), the safety profile of post-operative NSAID use after HTX-011 administration is not known. It appears that the Applicant plans to market this drug product as one which decreases post-operative opioid use, suggesting alternate treatment(s) in the setting of lack of efficacy is an important consideration.

The clinical benefits of HTX-011 administration during bunionectomy and IHR with mesh outweigh the risks discussed and include a safe and novel route of administration, extended duration of postsurgical analgesia, and an additional analgesic treatment option. The proposed route of HTX-011 administration is instillation into the surgical wound via a needleless Luer lock syringe with unique applicator, as pictured in Figure 3. The lack of injection, with a needle, obviates the risk of inadvertent intravascular administration, thereby increasing the margin of safety of this bupivacaine-based product beyond what is observed during injection of immediate release bupivacaine HCl. Intravascular and systemic absorption, however, is still a concern in the setting of large doses or use in areas of increased vascularity, but a narrowed postsurgical indication and limitations of use statement(s) can mitigate this risk.

HTX-011 has demonstrated safe and efficacious post-operative analgesia after bunionectomy and open IHR with mesh for up to 72 hours, a clear clinical benefit beyond immediate-release bupivacaine HCl wound infiltration. Additionally, there were statistically, and clinically, significant decreases in opioid analgesic use in patients treated with HTX-011 compared to those treated with saline placebo or bupivacaine HCl. Given the current opioid epidemic, any decrease in postsurgical use is relevant and important. It is worth mentioning, however, that the largest differences in opioid use appear to be early in the post-operative course, such that after 24 hours the clinical significance is less clear. A final benefit of HTX-011 is that it will offer clinicians an additional treatment option in the management of acute postsurgical pain after bunionectomy and open inguinal hernia repair with mesh, relatively common surgical procedures, with the potential to have a positive impact on a large number of patient outcomes.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Bunionectomy is a common orthopedic surgical procedure performed in the United States. They are typically performed under regional anesthesia, such as an ankle or Mayo nerve block, with intravenous sedation or monitored anesthesia care. General anesthesia is reserved for challenging patients or more complicated surgical procedures. - Inguinal herniorrhaphy is a common soft tissue surgical procedure, which can be performed either laparoscopically, Robot-assisted, or via the open technique. The open procedure is generally reserved for large, incarcerated, or strangulated hernias, or for patients with a history of previous major abdominal surgery. Postsurgical pain is generally increased after open inguinal hernia repair compared to hernias repaired laparoscopically or Robotic-assisted. - A large number of surgical procedures, including bunionectomy and open IHR, are performed in outpatient ambulatory surgical centers, where adequate postsurgical pain management is key	While exposure to bupivacaine may be low in the general population, patients undergoing a surgical procedure have a high likelihood of receiving bupivacaine. Due to the disease processes and anatomic pathology, the development of a bunion is more common in female patients and an inguinal hernia is more common in male patients, suggesting the post-market exposure to HTX-011 will be in both females and males. Both bunions and inguinal hernias can be bilateral and can require re-exploration and/or intervention, potentially resulting in repeat exposure to bupivacaine products, either in the same location or a new location. Bunionectomy and open inguinal herniorrhaphy are

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	to maintaining efficiency, lowering health care costs, and improving patient satisfaction. • Efficacious, rapidly-acting, and extended duration of action are the goals of all postsurgical pain management strategies and while there are a number of opioid analgesics that meet these criteria, the large numbers of opioid-related adverse events and deaths are a clear indication that alternate treatment options are needed.	ideal surgical models to evaluate the safety and efficacy of potentially longer acting local anesthetics for three reasons. First, the evaluation of bunionectomy provides information regarding a possible interaction between HTX-011 and hardware commonly used during orthopedic procedures. Second, although bunionectomy is a relatively common procedure performed on an outpatient basis, it is considered painful and debilitating, suggesting the demonstration of efficacy in this surgical model likely provides more useful information than from a less painful procedure. And third, both are relatively benign surgical procedures and rarely result in life-threatening complications.
<u>Current Treatment Options</u>	• Current treatment options for postsurgical pain include the following: – opioid analgesics – non-opioid analgesics – local anesthetics for wound infiltration, peripheral nerve blockade, or neuraxial anesthesia – non-traditional strategies, including acupuncture and massage therapy – physical therapy • Of the local anesthetics available for postsurgical pain management, lidocaine, ropivacaine, and bupivacaine, with and without epinephrine, are the most commonly used. Ropivacaine and bupivacaine are considered longer-acting than	While there are several marketed, approved bupivacaine products for use in the management of postsurgical pain, none have an extended release profile that reliably and significantly prolongs postsurgical analgesia beyond that observed after administration of immediate release bupivacaine.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	lidocaine and generally provide up to six hours of postsurgical pain relief when administered via wound infiltration. • There are currently no approved local anesthetics with an extended-release or slow release profile that have demonstrated reliable prolonged postsurgical analgesia. A continuous infusion of a dilute concentration of bupivacaine via a peripheral nerve or neuraxial catheter appears to be the only available mechanism to prolong the duration of action of bupivacaine.	
<u>Benefit</u>	• Bupivacaine has been used for decades in the treatment of postsurgical pain when administered for wound infiltration, peripheral nerve blockade, or neuraxial anesthesia/analgesia. It is an effective local anesthetic with a well-established safety profile. • For soft tissue surgical procedures, bupivacaine is most commonly administered via wound infiltration, which reduces postsurgical pain for a short period of time, generally up to six hours. For orthopedic procedures, bupivacaine is also administered via wound infiltration, in addition to its use as a regional anesthetic for peripheral nerve blockade and neuraxial anesthesia. Depending on the technique, postsurgical analgesia can last for several hours or days, if necessary. • Meloxicam is an orally administered NSAID indicated once daily for the treatment of a variety of arthritic conditions. Like other NSAID medications, orally administered meloxicam inhibits cyclooxygenase enzymes (COX-1 and COX-2), resulting in	Approval of HTX-011 would offer clinicians an additional bupivacaine product to administer for postsurgical pain management after bunionectomy and open inguinal herniorrhaphy. Additionally, HTX-011 is an extended-release product resulting in post-operative analgesia through 72 hours. The Phase 3 clinical studies conducted by the Applicant included a bupivacaine control treatment group, such that the efficacy and safety comparisons allowed a more relevant assessment of the true clinical benefit of HTX-011 over standard of care bupivacaine wound infiltration. There was a statistically significant decrease in post-operative opioid analgesic use through 72 hours in patients treated with HTX-011 compared to those treated with saline placebo or bupivacaine. Arguably, any decrease in opioid use is clinically

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	decreased production of inflammatory prostaglandins and ultimately analgesia. The mechanism of action when administered locally in HTX-011 is not completely understood, but may involve two separate mechanisms. First, it may act locally as an anti-inflammatory, thereby decreasing tissue swelling and pain. This seems less likely given the results of nonclinical studies, indicating an increase in local tissue inflammation after administration of HTX-011. The second possible mechanism, and the one the Applicant proposes, is based on the maintenance of physiologic pH in the setting of tissue injury, thereby allowing more nonionized bupivacaine to penetrate nerves and inhibit conduction of sensory information. While this is possible, nonclinical data indicate that during the 24 hours of reported maximum meloxicam release, there is not a large difference in tissue pH between animals treated with HTX-011 and those treated with placebo. • The Applicant has demonstrated the improved clinical benefit of HTX-011 compared to treatment with bupivacaine and meloxicam individually in the Biochronomer® vehicle after bunionectomy and open inguinal herniorrhaphy. • Well-controlled post-operative pain results in the following: – Improved patient outcomes, including decrease length of hospital stay – Improved patient satisfaction, which may translate into reimbursement assurances – Less time lost from work and school – Ability to perform procedures on an out-patient basis	relevant, however, it does appear that the largest difference in opioid use between treatment groups was early in the post-operative period, i.e., < 24 hours, which likely contributed to the persistent statistical significance through 72 hours. There was a trend toward a lower incidence of opioid-related adverse events in patients treated with HTX-011 compared to those treated with saline placebo or bupivacaine; however, review of concomitant medications indicated less impressive differences in the treatment of opioid-related adverse events, such as post-operative nausea and vomiting. Furthermore, there were three confounding variables that impacted the clinical significance of the reported opioid-related adverse events. First, because all patients received concomitant sedation (Study 301) or general anesthesia (Study 302) during the evaluated procedures, interpretation of the data is challenging. Second, it does not appear the study protocols stratified patients with a history of post-operative nausea and vomiting. And lastly, patient factors, such as gender and smoking history, impact the incidence of post-operative nausea and vomiting.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	– Improved mobility and ambulation, and less time for return to baseline function, depending on the procedure performed – Potential decreased health care cost and burden due to short-term disability	
<u>Risk and Risk Management</u>	The three safety issues of greatest concern with administration of HTX-011 include the development of LAST, CV thrombosis and GI-related adverse events as described in the Mobic® label boxed warnings, and impaired healing of the surgical wound. <u>LAST</u> • Factors influencing the development of LAST include the site of administration and total dose administered. The proposed maximum dose of bupivacaine in HTX-011 300 mg/9 mg is higher than the recommend dose in the Marcaine™ product label, 175 mg without epinephrine. Use of a higher than currently recommended dose may lead to increased incidence of LAST depending on the surgical location, specifically the vascularity of the surrounding tissue. • Because the PK profile of HTX-011 is variable in the surgical populations evaluated, use of the product in other surgical models or for other painful conditions is not recommended. While bupivacaine has a long history of clinical use and the safety profile is well-established, it is highly cardiotoxic due to its strong affinity for cardiac Na⁺ channels and the high degree of protein binding. Systemic exposure to increased amounts of bupivacaine poses the greatest risk for the development of toxicity and HTX-011 instillation	Despite the higher dose of bupivacaine administered in HTX-011 300 mg/9 mg than is currently approved in the Marcaine™ label, the risk of developing LAST appears low. In general, the maximum systemic exposure after administration of HTX-011 300 mg/9 mg was below the threshold, 1000 to 2000 ng/mL, for local anesthetic-induced neurotoxicity. There was a single patient in Study 302 with a serum concentration greater than 1000 ng/mL. The patient did experience a potential LAST-related adverse event, syncope, five hours after HTX-011 administration and did not have any further symptoms when the serum concentration exceeded 1000 ng/mL. Therefore, it is unlikely that this event was associated with LAST. In the Phase 3 clinical studies, there did not appear to be any cases of clinically significant LAST and the incidence of potential LAST-related treatment-emergent adverse events was similar between the HTX-011 and bupivacaine HCl treatment groups. The preferred terms that were reported with an

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	into highly vascular sites is likely to increase the risk above what has been characterized in the Applicant's Phase 3 clinical studies. • An additional concern regarding the variable PK profile of HTX-011 is the likelihood of patients being in an unmonitored setting around C_{max}, a time when the risk of toxicity is the highest. This can potentially be mitigated by adequate and comprehensive patient education regarding the signs and symptoms associated with bupivacaine toxicity. <u>CV Thrombosis</u> • NSAID use and the resulting inhibition of the cyclooxygenase enzymes has been linked to CV thrombotic events, including myocardial infarction (MI) and graft stenosis after coronary artery bypass graft surgery. Because meloxicam is an NSAID, oral administration can result in a CV thrombotic event and the product label includes the boxed warnings required for NSAID medications. • There were no reported adverse events related to CV-thrombosis. The single patient death in Study 301 on Day 17 may have been related to underlying cardiac disease, however, this was a patient in the bupivacaine HCl treatment group. • In Study 302, there were no clinically meaningful differences between treatment groups in mean or mean change from baseline for heart rate, PR or RR interval, or QRS duration. Additionally, there did not appear to be clinically meaningful differences between treatment groups in the QT or QTcF intervals and the highest post-baseline QTcF was also similar.	increased incidence in the HTX-011 treatment group in Study 302 included the following: hypotension, muscle twitching, paresthesia oral, and sinus arrhythmia. The difference between treatment groups for these preferred terms was less than 1%, suggesting the difference in incidence is not clinically relevant or significant. The development of LAST with use of this drug product can be mitigated by the following: • Narrow postsurgical indication, based on safety data captured from adequate and well-controlled Phase 3 studies • Avoid administration in highly vascular surgical sites (e.g., intrathoracic) or procedures (e.g., multilevel spinal fusion with instrumentation) • Avoid administration on denuded tissues, such as burns • Maximum recommended dose 300 mg/9 mg The proposed route of administration of HTX-011 offers a margin of safety that other injectable bupivacaine-containing products do not. Specifically, because HTX-011 is administered via needless Luer lock syringe, the risk of inadvertent intravascular injection, and hence catastrophic LAST, is low.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- Despite the lack of a demonstrable risk with HTX-011 administration in combination with the overall lower systemic meloxicam exposure, the CV thrombosis boxed warnings are likely required for the HTX-011 product label. <u>GI Bleeding, Ulceration, and Perforation</u> - Similar to the CV thrombosis adverse events, NSAID use has been linked to GI-related adverse events including bleeding, ulceration, and perforation of the stomach or intestines. Because meloxicam is an NSAID, oral administration can result in these adverse events and the product label includes the boxed warnings required for NSAID medications. - There were no reported adverse events related to GI bleeding, ulceration, or perforation. The adverse event preferred terms in the Gastrointestinal Disorders System Organ Class (SOC) that were most commonly reported in Study 302 included nausea, constipation, and vomiting. - Despite the lack of a demonstrable risk with HTX-011 administration in combination with the overall lower systemic meloxicam exposure, the GI-related adverse event boxed warnings are likely required for the HTX-011 product label. <u>Surgical Wound Healing</u> - An extensive review of surgical wound healing data indicated that there is an increase in wound-related adverse events in patients treated with HTX-011 after certain surgical procedures, specifically bunionectomy and abdominoplasty.	While there were no reported adverse events concerning for CV thrombosis or GI-related adverse events after administration of HTX-011 and the overall systemic meloxicam exposure is lower than that observed after oral administration, however, it is not clear if there is a level of exposure that would negate the risk and eliminate the need for the boxed warnings in the label. The majority of wound-related adverse events reported during Study 301 were graded as mild in severity and resolved by Day 42, the end of the study. The incidence of adverse events related to bone healing or hardware failure was similar across treatment groups. Specifically, there were a total of seven patients with either mal-union or delayed bone healing as identified in post-operative x-rays. Three patients in the HTX-011 treatment group experienced mal-union; two were thought to be due to poor compliance with post-operative care and one was due to trauma. Four patients had delayed bone healing; one each in the HTX-011 and saline placebo treatment groups and two in the bupivacaine HCl treatment group. A possible explanation for the increased incidence of wound-related adverse events in patients

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Bunionectomy: – In Study 301, the adverse events with the highest incidence across all treatment groups included incision site oedema (sic), erythema, and impaired healing. In general, the HTX-011 treatment group had approximately 1% to 3% higher incidence of these adverse events. – For the more clinically significant adverse events of incision site cellulitis and wound dehiscence, the HTX-011 treatment group had approximately 2% to 3% higher incidence. – The cause of these wound-related adverse events is not fully understood and may be due to an excipient in the Biochronomer® formulation (b) (4). Leakage of excess HTX-011 from the small bunionectomy wound, resulting in local inflammation, as proposed by the Applicant, is also a reasonable possibility. • Complete abdominoplasty: – With respect to patients treated with HTX-011 300 mg/9 mg who underwent complete abdominoplasty, there was high incidence, 20%, of wound dehiscence reported post-operatively. These patients received HTX-011 via combination of multiple injections and instillation. – Until additional safety information can be provided, HTX-011 administration should be limited to the surgical procedures that were extensively evaluated in the Phase 3 studies.	undergoing bunionectomy is that excess HTX-011 leakage from the small surgical wound may have resulted in poor approximation of the wound edges, local inflammation, and delayed soft tissue healing. A possible explanation for the increased incidence of wound dehiscence in patients undergoing complete abdominoplasty (in the HTX-011 300 mg/9 mg combination administration treatment group) may be due to the injection route of administration. Specifically, multiple injections of a viscous liquid into the posterior rectus sheath plication may have disrupted the repair and ultimately adversely impact wound healing. Mitigation strategies to minimize the wound-related adverse events that will be included in the product label include the following (final language to be determined): • Avoid excess HTX-011 administration; i.e., instill only as much volume as the surgical space will accommodate • Ensure complete closure of the surgical wound and approximation of the wound edges • Only administer HTX-011 during surgical procedures for which the safety and efficacy has been thoroughly evaluated.

NDA 211988
Bupivacaine and Meloxicam Extended-Release Solution

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		In conclusion, I recommend approval of HTX-011 60 mg/1.8 mg for the management of postsurgical pain after bunionectomy and HTX-011 300 mg/9 mg for the management of postsurgical pain after open inguinal hernia repair with mesh.

Clinical Review
Petit-Scott, M.D.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
☐	Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
☐	Patient reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Given the current opioid crisis facing the United States, postsurgical pain management has become a rapidly advancing field. The goal is to decrease opioid prescriptions and use postoperatively via a multimodal peri-operative approach, including use of local anesthetics for wound infiltration, peripheral nerve blockade, and neuraxial blockade. A variety of soft tissue surgical procedures are amenable to local anesthetic administration and, depending on the location, patient comorbid conditions, concomitant medications, and contraindications, is considered standard of care. The local anesthetics currently approved for use in the management of post-operative pain are considered immediate release and there are no approved products labeled for extended release.

The Applicant has described Zynrelef™ as an “*extended-release solution*” in proposed product labeling based on the pharmacokinetic (PK) profile (to be discussed in detail in Section 4.5. Clinical Pharmacology). The extended bupivacaine release from Zynrelef™ is expected to prolong postsurgical analgesia observed after administration of immediate release products. While the data from the Applicant’s pharmacokinetic studies is supportive of prolonged bupivacaine release when compared to Marcaine™, clinically, the pharmacokinetics of local anesthetics do not translate into efficacy, or in this case prolonged analgesia. More simply stated, the PK profile does not correlate to the pharmacodynamic (PD) responses. Furthermore, prolonged bupivacaine release may ultimately have an adverse impact on the safety profile of the drug product. As will be discussed throughout this review, the determination of safety and efficacy of local anesthetic products developed to extend the analgesic benefit of immediate release products is complicated. While the opioid epidemic in the U.S. is an overwhelming challenge facing practitioners, researchers, and pharmaceutical companies alike, product development that is unsafe or no more efficacious than currently available standard of care products may predictably result in equally serious adverse outcomes.

2.2. Analysis of Current Treatment Options

The management of postsurgical pain involves a multimodal approach utilizing local anesthetics, non-opioid analgesics, and opioid analgesics. Anti-depressants and anti-seizure medications are also commonly used depending on the comorbid medical conditions of the patient and the procedure performed. Opioid analgesics have been the mainstay for the management of not only acute pain conditions, including post-operative pain, but also for chronic pain conditions. Current strategies, however, are focused on alternate pain treatments, including local anesthetic wound infiltration, peripheral nerve blockade, and neuraxial anesthesia. This paradigm shift has resulted in increasing interest in developing products that prolong the efficacy of immediate release local anesthetics, such as Zynrelef™. As previously mentioned, however, there is no approved extended-release local anesthetic product that has

reliably and predictably extended the duration of analgesia observed after administration of immediate-release local anesthetics.

The following table summarizes the local anesthetics most commonly used in the peri-operative period for analgesia.

Table 1: Summary of FDA-Approved Local Anesthetics for Postsurgical Analgesia

Product Name NDA #	Relevant Indication	Route of Administration	Efficacy Information	Important Safety and Tolerability Issues
Exparel (022496)	For single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia	Local infiltration	Liposomal bupivacaine HCl used for postsurgical analgesia. No clear efficacy benefit demonstrated when compared to bupivacaine HCl.	The safety issue with all local anesthetics involves systemic and local toxicities. LAST presents as central nervous system excitation and/or depression and cardiotoxicity. As documented in the Adverse Reactions section of the bupivacaine labeling, but applicable to all local anesthetics, the following LAST reactions are described by system: <u>Central nervous system</u> Excitation and/or depression; restlessness, anxiety, dizziness, tinnitus, blurred vision, tremors, convulsions <u>Cardiovascular system</u> High doses or inadvertent intravascular injection may result in myocardial depression, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmias, cardiac arrest. Bupivacaine HCl is considered the most cardiotoxic local anesthetic due to its potency in blocking nerve conduction and depressing cardiac contractility. Local reactions can include persistent anesthesia, paresthesia, weakness, or paralysis
Bupivacaine HCl (016964)	Production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures	Local infiltration	First approved in 1972. Many approved bupivacaine products are widely used for postsurgical analgesia, either as wound infiltrate or nerve block. Considered a long-acting local anesthetic with a duration of action ranging from 4 to 18 hours, depending on the route and site of administration.	
Ropivacaine HCl (20533)	Production of local or regional anesthesia for surgery and for acute pain management	Local infiltration	Similar efficacy benefits as bupivacaine HCl but with more favorable cardiotoxicity profile. Considered a long-acting local	

Product Name NDA #	Relevant Indication	Route of Administration	Efficacy Information	Important Safety and Tolerability Issues
			anesthetic with a duration of action ranging from 4 to 18 hours.	
Mepivacaine HCl (12250)	Production of local or regional analgesia and anesthesia by local infiltration, peripheral nerve block techniques, and central neural techniques	Local infiltration	Considered an intermediate-acting local anesthetic with a duration of action ranging from 90 to 180 minutes.	
Lidocaine HCl (006488)	Production of local or regional anesthesia by infiltration techniques and intravenous regional anesthesia, by peripheral nerve block techniques, and by central neural techniques, when the accepted procedures for the techniques as described in standard textbooks are observed.	Local infiltration	First approved in 1948 as Xylocaine® 2% injectable solution. Considered an intermediate-acting local anesthetic with a duration of action ranging from 90 to 180 minutes.	

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The bupivacaine-meloxicam drug product has not been marketed anywhere in the world. The individual components, bupivacaine and meloxicam, have a long history of clinical use with the following indications:

- Bupivacaine HCl is indicated for the production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures (Marcaine™ product label, 2018).

- Meloxicam is a non-steroidal anti-inflammatory drug indicated for osteoarthritis, rheumatoid arthritis, and juvenile rheumatoid arthritis in patients who weigh ≥ 60 kg (Mobic® product label, 2016).

3.2. Summary of Presubmission/Submission Regulatory Activity

Heron Therapeutics, Inc. opened IND 125927 on May 7, 2015, for evaluation of HTX-011 in patients undergoing bunionectomy. The following table is a high-level summary of the key interactions between the Agency and Heron Therapeutics, Inc.

Table 2. Summary of Pre-Submission and Submission Regulatory Activities

Meeting/Communication/Date	Event/Key Clinical Issues
IND 125927 opened / May 7, 2015	Study HTX-011-C2015-201 allowed to proceed / June 14, 2015
End of Phase 2 (EOP2) Meeting / June 15, 2017	The major clinical topics for discussion during the EOP2 meeting were as follows: – Primary, key secondary, other secondary, and exploratory efficacy endpoints – Broad indication – Reduced need for postoperative opioid analgesics – Active versus placebo control – Requirements for a superiority claim over active control – Method of administration of HTX-011 – Phase 2b efficacy results and their possible inclusion in the label – Evaluation of bupivacaine as the disease-active ingredient – Safety database – Human Factors study – Convenience kit and co-packaging of the drug and device
Initial Pediatric Study Plan (iPSP) Received/August 13, 2017	Written feedback in the form of a tracked-changes document was sent to the Sponsor.
Fast Track Designation / October 24, 2017	The preliminary data for the to-be-marketed formulation of HTX-011 treats a serious condition and appears to demonstrate the potential to address an unmet clinical need.
Type C Meeting / April 3, 2018	The major clinical topics for discussion during this Type C meeting were as follows: – Necessary scientific bridge for HTX-011 and Mobic (referenced Advisory Committee meeting material for Exparel)

NDA 211988
Bupivacaine and Meloxicam Extended-Release Solution

Meeting/Communication/Date	Event/Key Clinical Issues
	- Renal impairment study likely not needed based on the active moieties in HTX-011 (b) (4) plasma concentrations and patients with renal impairment - Measuring the bupivacaine metabolite PPX is not required - Both C_{max} and AUC will be used for systemic exposure comparisons of HTX-011 to Marcaine - The PK profile and administration technique do not reduce the risk of LAST alone - Acceptability of a thorough QT evaluation waiver - PK profiles are needed for every route of administration studied - Acceptability of the ISE in Module 2 - Route of administration
Breakthrough Therapy Designation / June 14, 2018	Based on preliminary data from two Phase 3 clinical studies, demonstrating a significant improvement over the current standard-of-care, bupivacaine HCl, in both pain intensity scores and duration of pain control.
Pre-NDA Meeting / June 20, 2018	The major clinical topics for discussion during the Pre-NDA meeting were as follows: - Necessary PK data to establish a scientific bridge - Highly vascular surgical sites include the thoracic cavity, head and neck procedures, and large spine procedures - Possible Advisory Committee Meeting - The PK profile of HTX-011 does not demonstrate a consistent, predictable PK profile (Phase 2 study results)
Rolling Review Request / August 30, 2018	As discussed during the Pre-NDA meeting, a formal request for a proposed Rolling Review was submitted.
Rolling Review Granted / September 12, 2018	No additional advice provided.
Agreed Initial Pediatric Study Plan (iPSP) / September 27, 2018	No additional advice provided.
NDA 211988 Submission (clinical data) / Oct. 30, 2018	NDA received.
NDA 211988 Filed / December 28, 2018	Potential clinical review issues include the following: - The maximum recommended HTX-011 labeled dosing, 400 mg/12 mg, was not evaluated in the pivotal Phase 3 studies. - The impact of HTX-011 on wound healing. - The clinical significance of the reported adverse event (preferred term) "skin odour abnormal".

Meeting/Communication/Date	Event/Key Clinical Issues
	– Dosing recommendations based on the size of the surgical site. – Clarification of the route of administration. – Acceptability of omission of the boxed warning for meloxicam regarding gastrointestinal and cardiovascular risks.

3.3. Foreign Regulatory Actions and Marketing History

HTX-011 is not marketed anywhere in the world. As previously mentioned, the individual drugs, bupivacaine and meloxicam, have a long history of clinical use throughout the world.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

In consultation with the Office of Scientific Investigations, Clinical Study Sites 005 (Principal Investigator Dr. Richard Pollack) and 024 (Principal Investigator Dr. Derek Muse) were selected for inspection. These study sites participated in both Phase 3 studies conducted by the Applicant and were selected for inspection based on the following, as outlined in the consultation request:

- Relatively high patient enrollment (approximately 28% of patients enrolled in Study 301 and approximately 24% of patients enrolled in Study 302)
- Relatively high number of non-serious adverse events, particularly Site 5 for Study 301 and Site 24 for Study 302
- Large treatment effect reported for the HTX-011 treatment group
 - the largest treatment effect reported for HTX-011 during both Study 301 and Study 302 was at Site 24

Clinical study sites involved in the Phase 2 studies that the Applicant has included as pertinent to the claimed indication were not considered for inspection based on clinical judgement after evaluation of surgical population, dose(s) studied, and number of treated patients.

The final OSI inspection report indicated that the Applicant adhered to the statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. The inspector had no concerns regarding the conduct of the Phase 3 studies that would impact the reported efficacy and safety findings.

4.2. **Product Quality**

The Applicant conducted three extractable/leachable studies in support of this application. The review team in the Office of Product Quality determined that none of the three studies is adequate to support regulatory approval.

Additionally, the dosage form and strength, as described in the product label and included below, will likely be adjusted to accommodate the approved dosing recommendations, HTX-011 300 mg/9 mg and 60 mg/1.8 mg. The proposed product label includes the following dosage forms and strengths:

- 400 mg bupivacaine and 12 mg meloxicam, 20 mL single-dose glass vial
- 200 mg bupivacaine and 6 mg meloxicam, 10 mL single-dose glass vial
- 60 mg bupivacaine and 1.8 mg meloxicam, 10 mL single-dose glass vial

For a discussion regarding the recommended delivered volume in milliliters and the milligram amount of each medication administered, refer to Section 4.6. Devices and Companion Diagnostic Issues.

4.3. **Clinical Microbiology**

HTX-011 is not an antimicrobial agent, therefore, clinical microbiology information was not submitted in the NDA.

4.4. **Nonclinical Pharmacology/Toxicology**

A comprehensive review of the nonclinical information is provided by Dr. Jaime D'Agostino, therefore, only a high-level summary of the key nonclinical information will be provided here.

An issue of clinical concern based in part on the nonclinical data is the impact of HTX-011 on wound healing. Table 3 highlights the wound healing issues identified in the nonclinical development program. In summary, HTX-011 had slightly increased incidence and/or severity of dermal, wound, and histopathological findings compared to saline control in several animal models. Based on the reported findings in the studies below, Dr. D'Agostino believes these observations may be related to excipients, (b) (4) although a role for meloxicam has not been completely excluded.

Table 3: Summary of Nonclinical Study Wound Findings

Study	Population, Species	Relevant Finding(s)
Non-GLP Study 33-38	Hernia repair Rabbit	- Increased incidence and/or severity of dermal, wound, and histopathological findings - Observed after treatment with other formulations, bupivacaine comparator, and vehicle
Non-GLP Study 33-39	Bone healing Rat	- Increased skin lesions - Observed after treatment with other formulations and bupivacaine comparator
GLP Study 33-54 (considered a more robust assessment compared to Studies 33-38 and 33-39 of wound healing)	Wound healing - Larger volume - Higher dose Minipig	- Increased severity and incidence of dermal and wound observations - Similar to saline treatment by Day 15 - Observed after treatment with other formulations and bupivacaine comparator
GLP Study 33-41	Wound healing Minipig	- Increased severity and incidence of dermal and wound observations - Similar to saline treatment by Day 15 - Observed after treatment with other formulations and bupivacaine comparator

Source: Adapted from toxicology information provided by Dr. Jaime D'Agostino, personal communication.

Additional studies intended to evaluate subcutaneous toxicity, Study 33-85 in rats and Study 33-86 in dogs, have identified the presence of chronic inflammation at the injection site that only partially recovers by study Day 28. The results from the clinical development program, in combination with all the nonclinical findings and information from the published literature, will inform the final regulatory decision.

4.5. Clinical Pharmacology

4.5.1. Mechanism of Action

Nerve cells maintain a resting membrane potential (RMP) at -70 millivolts (mV) using an active Na⁺-K⁺ pump, which transports Na⁺ out of the cell and K⁺ into the cell. This pump results in a concentration gradient favoring intracellular Na⁺ flux and extracellular K⁺ flux via ion specific channels. Because the cell membrane is more permeable to K⁺, there is greater efflux of K⁺ versus influx of Na⁺, which results in the negative RMP. During an electrical impulse, Na⁺ channels are activated resulting in a sudden and fast influx of Na⁺. The nerve membrane depolarizes and if it reaches the threshold level of -55 mV, the impulse is propagated as an action potential. As a result of this substantial influx of Na⁺, the membrane potential rises to +35 mV, the Na⁺ channels inactivate, and the membrane potential returns to -70 mV, the RMP.

Bupivacaine is an amide local anesthetic, which binds Na⁺ channels in the inactive state, thereby preventing subsequent neuronal cell depolarization to the threshold level. Because the impulse is not properly conducted, sensation and motor function are impaired, depending on nerve fiber diameter, myelin composition, and conduction velocity. In general, small, unmyelinated fibers that mediate pain and temperature sensations are more readily blocked than larger, unmyelinated fibers. Bupivacaine is a potent local anesthetic due to its high lipid solubility and it has a longer duration of action than lidocaine due to its high degree of protein binding.

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties currently approved for the treatment of osteoarthritis, rheumatoid arthritis, and juvenile rheumatoid arthritis. While its mechanism of action is not completely elucidated, orally administered meloxicam inhibits cyclooxygenase enzymes, COX-2 more so than COX-1. This action results in the inhibition of the synthesis of prostaglandins, which are known to sensitize afferent sensory nerves and potentiate the pain-inducing action of bradykinin in animal models. The decreased production of prostaglandins with administration of meloxicam is believed to be the main mechanism by which it treats the inflammation associated with the above-mentioned arthritides. The meloxicam component of HTX-011 may act via a similar proposed mechanism, however, the nonclinical data suggest an increase in chronic inflammation at the injection site which only partially resolves at study day 28. The observed chronic inflammation may be due to excipients in HTX-011, but does partially contradict the currently proposed mechanism of action of meloxicam.

The Applicant proposes

(b) (4)

For additional nonclinical information, refer to the pharmacology-toxicology review completed by Dr. Jaime D'Agostino.

As will be discussed elsewhere in this review, the risk of cardiovascular thrombotic events associated with NSAID use is likely due to inhibition of COX-2-dependent prostacyclin production in combination with insufficient COX-1-dependent platelet inhibition, via thromboxane B₂, such that prothrombotic mediators are in greater concentration than those inhibiting clot formation.

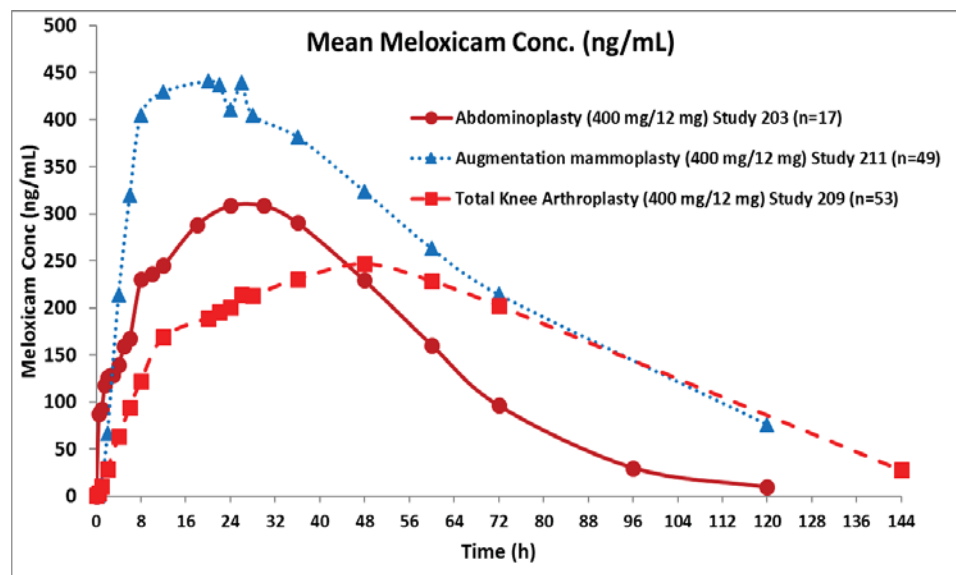
4.5.2. Pharmacokinetics (PK)

Meloxicam in HTX-011

The Applicant is relying on the Agency's previous findings of safety and efficacy for Mobic® and Marcaine™, and as such, conducted relative bioavailability (BA) studies for both active pharmaceutical ingredients (APIs) to establish a scientific bridge. The results indicate that exposure to meloxicam after treatment with HTX-011 is lower than that observed after treatment with oral Mobic®. Specifically, the Mobic® package insert states that the mean C_{max} after oral administration of 7.5 mg in healthy volunteers is 1050 ng/mL. The AUC_{inf} is calculated based on clearance values identified in the label and determined to be 85227 ng·h/mL for three days and 142045 ng·h/mL for five days. The highest mean C_{max} , 527 ng/mL, and AUC_{inf} , 41808 ng·h/mL, were observed after HTX-011 400 mg/12 mg administration during bilateral augmentation mammoplasty. These results appear to support the proposed scientific bridge between Mobic® and the meloxicam component of HTX-011 400 mg/12mg, however, I have two comments.

First, the PK profile of meloxicam is variable depending on the surgical models evaluated, as indicated in the following figure and table.

Figure 1: Meloxicam Profile Comparison after HTX-011 400 mg/12 mg Administration



Source: Dr. Suresh Naraharisetti, Clinical Pharmacology Mid-Cycle Meeting Presentation, January 29, 2019.

Table 4: Measured Meloxicam PK Parameters After Administration of HTX-011 400 mg/12 mg in Three Surgical Models

PK Parameter (Mean Values)	<u>Total Knee Arthroplasty</u> Study 209, Cohort 2 (N=53)	<u>Complete Abdominoplasty</u> Study 203, Part C (N=17)	<u>Augmentation Mammoplasty</u> Study 211 (N=49)
C _{max} (ng/mL)	275 ± 134	142 ± 72	527 ± 149
AUC ₀₋₂₄ (ng·h/mL)	3350 ± 1442	2016 ± 631	9034 ± 1924
AUC _{inf} (ng·h/mL)	25673 ± 17666	10069 ± 4123	41808 ± 38413
t _{1/2} (h)	42 ± 37	30 ± 23	42 ± 70
T _{max} (h)	36 [12, 72]	24 [9, 97]	20 [6, 49]

C_{max}: maximum plasma concentration; AUC: area under the curve; t_{1/2}: half-life;

Source: Adapted from Dr. Suresh Naraharisetti, Clinical Pharmacology Mid-Cycle Meeting Presentation, January 29, 2019.

And second, there were several patients in Study 209, who received HTX-011 400 mg/12 mg, with measured C_{max} values that were either equal to or greater than those described in the Mobic® package insert. Specifically, there were ten patients in Study 209, excluded from the Applicant's PK analyses, with maximum serum concentrations ranging from 581 to 3400 ng/mL measured at 144 hours post-dose and 1410 to 3390 ng/mL measured at 240 hours post-dose. In response to an Information Request dated December 4, 2018, the Applicant stated the following:

"...from Study 209 were excluded from the meloxicam non-compartmental analysis (NCA) due to significant increases in meloxicam levels inconsistent with the typical meloxicam PK profile for HTX-011. The Study 209 protocol specified that subjects were not allowed to use nonsteroidal anti-inflammatory drugs (NSAIDs) from the time the subject signed the informed consent form (ICF) through 72 hours after study drug administration; however, meloxicam usage after 72 hours was not restricted. Following database lock of Study 209, concomitant medication for subjects with inconsistent meloxicam PK profiles were reviewed for meloxicam usage, and the bupivacaine and meloxicam PK profiles were evaluated.

...This increase could have been a result of an additional dose of meloxicam given prior to the 144- hour sample."

Based on the additional information provided by the Applicant, it is possible that the increased serum concentrations were due to oral administration of meloxicam in these select patients, however, it is also possible that some patients had increased serum concentrations based on the administration of HTX-011 alone.

Bupivacaine in HTX-011

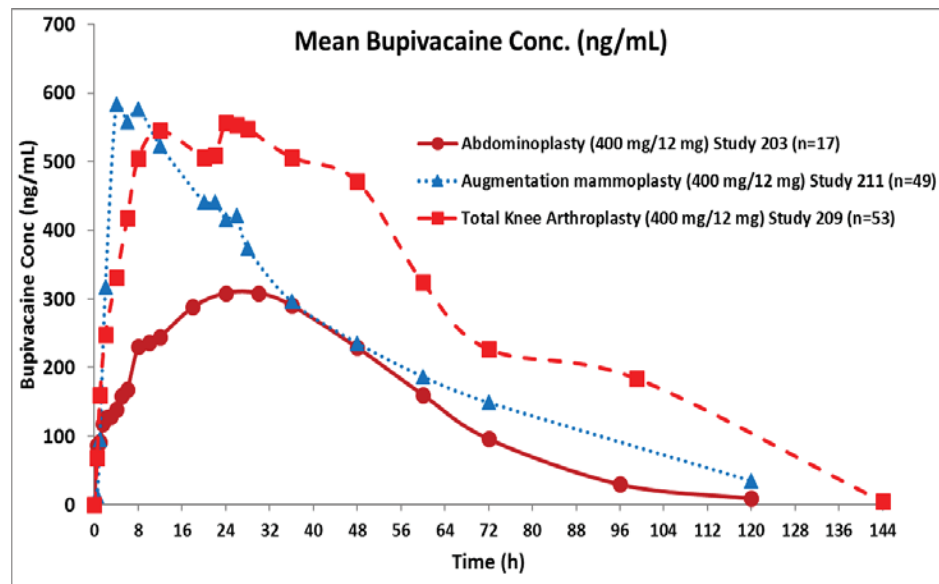
Because there are no PK data in the Marcaine™ label, the Applicant established the proposed scientific bridge to HTX-011 using C_{max} values from the HTX-011 development program and information from a single article in the published literature. Specifically, the Applicant compared the highest mean C_{max} of bupivacaine (710 ng/mL) after instillation administration of HTX-011 400 mg/12 mg to mean C_{max} data for bupivacaine HCl reported in the published literature (2160 ng/mL; Wildsmith, 1977).

There are four concerns with this approach to establishing the scientific bridge. First, the definitive peak concentration at which toxicity can be observed for any drug product is variable and depends on underlying individual comorbid medical conditions and concomitant medication administration. Second, the highest mean C_{max} , 710 ng/mL, in studies evaluating HTX-011 400 mg/12 mg was in Study 211, patients undergoing bilateral augmentation mammoplasty. The dosing in this study was divided such that each mammoplasty site received HTX-011 200 mg/6 mg separated in time, suggesting that the PK information is more reflective of two HTX-011 200 mg/6 mg sequential administrations versus a single HTX-011 400 mg/12 mg administration. Third, the release profile for bupivacaine from HTX-011 is variable and somewhat unpredictable, as indicated by the clinical pharmacology data presented below. And lastly, the Applicant did not compare the AUC values between bupivacaine HCl and HTX-011. Additionally, the single cited published literature article is problematic because it did not describe bioanalytical method validation and because the tradename for the referenced bupivacaine product was not included, Marcaine™ may not have been the product used.

In response to an Information Request sent by the clinical pharmacology review team on November 19, 2018, the Applicant responded with the following additional rationale in support of their proposed scientific bridge to Marcaine™. They argue that because approximately 50% of HTX-011 and 70% of bupivacaine HCl exposure occurs within the first 24 hours after administration, a more relevant comparison of bupivacaine AUC values, after HTX-011 and bupivacaine HCl administration, would be for the first 24 hours only. Additionally, they argue that because Marcaine™ is not indicated in doses greater than 175 mg without epinephrine, extrapolated AUC information based on dose-matching to HTX-011 is an acceptable alternative. Specifically, they compared extrapolated AUC information, based on theoretical bupivacaine HCl 400 mg doses, compared to the AUC for bupivacaine after HTX-011 400 mg/12 mg administration. For reasons more completely discussed in Dr. Suresh Naraharisetti's review, this approach is not acceptable.

An additional issue, similar to the observed meloxicam exposure during various surgical procedures, is that the PK profiles after administration of the same dose of HTX-011, 400 mg/12 mg, are variable, as demonstrated in the following figure and table.

Figure 2: Bupivacaine Profile Comparison after HTX-011 400 mg/12 mg Administration



Source: Dr. Suresh Naraharisetti, Clinical Pharmacology Mid-Cycle Meeting Presentation, January 29, 2019.

Table 5: Measured Bupivacaine PK Parameters After Administration of HTX-011 400 mg/12 mg in Three Surgical Models

PK Parameter	TKA Study 209, Cohort 2 N=53	Complete Abdominoplasty Study 203, Part C N=17	Augmentation Mammoplasty Study 211 N=49
C _{max} (ng/mL)	695 ± 411	366 ± 127	710 ± 246
AUC ₀₋₂₄ (ng·h/mL)	11223 ± 6142	5327 ± 1590	11758 ± 3990
AUC _{inf} (ng·h/mL)	38173 ± 29400	18247 ± 7069	31072 ± 17998
t _{1/2} (h)	17 ± 7	14 ± 3	25 ± 20
T _{max} (h)	21 [4, 59]	25 [9, 38]	4 [1, 35]

Source: Adapted from Dr. Suresh Naraharisetti, Clinical Pharmacology Mid-Cycle Meeting Presentation, January 29, 2019.

The above figure and table indicate the wide variability in measured PK parameters for each study in which the same, highest dose of HTX-011 was administered via the same route, instillation. (b) (4)

There are many factors influencing the systemic exposure after local anesthetic administration, including, but not limited to, the vascularity and tissue composition of the site, the dose administered, the route of administration, and the use of a limb tourniquet for surgical hemostasis. The vascularity of a surgical site tends to be the most important variable when considering the potential toxicity associated with local anesthetic administration, such that highly vascular sites are generally associated with increased systemic exposure and toxicity. Less vascular sites with large surface area exposure, however, can also lead to increased systemic levels and potentially toxicity. Additionally, the use of limb tourniquets in orthopedic procedures influences the systemic absorption, exposure, and potential toxicity after administration of local anesthetics. Specifically, an inflated limb tourniquet limits systemic absorption, however, tourniquet deflation results in rapid systemic uptake of locally-produced metabolites and administered medications such that toxicity could occur.

In conclusion, the systemic exposure to both meloxicam and bupivacaine after instillation administration of HTX-011 400 mg/12 mg is variable depending on the surgical procedure performed. (b) (4)



4.6. Devices and Companion Diagnostic Issues

Under 21 Code of Federal Regulations 3.2(e), HTX-011 is considered a drug/device combination product comprised of bupivacaine and meloxicam, the drugs, and the syringe with applicator, the device. The following figure illustrates HTX-011 in the proposed delivery device.

Figure 3: Proposed Drug Delivery Device



Source: Clinical Overview, p. 10 (PDF), Applicant's submission, NDA 211988

CDRH and Office of Combination Products will address the potential issues surrounding this combination product and delivery device in consultation responses. However, based on concerns surrounding the sterilization of the Luer lock syringe tip cap, a Class I device recommended for use with the Class II syringes, the review team in CDRH has concluded that the application is not approvable.

The review teams from the Division of Medication Error Prevention and Analysis (DMEPA) and CMC have identified three issues surrounding the stated volumes to withdraw and deliver, and the actual dose of HTX-011 administered. First, results from the Final Human Factors Validation Study indicated that several surgical technicians overfilled the Luer lock syringes by up to 2 mL for the HTX-011 400 mg/12 mg dose. Specifically, two syringes were filled to 8 mL each, such that the total volume was 16 mL as opposed to the recommended 14 mL. This overfilling would result in administration of bupivacaine 468 mg and meloxicam 14.1 mg. If the entire 18 mL volume in the HTX-011 400 mg/12 mg vial is administered, the total dose of bupivacaine and meloxicam administered would be 526.5 mg and 15.8 mg, respectively. Both doses are in excess of those evaluated in adequate and well-controlled studies and present a safety concern. Specifically, this dose of bupivacaine may increase the risk of developing LAST and this dose of meloxicam may increase the risk of developing the adverse events described in the boxed warnings in the Mobic® label.

In clinical practice, however, it is not uncommon to have additional medication in a vial beyond what is recommended for administration. Presumably this overfill is intended to compensate for any spillage or waste that may occur in the setting of clinical practice. Healthcare providers, including surgical technicians, are aware of this overfill and know the amount required for administration. Furthermore, surgeons confirm the dose, such that overfill is likely identified

prior to administration to the patient, reducing the true risk of medication error and overdose. Therefore, while overfill is a concern for clinically relevant medication overdose, it is unlikely the dose would actually be administered. In my opinion, this potential safety risk can be mitigated by clear and comprehensive information in the package insert.

The second issue is the individual drug amounts in the combination HTX-011 drug product. The calculated amount of individual drug, total amount of drug divided by delivered volume, is different than that stated on the carton label. Specifically, HTX-011 400 mg/12 mg is delivered in 14 mL, making the concentration of bupivacaine HCl 28.6 mg/mL and meloxicam 0.86 mg/mL. However, the carton indicates the bupivacaine HCl amount is 29.25 mg/mL and the meloxicam amount is 0.88 mg/mL. It appears that because HTX-011 is a viscous liquid, the density must be considered when calculating the total amount of drug delivered. In response to an Information Request regarding this issue, the Applicant provided the following information for clarification (Response to IR, April 13, 2018):

“For clarity, in the calculation of the delivered dose of bupivacaine and meloxicam per volume of HTX-011 drug product, the % w/w of the active ingredients and the density of HTX-011 (1.17 g/mL) must be taken into account as follows:

Bupivacaine in HTX-011:

2.5% w/w: $0.025 \times 1000 \text{ mg/g} \times 1.17 \text{ g/mL} = 29.25 \text{ mg/mL}$

Meloxicam in HTX-011:

0.075% w/w: $0.00075 \times 1000 \text{ mg/g} \times 1.17 \text{ g/mL} = 0.8775$ rounded to 0.88 mg/mL

The discrepancies noted by the FDA are primarily related to the rounding of numbers that relate to the viscous nature of the product...Due to the high viscosity of HTX-011, the vial fill volumes account for the extractable volume from the vials, the hold-up volume from the preparation and delivery components, and the delivered volumes as presented... The variability in the delivered dose from a syringe can be $\pm \frac{(b)(4)}{100}\%$, so the delivered dose in mg is rounded up when describing the nominal dose in mg specific to the vial fill (eg, $\frac{(b)(4)}{100}$ mg is rounded up to $\frac{(b)(4)}{100}$ mg).”

The following table was included in response to the IR.

Table 6: Planned Vial Fill Volumes and Commercial Kit Presentations for HTX-011 (bupivacaine 29.25 mg/mL and meloxicam 0.88 mg/mL)

Bupivacaine/ Meloxicam Nominal Dose (mg/mg)	Approx. Targeted Vial Fill Volume (mL)	Instructed Amount to be Withdrawn (mL) ^a	Number of Syringes and LLAs (Syringe Size)	Avg. Hold-up Volume of LLA (mL)	Actual Delivered Volume (mL)	Bupivacaine Delivered Dose (mg)	Meloxicam Delivered Dose (mg)
60/1.8	(b) (4)	2.3	1 (3 mL)	(b) (4)			
200/6	(b) (4)	7.0	1 (12 mL)	(b) (4)			
300/9	(b) (4)	10.5	1 (12 mL)	(b) (4)			
400/12	(b) (4)	14.0	2 (12 mL)	(b) (4)			

Abbreviations: Approx., approximate; LLA, Luer lock applicator; avg, average

^a The 3 mL syringes have 0.1 mL graduations, and the 12 mL syringes have 0.5 mL graduations.

Source: Response to IR, p. 2 (PDF), April 13, 2018, IND 125927.

And third, while the response to the IR did provide additional information which partially clarified the discrepancy, an additional issue involving the syringe hold-up volumes was identified. Specifically, it appears that the Applicant accounted only for the hold-up volume in the Luer lock applicator ((b) (4) mL, depending on size), but not the hold-up volume in the syringe ((b) (4) mL), which would require a larger amount be withdrawn (in the syringe) than that stated in the above table. In response to an additional IR sent on March 11, 2019, the Applicant stated that the hold-up volume in the syringe Luer tip would be the same before and after delivery of the drug product and is common for all syringes regardless of the volume or viscosity of the contained drug. Therefore, no adjustment to the recommended volumes for withdrawal is needed. Dr. Venkateswara Pavuluri, the CMC reviewer from the Office of Product Quality, agrees with the Applicant's assessment. For additional information regarding the hold-up volume calculation, the adequacy of the Applicant's response, and recommended withdrawal volumes refer to Dr. Pavuluri's review.

From a clinical perspective, the potential discrepancies in reported volumes and subsequent milligram amounts of drug delivery are sufficiently small (b) (4)

(b) (4) that there is unlikely to be an adverse impact on the reported safety and efficacy data in adult patients. However, these discrepancies do represent a lack of attention to detail, which is not acceptable, and may impact the safety of planned HTX-011 use in pediatric patients.

An additional issue is (b) (4)

(b) (4) Specifically, the proposed dosage forms do not include the recommended HTX-011 300 mg/9 mg dose. Detailed instructions will be included in the label to mitigate the potential risk of dosing error for recommended doses without a corresponding vial. Additional recommendations from other review teams will be incorporated into this

review when available.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

APPEARS THIS WAY ON ORIGINAL

Table 7: Clinical Studies Supporting NDA 211988

Study Identity	NCT #	Study Design	Regimen and Route	Primary Study Endpoints	No. of Patients Dosed	Study Population	No. and Location of Centers
<i>Adequate and Well-Controlled Studies to Support Efficacy and Safety</i>							
HTX-011-209 Cohort 2	03015532	Randomized, double-blind, active and saline placebo-controlled	<u>Via instillation or comb:</u> HTX-011 200 mg/6 mg <u>Via instillation:</u> HTX-011 400 mg/12 mg via ± ropiv. <u>Via injection:</u> BPV 0.25% 125 mg or PBO	Mean AUC of the NRS-R of pain intensity scores through 48h (AUC ₀₋₄₈) for HTX-011 compared with PBO	HTX + ropiv. = 56 HTX = 58 PBO = 53 BPV = 55	Adult patients undergoing total knee arthroplasty	15 sites in the U.S.
HTX-011-301	03295721	Randomized, double-blind, active and saline placebo-controlled	<u>Via instillation:</u> HTX-011 60 mg/1.8 mg or PBO <u>Via injection:</u> BPV 0.5% 50 mg	Mean AUC of the NRS-A of pain intensity scores through 72h (AUC ₀₋₇₂) for HTX-011 compared with PBO	HTX = 157 PBO = 100 BPV = 155 Total = 412	Adult patients undergoing unilateral bunionectomy	13 sites in the U.S.
HTX-011-302	03237481	Randomized, double-blind, active and saline placebo-controlled	<u>Via instillation:</u> HTX-011 300 mg/9 mg or PBO <u>Via injection:</u> BPV 0.25% 75 mg	Mean AUC of the NRS of pain intensity scores with activity (NRS-A) through 72h (AUC ₀₋₇₂) for HTX-011 compared with PBO	HTX = 164 PBO = 82 BPV = 172 Total = 418	Adult patients undergoing unilateral open inguinal herniorrhaphy	16 sites in the U.S. 1 site in Europe
<i>Supportive Phase 2a Studies</i>							
HTX-011-202	02504580	Randomized, blinded, active- and saline placebo-controlled	<u>Via instillation and/or injection:</u> HTX-011 200 mg/6 mg, 300 mg/9 mg, or 400 mg/12 mg; HTX-011-19 200 mg/6 mg, 400 mg/12 mg; HTX-011-49 200 mg/6 mg, 400 mg/12 mg; HTX-002 200mg, 400 mg; HTX-009 12 mg; BPV 0.25% 75 mg; PBO	Summed pain intensity scores over the first 24h (SPI ₀₋₂₄)	HTX = 131 HTX-011-19 = 89 HTX-011-49 = 39 HTX-002 = 51 HTX-009 = 18 BPV = 32 PBO = 103	Adult patients undergoing unilateral open inguinal herniorrhaphy	3 sites in the U.S.

Study Identity	NCT #	Study Design	Regimen and Route	Primary Study Endpoints	No. of Patients Dosed	Study Population	No. and Location of Centers
HTX-011-203	02689258	Randomized, blinded, active and saline placebo-controlled	<u>Via instillation and/or injection:</u> HTX-011 200 mg/6 mg, 300 mg/9 mg, 400 mg/12 mg, 600 mg/18 mg; HTX-011-49 200 mg/6 mg; HTX-002 400 mg; BPV 0.25% 100 mg; PBO	Summed pain intensity scores over the first 24h (SPI ₀₋₂₄)	HTX = 125 HTX-011-49 = 20 HTX-002 = 18 PV = 17 PBO = 95	Adult patients undergoing mini- or completed abdominoplasty	8 sites in the U.S.
HTX-011-208	02762929	Randomized, blinded, active and saline placebo-controlled	<u>Via instillation or injection:</u> HTX-011 30 mg/0.9 mg, 60 mg/1.8 mg, 120 mg/3.6 mg, 200 mg/6 mg; HTX-011-49 200 mg/6 mg; HTX-002 60, 120, 200 mg; HTX-009 3.6 mg; PBO	Summed pain intensity scores over the first 24h (SPI ₀₋₂₄)	HTX = 174 HTX-011-49 = 33 HTX-002 = 64 HTX-009 = 30 BPV = 25 PBO = 104	Adult patients undergoing bunionectomy	5 sites in the U.S.
Supportive Phase 2b Studies							
HTX-011-209 Cohort 1	03015532	Randomized, double-blinded, active and saline placebo-controlled	<u>Via instillation or comb:</u> HTX-011 200 mg/6 mg <u>Via injection:</u> BPV 0.25% 125 mg or PBO	Mean AUC of the NRS-R of pain intensity scores through 48h (AUC ₀₋₄₈) for HTX-011 compared with PBO	HTX = 42 BPV = 65 PBO = 64	Adult patients undergoing total knee arthroplasty	15 sites in the U.S.
HTX-011-211	03011333	Randomized, double-blind, active- and saline placebo-controlled	<u>Via bilat. u/s guided lateral and medial pectoral nerve block:</u> HTX-011 60 mg/1.8 mg, 120 mg/3.6 mg, 240 mg/7.2 mg, 400 mg/12 mg, BPV 0.25% 50 mg, PBO <u>Via instillation:</u> HTX-011 400 mg/12 mg	Mean AUC of the NRS-A pain-intensity scores through 24h (AUC ₀₋₂₄)	Nerve block: HTX = 111 BPV = 41 PBO = 41 Instillation: HTX = 50	Adult patients undergoing bilateral augmentation mammoplasty	3 sites in the U.S.

Abbreviations: BPV: bupivacaine; comb: combination route of administration, instillation + injection/infiltration; NRS-A: numeric rating scale with activity; NRS-R: numeric rating scale at rest; PBO: placebo; ropiv: ropivacaine.

NDA 211988

Bupivacaine and Meloxicam Extended-Release Solution

HTX designations: HTX-011-19 and HTX-011-49 represent earlier formulations of the bupivacaine-meloxicam drug product; HTX-002 represents the commercial formulation with bupivacaine only; HTX-009 represents the commercial formulation with meloxicam only.

APPEARS THIS WAY ON ORIGINAL

Clinical Review
Petit-Scott, M.D.

5.2. Review Strategy

The following sources of information were included in the review of this 505(b)(2) marketing application.

Studies performed by Heron Therapeutics, Inc.

The Applicant has conducted a total of eight clinical studies to support this marketing NDA; one Phase 1, three Phase 2a, two Phase 2b, and two Phase 3 studies. A brief overview of these supportive studies is included in the Table of Clinical Studies Supporting NDA 211988 above. This clinical review will focus on the safety and efficacy information provided in the adequate and well-controlled studies, Study 209 (Cohort 2), Study 301, and Study 302, and in combination with relevant information from the published literature, will provide the basis for the regulatory decision regarding this NDA.

Listed drugs referenced in this NDA

The Applicant has indicated reliance on the Agency's previous findings of safety and effectiveness for Marcaine™ 0.25% (NDA 016964) and Mobic® (NDA 020938). However, in response to an Information Request sent on November 19, 2019, the Applicant clarified that due to drug shortages, including Marcaine™, bupivacaine HCl was used as the active comparator in Study 209, Cohort 2, Study 301, and Study 302. The specific products used are considered therapeutically equivalent to Marcaine™, as indicated in the FDA Approved Drug Products with Therapeutic Equivalence Evaluations publication, commonly referred to as the Orange Book. From a regulatory perspective, use of therapeutic equivalents is acceptable provided the Applicant submits an updated 356h form. The acceptability for use of these products from a clinical pharmacology perspective, however, has not been determined at the time of this clinical review.

The scientific rationale for such reliance is based on the clinical pharmacology data from studies evaluating the highest recommended HTX-011 dose, 400 mg/12 mg, which demonstrated *generally* similar or lower mean C_{max} values than those documented for each active ingredient, the listed drugs. The Applicant suggests this data is adequate to establish the scientific bridge because additional PK parameters, such as T_{max} and AUC, are expected to be different (i.e., later and larger, respectively) based on the extended-release profile of this drug product. As previously mentioned, however, the rationale for lack of supportive AUC data will be more adequately addressed in the Clinical Pharmacology review by Dr. Suresh Naraharisetti.

The Applicant is relying on the prescribing information for both listed drugs, including CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS, USE IN SPECIAL POPULATIONS, OVERDOSAGE, CLINICAL PHARMACOLOGY, NONCLINICAL TOXICOLOGY, and PATIENT COUNSELING.

Information from the published literature

The Applicant is relying on information in the published literature to support the safety, efficacy, and clinical pharmacology of HTX-011.

6. Review of Relevant Individual Trials Used to Support Efficacy

The adequate and well-controlled studies used to support the proposed indication include one Phase 2b and two Phase 3 studies.

6.1. A Phase 2b, Randomized, Double Blind, Saline Placebo- and Active-Controlled, Multicenter Study of HTX-011 via Infiltration for Postoperative Analgesia in Subjects Undergoing Total Knee Arthroplasty (Study 209)

6.1.1. Study Design

Overview and Objective

Study 209 was designed to evaluate the analgesic efficacy, safety, and pharmacokinetics of HTX-011 administered as a single dose into the surgical site compared with bupivacaine HCl (standard of care) and saline placebo in patients undergoing total knee arthroplasty (TKA). There were two cohorts described as follows:

- Cohort 1 – dose- and administration technique-finding cohort
- Cohort 2 – adequate and well-controlled cohort that evaluated HTX-011 using a single dose and single administration technique selected after an interim review of results from Cohort 1. No interim analysis was included in Cohort 2.

The study objectives (verbatim) were as follows:

- Primary objective – to compare the efficacy and duration of analgesia achieved following periarticular infiltration (*sic*) of HTX-011 with that of saline placebo in subjects undergoing unilateral TKA.
- Secondary objectives –
 - to compare the efficacy and duration of analgesia for HTX-011 with that of bupivacaine HCl without epinephrine in this study population
 - to evaluate additional efficacy parameters, including opioid load, in this study population
 - to evaluate the efficacy and duration of analgesia for HTX-011 administered using different techniques in this study population
 - to characterize the bupivacaine and meloxicam pharmacokinetic profiles following administration of HTX-011 in this study population

- to assess the safety and tolerability of HTX-011 in this study population.

Trial Design

This study was a Phase 2b, randomized, double-blind, saline placebo- and active-controlled, multicenter study to evaluate the analgesic efficacy, safety, and PK of HTX-011 administered into the surgical site in subjects undergoing primary unilateral TKA under either general or spinal anesthesia.

In Cohort 2, 222 patients were randomized in a 1:1:1:1 ratio and treated with one of the four following treatments:

- HTX-011 400 mg/12 mg via periarticular instillation (HTX-011 was directly applied to the periosteum and joint capsule after cementation of the components)
- HTX-011 400 mg/12 mg via periarticular instillation and ropivacaine 0.5% 50 mg via periarticular injection (posterior capsule injection)
- Saline placebo via periarticular injection
- Bupivacaine HCl 0.25% 125 mg via periarticular injection

Preoperative analgesic medications for patients in Cohort 2 included pregabalin orally 150 mg and acetaminophen IV up to 1000 mg, administered just prior to surgery.

Patients received intraoperative analgesia with fentanyl IV, up to 4 mcg/kg total dose. Patients received a standardized dose of 75 mcg of fentanyl, increased from 50 mcg beginning with Protocol Version 4 due to high initial pain scores, after study drug administration and before wound closure. Patients remained at the hospital or research facility for a minimum of 72 hours post-study drug administration. After the 72-hour assessments were performed, patients could be discharged. Patients returned on Days 10 and 28 for follow-up assessments.

Opioid rescue medication, limited to morphine IV and/or immediate-release (IR) oxycodone, was permitted upon request during the 72-hour post-operative observation period. Analgesic prophylaxis was not permitted. During the first two hours in the Post-Anesthesia Care Unit (PACU), patients could receive up to 15 mg morphine IV, and then up to 10 mg in a two-hour period. Oxycodone IR 10 mg orally was permitted within any four-hour period as needed. Non-opioid analgesics were not permitted as rescue medication during the 72-hour post-operative period. Efficacy assessments included the following at various timepoints:

- evaluations of pain intensity using the Numeric Rating Scale (NRS) at rest and with activity (NRS-R and NRS-A, respectively)
- use of opioid analgesic medications
- Patient Global Assessment (PGA) of pain control
- assessments of rehabilitation, ambulation, and discharge readiness as assessed via the Modified Postanesthetic Discharge Scoring System (MPADSS)
- patient satisfaction with pain control

- overall benefit of analgesia score (OBAS)

Safety assessments included the following:

- adverse event recording, local anesthetic systemic toxicity (LAST) assessments
- physical examinations, vital signs
- ECGs, holter monitoring
- motor function assessments
- lab evaluations including hematology, chemistry
- wound healing assessments (Southampton Wound Scoring System)

Pharmacokinetic assessments included scheduled blood sampling for bupivacaine and meloxicam PK analysis.

The schedule of assessments during this study is summarized in the following table.

Table 8: Schedule of Events, Study 209, Cohort 2

9.5.5. Schedule of Events

Assessments	Time Window	Screening		Day 0		Time After Study Drug Administration*																								ET ^a		
		≤21 days	≤1 day	Preop	OR	1hr ±5 min	2hr ±15 min	4hr ±15 min	6hr ±30 min	8hr ±30 min	12hr ±30 min	20hr ±1hr	22hr ±1hr	24hr ±1hr	26hr ±1hr	28hr ±1hr	36hr ±2hr	48hr ±2hr	60hr ±2hr	72hr ±2hr	D6 ±1d	D10 ±2d	D28 ±4d									
Obtain informed consent		X																														
Assess/confirm eligibility		X		X																												
Medical history		X																														
Demographics		X																														
Urine pregnancy test (WOCBP only) ^b		X		X																												
Urine drug screen ^b		X		X																												
Physical examination		X ^c																		X												X ^d
Vital signs		X		X										X				X		X												X ^d
12-lead ECG (triplicate)		X																														
Timed 20-meter walk test		X							X		X			X				X		X												X ^e
Subject training for pain assessments		X		X																												
Holter monitoring ^f			←																													
Randomize subject ^h			X																													
Hematology and serum chemistry tests ⁱ		X													X					X		X										X ^d
Administer oral pregabalin ^j				X ^j																												
Administer tranexamic acid (TXA) ^k				X ^k																												
Administer IV acetaminophen ^l				X ^l																												
Surgery					X																											
Administer study drug				X																												
Record any opioid rescue medication																																
Pain intensity assessment (NRS-R) ^m			X		X	X	X	X	X	X	X			X				X	X	X	X		X	X								X ^d
Pain intensity assessment (NRS-A) ⁿ			X		X	X	X	X	X	X	X			X				X	X	X	X		X	X								X ^d
Rehabilitation assessment								X		X				X				X	X	X	X											
Ambulation assessment ^o			X					X		X				X				X		X												
Discharge readiness per MPADSS ^p							X	X	X	X	X			X				X	X	X	X											
Wound healing assessment ^q																				X												X
PK blood sample ^r			X	X ^r	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ^{s,u}	X ^u										
Subject's satisfaction with pain control														X				X		X												
PGA of pain control														X				X		X												X ^f
OBAS assessment														X				X		X												X
Subject daily diary ^v																																
Concomitant medications ^w		←																														X
Adverse events ^{t, s}		←																														X

Abbreviations: BMI, body mass index; d, day; ECG, electrocardiogram; ET, Early Termination Visit; hr, hour; IV, intravenous(ly); min, minutes; MPADSS, Modified Postanaesthetic Discharge Scoring System; NRS-A, Numeric Rating Scale with activity; NRS-R, Numeric Rating Scale at rest; OBAS, overall benefit of analgesia score; OR, operating room; PGA, Patient Global Assessment; PK, pharmacokinetic; Preop, preoperative; WOCBP, women of child-bearing potential; D10, Day 10; D28, Day 28.

* Note: The start of study drug administration was considered as Time 0 for all efficacy, safety, and PK assessments. The start of HTX-011 administration was considered as Time 0 whether or not administered with ropivacaine. The study protocol referred to the day of surgery and study drug administration as "Day 0," but "Day 1" was used for statistical analyses to conform to Clinical Data Interchange Standards Consortium (CDISC) standards. In this document, the day of surgery and study drug administration is referred to as "Day 0" in the descriptions of the study methodology and as "Day 1" in the descriptions of the study results.

For assessments at timepoints when the subject was asleep, study staff were to attempt to wake the subject. If there was no response, the assessments at these timepoints may have been recorded as "Not Done." Assessments that could be done without awakening the subject (eg, blood collection for PK sample) were to be completed. See Section 9.5 for more information on study procedures and assessments.

^a Subjects who withdrew from the study before their Day 28 Visit were asked to complete Early Termination procedures.

^b Result must have been negative and confirmed prior to initiation of surgery. A subject who failed the drug test may have been rescreened at the discretion of the Investigator. Subjects with a positive drug screen who were taking an allowed, prescribed medication that was known to result in a positive drug test (eg, amphetamine and dextroamphetamine for attention-deficit/hyperactivity disorder, benzodiazepine for anxiety disorder) may have been eligible for participation in the study. Subjects taking medical marijuana were not allowed to participate in the study.

^c Included height, weight, and BMI calculation.

^d Only if subject withdrew prior to 72 hours.

^e Only if subject withdrew prior to Day 10.

^f Only if subject withdrew prior to Day 28.

^g Subjects were required to have continuous reading of the Holter monitor at least 24 hours before surgery. If a Holter monitor safety alert was received after study drug administration, vital sign measurements were to be obtained and a blood sample was to be collected for PK analysis to evaluate for local anesthetic systemic toxicity (LAST).

^h Subjects who met the Screening eligibility criteria were randomized. Randomization may have been done up to 1 business day prior to study drug administration. Subject did not need to be present for randomization to occur.

ⁱ Hematology at 24 hours; hematology and serum chemistry at all other timepoints.

^j Each subject in Cohort 2 was given a single, oral dose of pregabalin 150 mg prior to the start of surgery.

^k TXA 1 g IV was administered prior to the start of surgery. A second dose was administered up to approximately 8 hours after the initial dose.

^l Each subject in Cohort 2 was administered a single dose of acetaminophen IV (no more than 1 g [1000 mg] in a 6-hour window, as per the approved prescribing information) prior to the start of surgery.

^m NRS-R was to be assessed while the subject was either seated comfortably or lying down.

ⁿ NRS-A assessments were to be performed after NRS-R. The prescribed activity for NRS-A was a straight leg raise of the surgical leg while the subject was lying down or seated in a recliner (recumbent). If the subject could not perform the activity, the NRS was still to be completed.

^o Defined as the ability to walk more than 3 steps with an assisted device.

^p This study instrument assessed a subject's potential readiness to be discharged and was to be repeated at all scheduled timepoints. It was not meant to be used to decide on whether or not to discharge a subject from the hospital/research facility. Discharge readiness assessments were to be repeated for any subject who remained hospitalized at 96 and 120 hours.

^q Wound healing assessments were repeated for any subject who remained hospitalized at 96 and 120 hours.

^r If a cardiac or neurological treatment-emergent adverse event occurred during the study, a blood sample was to be collected at the time that the event was noted to determine the plasma bupivacaine concentration.

^s A PK sample was to be collected 30 minutes (± 5 min) after the start of study drug administration even if the subject was still in the operating room.

^t PK samples may have been collected by a visiting nurse or at the study site.

^u Collection of PK samples on Days 6 and 10 was added per protocol amendment (ie, Protocol Version 6). Because this amendment was approved after enrollment for Cohort 1 had been completed and enrollment for Cohort 2 had already begun, PK samples were not collected on Days 6 and 10 for any of the subjects in Cohort 1 and were not collected for some of the subjects in Cohort 2.

^v Subjects completed a daily diary to record use of opioids for pain from 72 hours through Day 28.

^w At the Screening Visit, study staff were to ensure that subject was not taking any prohibited medications. All medications taken between the day of signing the Informed Consent Form and Day 28 were to be recorded.

^x Adverse events were to be collected from the time the subject signed the Informed Consent Form through Day 28.

Source: HTX-011-209 Study Report Body, p. 48 (PDF), Applicant's submission, NDA 211988

Eligibility Criteria

Pertinent inclusion criteria include the following:

- adult male or female, at least 18 years of age
- scheduled to undergo primary unilateral TKA under general anesthesia
- no previous TKA, ipsi- or contralateral
- ASA Physical Status three or less
- able to perform timed 20-meter walk unassisted, optional 4-legged walker for balance
- non-pregnant, non-lactating females

Pertinent exclusion criteria include the following:

- planned concurrent surgical procedure (e.g., bilateral TKA)
- pre-existing concurrent acute or chronic painful condition requiring analgesic treatment in the post-operative period

- contraindication or known hypersensitivity to bupivacaine, ropivacaine, or other local anesthetics, meloxicam or other NSAIDs, oxycodone, morphine, tranexamic acid, pregabalin, acetaminophen, aspirin, or fentanyl
- known or suspected daily opioid use for seven or more consecutive days in the preceding six months; had taken long-acting opioids within three days of surgery; had taken any opioids within 24 hours of surgery
- NSAID use within 10 days of surgery with the exception of low-dose aspirin (≤ 100 mg daily)
- received bupivacaine within five days of the surgery or any local anesthetic within 72 hours of surgery
- initiated any of the following medications to control pain within one month of surgery: selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin, or cyclooxygenase-2 (COX-2) inhibitors (if taking one of these medications not for pain control, must have been on a stable scheduled dose for at least one month)
- systemic steroids within five half-lives or 10 days prior to surgery (inhaled steroids excepted)
- medical condition that, in the opinion of the investigator, participating in the study would pose a health risk to the subject or confound the postoperative assessments, including the following:
 - myocardial infarction six months of signing the ICF, NY Heart Association Class three or higher, or clinically significant abnormalities of ECG or cardiac function
 - coronary artery bypass graft surgery within 12 months of signing ICF
 - severe liver function impairment (Child-Pugh Class C or higher, AST > three times upper limit of normal, ALT > three times upper limit of normal)
 - severe kidney function (creatinine clearance < 30 mL/min, on dialysis, and/or having serum creatinine > two times upper limit of normal)
 - coagulopathy or uncontrolled anticoagulation
 - loss of sensation in extremities or significant peripheral neuropathy
- history of Hepatitis B or C, human immunodeficiency virus (HIV)
- uncontrolled psychiatric or neurological disorder
- chronic neuromuscular deficit of either femoral nerve function or thigh musculature
- chronic condition or disease that would compromise neurological or vascular assessments
- history of malignancy
- alcohol or substance abuse
- history of three or more surgeries in the 12 months prior to signing the ICF
- BMI > 39 kg/m²

Study Endpoints

- Primary efficacy endpoint – Mean area AUC of the NRS-R pain intensity scores through 48 hours (AUC₀₋₄₈) for both HTX-011 treatment groups compared with saline placebo.
- Key secondary efficacy endpoint – Mean AUC₀₋₇₂ for both HTX-011 treatment groups compared with saline placebo.
- Additional secondary and exploratory efficacy endpoints –
 - Mean area AUC₀₋₄₈ of the NRS-R pain intensity scores for both HTX-011 treatment groups compared with bupivacaine HCl
 - Mean AUC₀₋₇₂ of NRS-R pain intensity scores for both HTX-011 treatment groups compared to bupivacaine HCl
 - Mean total postoperative opioid consumption (in morphine equivalents) through 24, 48, and 72 hours
 - Median time in hours to first opioid rescue administration
 - Mean AUC of the NRS-A pain intensity scores at the following intervals: 0-6, 0-12, 12-24, 0-24, 24-48, 0-48, 48-72, and 0-72 hours
 - Mean AUC of the NRS-R pain intensity scores at the following intervals: 0-6, 0-12, 12-24, 0-24, 24-48, and 48-72 hours
 - Mean NRS-R pain intensity scores at each assessed timepoint
 - Mean NRS-A pain intensity scores at each assessed timepoint
 - Integrated Rank Analysis of Silverman using the NRS-R pain intensity AUC scores and total opioid consumption through 24, 48 and 72 hours
 - Proportion of subjects achieving a score of “good” or better (>1) pain control based on PGA at 24, 48, and 72 hours, and Day 28
 - Proportion of subjects who are pain-free at rest (defined as an NRS-R pain intensity score of 0 or 1) at each assessed timepoint
 - Proportion of subjects who are pain-free with activity (defined as an NRS-A pain intensity score of 0 or 1) at each assessed timepoint
 - Proportion of subjects who are opioid-free through 24, 48, and 72 hours
 - Proportion of subjects who are opioid-free from 72 hours through Day 10 and Day 28
 - Proportion of subjects who complete first rehabilitation session at 6, 12, 24, 36, 48, 60, and 72 hours
 - Proportion of subjects who are ambulatory at 6, 12, 24, 48, and 72 hours
 - Proportion of subjects who first achieve a Modified Postanesthetic Discharge Scoring System (MPADSS) score ≥ 9 at 2, 4, 6, 8, 12, 24, 36, 48, 60, 72, 96, and 120 hours
 - Mean subject’s satisfaction with postoperative pain control at 24, 48, and 72 hours, and Day 10
 - Mean OBAS at 24, 48, and 72 hours, and Day 28.

All doses of opioid rescue analgesia were expressed as IV mg morphine equivalents (MME).

Statistical Analysis Plan

Cohort 1 and Cohort 2 results were analyzed separately, no pooling occurred. Unless otherwise specified, statistical analyses were performed using two-sided hypothesis testing at the 5% level of significance. Continuous data are presented using descriptive statistics, as follows: number of subjects, mean, standard deviation (SD), median, minimum and maximum. Descriptive statistics on efficacy measures also include the standard error of the mean (SEM). Categorical data were summarized by the number and percent of subjects. Confidence intervals are 95% and two-sided, unless otherwise specified.

The following populations were included in the analyses:

- Intent-to-Treat (ITT) – all patients who were randomized and received study drug. This population was used for the primary analysis for all efficacy endpoints.
- Safety – all patients who received study drug.
- PK – all patients who received at least 1 dose of HTX-011 or bupivacaine HCl, had sufficient data to calculate PK parameters and did not have adverse events thought to significantly impact the PK of either API in HTX-011.

Multiple endpoint handling was as follows:

- Cohort 2 – the following treatment comparisons were performed in a hierarchical order for the primary and key secondary endpoints:
 - Mean AUC₀₋₄₈ of the NRS-R pain intensity scores for HTX-011 400 mg/12 mg via periarticular instillation and ropivacaine 50 mg via periarticular injection vs. saline placebo
 - Mean AUC₀₋₄₈ of the NRS-R pain intensity scores for HTX-011 400 mg/12 mg via periarticular instillation vs. saline placebo
 - Mean AUC₀₋₇₂ of the NRS-R pain intensity scores for HTX-011 400 mg/12 mg via periarticular instillation and ropivacaine 50 mg via periarticular injection vs. saline placebo
 - Mean AUC₀₋₇₂ of the NRS-R pain intensity scores for HTX-011 400 mg/12 mg via periarticular instillation vs. saline placebo.

Multiple treatment comparisons were accounted for by a strict hierarchical testing to control the study-wise alpha level at 0.05. Specifically, if the first treatment comparison was statistically significant ($p \leq 0.05$), then the second comparison was tested, and so on. Once a treatment comparison failed to reach statistical significance, all subsequent comparisons were considered exploratory.

Missing NRS data was imputed via last observation carried forward (LOCF), in which the last post-dose nonmissing value was used for a subsequent missing value. If there was no post-dose value available, then the median of values from patients with nonmissing values within the same treatment group at the relevant time point were used. Pre-dose values were not

carried forward to post-dose timepoints. For binary endpoints not involving the NRS-R or NRS-A, missing data was handled using the non-responder imputation.

Refer to the statistical review by Dr. Yi Ren for additional information.

Protocol Amendments

The protocol was amended five times during the study. A brief overview of the changes associated with each amendment are described below:

- Protocol Version 2 – the main purpose of this amendment was to align the efficacy endpoints and data analyses with those planned in the Phase 3 studies, provide additional laboratory and wound healing assessments, adjust study drug volumes to be equal in active treatment and placebo groups in Cohort 1, and to standardize the intraoperative fentanyl dosing, 50 mcg.
- Protocol Version 3 – the main purpose of this amendment was to ensure consistent technique for study drug administration, accurate postoperative pain assessments, redefining eligibility criteria, and consistent and appropriate safety reporting.
- Protocol Version 4 – the main purpose of this amendment was to standardize postoperative analgesia across all treatment groups through 72 hours, DVT prophylaxis, and standardize steroid administration. Additionally, the permissible dose of intraoperative fentanyl was increased to 75 µcg just prior to the end of surgery.
- Protocol Version 5 – the main purpose of this amendment was to change Cohort 2 to be an adequate and well-controlled cohort, with adjustments to efficacy endpoints and without an interim analysis. Additionally, a multimodal approach to pain control was added in this cohort.
- Protocol Version 6 – the main purpose of this amendment was to revise primary and secondary efficacy endpoints, increase the sample size for Cohort 2, and adjust the planned efficacy analyses. Specifically, the primary efficacy endpoint was changed to mean AUC₀₋₄₈ of the NRS-R (from mean AUC₀₋₇₂ NRS-A) pain intensity scores due to high pain scores postoperatively at rest and increased variability of postoperative pain scores after 48 hours. Additionally, spinal anesthesia was removed as an anesthetic option, based on observed lower pain scores in the first few hours postoperatively.

6.1.2. Study Results

The study results for Cohort 2 presented by the Applicant are discussed in this section. The reviewer's analyses and interpretation of efficacy results are discussed in Section 7, Integrated Review of Effectiveness.

Compliance with Good Clinical Practices

Per the Study Report Body for Study 209, *"This study was conducted in compliance with the protocol and all applicable regulatory requirements in accordance with International Council for*

Harmonisation (ICH)/Good Clinical Practice (GCP) and in general conformity with the most recent version of the Declaration of Helsinki.”

Financial Disclosure

Robert E. Hoffman, Chief Financial Officer and Senior Vice President, Finance, signed FDA form 3454 on October 19, 2018, certifying that he has not entered into any financial arrangement with any of the listed clinical investigators. He further certified that none of the individual investigators has a proprietary interest in this drug product or a significant equity in the Sponsor per 21 CFR 54.2(b) or received payments in excess of what is permitted per 21 CFR 54.2(f).

Patient Disposition

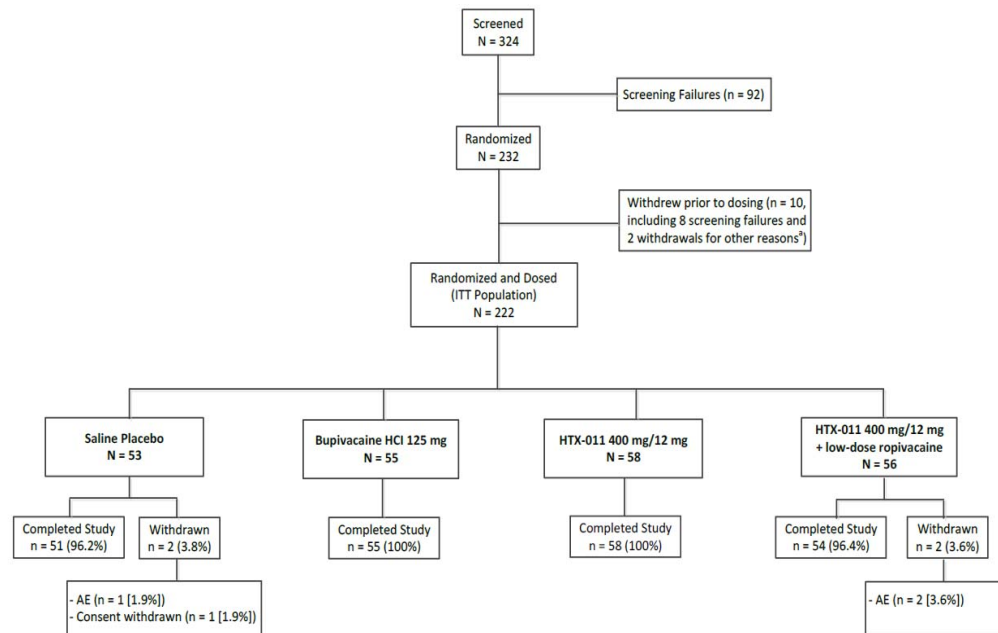
Cohort 2 – a total of 222 patients were randomized and treated as follows:

- Saline placebo – 53
- Bupivacaine HCl 0.25% (50 mL) 125 mg – 55
- HTX-011 4200 mg/12 mg instillation – 58
- HTX-011 400 mg/12 mg instillation + ropivacaine 0.5% 50 mg – 56

Of the 222 treated patients, 218 completed the study, four withdrew (two each in the saline placebo and HTX-011 400 mg/12 mg + ropivacaine groups). Three of these patients were withdrawn due to adverse events. The following figure summarizes patient disposition for Cohort 2.

APPEARS THIS WAY ON ORIGINAL

Figure 4: Patient Disposition, Cohort 2



Abbreviations: AE, adverse event; ITT, Intent-to Treat.

Notes: Screened was defined as signing an informed consent form. Completed the study was defined as completing the Day 28 Safety Follow-Up Visit.

^a Two subjects were randomized but withdrawn from the study prior to study drug administration due to other reasons. Subject 028-0012 was withdrawn because Holter monitor cards were not available. Subject 028-0013 was withdrawn due to a scheduling error (ie, surgery was started before the study team arrived).

Source: HTX-011-209 Study Report Body, p. 77 (PDF), Applicant's submission, NDA 211988

Protocol Violations/Deviations

The majority of patients in all treatment groups had at least one protocol deviation and the proportion of patients with a deviation was lower in both HTX-011 groups. The most commonly reported deviations included taking prohibited medications, errors in completing study procedures such as efficacy ratings, ECG, or physical examinations, completion of assessments or study visits outside of the specified time frame, and deviations associated with laboratory assessments. One patient in the bupivacaine HCl treatment group received bupivacaine HCl 0.75% for spinal anesthesia, which was not recorded as a concomitant medication. It was identified as a protocol deviation after database lock, therefore, not included in the data listings.

Important protocol deviations were defined as those that could significantly impact the accuracy of the data. Forty patients, including nine in the HTX-011 400 mg/12 mg group, twelve in the HTX-011 400 mg/12 mg + ropivacaine group, twelve in the saline group, and seven in the bupivacaine HCl group, had at least one important deviation. These deviations are summarized in the following table:

Table 9: Incidence of Important Protocol Deviations in Cohort 2 (ITT Population)

	Saline Placebo (N=53)	Bupivacaine HCl 125 mg (N=55)	HTX-011 400 mg/12 mg (N=58)	HTX-011 400 mg/12 mg + low- dose ropivacaine (N=56)
Any Important Protocol Deviation	12 (22.6%)	7 (12.7%)	9 (15.5%)	12 (21.4%)
ICF Procedures	0	0	0	0
Eligibility Criteria ^a	0	0	0	1 (1.8%)
Prohibited Concomitant Medication/Therapy ^b	8 (15.1%)	6 (10.9%)	5 (8.6%)	8 (14.3%)
Laboratory Assessments ^c	0	0	1 (1.7%)	1 (1.8%)
Study Procedures (eg, efficacy ratings, ECG, PE, etc.)	2 (3.8%)	1 (1.8%)	0	2 (3.6%)
Safety Reporting	0	0	0	0
Randomization/Blinding	0	0	0	0
Study Drug Dosing/Administration ^d	2 (3.8%)	0	0	0
Visit Schedule/Windows	1 (1.9%)	0	0	0
Other ^e	3 (5.7%)	0	4 (6.9%)	2 (3.6%)

Abbreviations: ECG, electrocardiogram; ICF, informed consent form; ITT, Intent-to-Treat; PE, physical examination.

^a Includes 1 subject who had a history of intolerance to Vicodin (ie, met exclusion criterion 3)

^b Includes subjects who received a prohibited medication or who received too much of a permitted rescue medication during the requisite periods specified in the protocol.

^c Two subjects did not have hematology assessed on Day 2.

^d Although all subjects received the study drug to which they were assigned, study drug was not administered per the instructions in the pharmacy manual for 2 subjects in the saline placebo group.

^e Other important deviations included failure to administer a protocol-specified medication (ie, pregabalin and/or acetaminophen preoperative or fentanyl intraoperatively) in 8 subjects and administration of enoxaparin instead of acetylsalicylic acid for deep vein thrombosis (DVT) prophylaxis in 1 subject.

Source: HTX-011-209 Study Report Body, p. 79 (PDF), Applicant's submission, NDA 211988

Demographic and Baseline Characteristics

Demographic and other baseline characteristics are presented in the following table. Briefly, the majority of patients were white (87%), not Hispanic or Latino (76%), and the mean age was 62 years. Based on the disease process, the older aged population is expected. In general, there were slight differences in demographic characteristics across the treatment and placebo groups, that are likely not clinically significant.

Table 10: Demographic and Baseline Characteristics in Study 209, Cohort 2 (Safety Population)

	Saline Placebo (N=53)	Bupivacaine HCl 125 mg (N=55)	HTX-011 400 mg/12 mg (N=58)	HTX-011 400 mg/12 mg + low-dose ropivacaine (N=56)	Total (N=222)
Age (years)					
Mean (SD)	61.5 (8.31)	61.4 (9.37)	62.5 (8.63)	63.2 (9.36)	62.1 (8.90)
Median	62.0	63.0	62.0	61.5	62.0
Min, Max	40, 82	33, 80	43, 79	43, 85	33, 85
Sex, n (%)					
Male	28 (52.8%)	20 (36.4%)	32 (55.2%)	29 (51.8%)	109 (49.1%)
Female	25 (47.2%)	35 (63.6%)	26 (44.8%)	27 (48.2%)	113 (50.9%)
Ethnicity, n (%)					
Hispanic or Latino	12 (22.6%)	16 (29.1%)	9 (15.5%)	16 (28.6%)	53 (23.9%)
Not Hispanic or Latino	41 (77.4%)	39 (70.9%)	49 (84.5%)	40 (71.4%)	169 (76.1%)
Race, n (%)					
American Indian or Alaska Native	0	0	1 (1.7%)	1 (1.8%)	2 (0.9%)
Asian	0	1 (1.8%)	0	1 (1.8%)	2 (0.9%)
Black or African Descent	8 (15.1%)	7 (12.7%)	6 (10.3%)	5 (8.9%)	26 (11.7%)
Native Hawaiian or Pacific Islander	0	0	0	0	0
White	45 (84.9%)	47 (85.5%)	51 (87.9%)	49 (87.5%)	192 (86.5%)
BMI (kg/m²)					
Mean (SD)	32.08 (4.090)	32.41 (4.367)	31.68 (4.214)	31.24 (4.909)	31.84 (4.401)
Median	32.34	32.70	31.81	31.44	32.01
Min, Max	22.8, 38.9	21.9, 39.0	23.7, 39.0	21.5, 38.6	21.5, 39.0

Abbreviations: BMI, body mass index.

Note: The Safety Population included all subjects who received study drug.

Source: HTX-011-209 Study Report Body, p. 96 (PDF), Applicant's submission, NDA 211988

APPEARS THIS WAY ON ORIGINAL

Other Baseline Characteristics

The surgical population was comprised of patients undergoing a first TKA, the majority (96%) of which were completed under general anesthesia. Eight patients received spinal anesthesia for the surgery; three patients in the HTX-011 400 mg/12 mg group, one in the HTX-001 400 mg/12 mg + ropivacaine group, one in the saline group, and three in the bupivacaine HCl group. Seven patients received ropivacaine 0.5% and one received bupivacaine HCl 0.75% as part of the spinal anesthetic.

The most common medical histories reported for patients in all groups were osteoarthritis and hypertension. There was a lower percentage of patients treated with HTX-011 400 mg/12 mg + ropivacaine with a history of arthroscopy or meniscus injury, but a higher percentage with arthralgia, compared to the other treatment groups. Other differences in baseline medical history do not appear relevant to the surgical procedure performed and unlikely to impact either the reported safety or efficacy findings.

Prior medications were taken by 64% of the overall study population and there did not appear to be clinically meaningful differences in medications taken between the study groups. Opioid and NSAID medications were prohibited prior to study start.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study drug compliance was 100% for patients who received study drug.

All patients received at least one concomitant medication during the study. There appeared to be no differences in medications taken between treatment groups. As previously mentioned, eight patients received additional local anesthesia as part of a spinal anesthetic. The majority of patients (99%) received the required 75 mcg of fentanyl IV prior to the end of surgery. Thirteen patients received fentanyl after surgery, which was included as a protocol deviation.

A total of 22 patients (10%) received a prohibited medication during the 72-hour postoperative period; four patients in the HTX-011 400 mg/12 mg group, six patients in the HTX-011 400 mg/12 mg + ropivacaine group, eight patients in the saline group, and four patients in the bupivacaine HCl group. The prohibited medications included opioid analgesics, paracetamol, NSAIDs, gabapentin, and ondansetron as nausea prophylaxis.

With respect to medication use for the treatment of opioid-related adverse events, it appears that fewer patients treated with HTX-011 400 mg/12 mg and HTX-011 400 mg/12 mg + ropivacaine were treated for constipation, although the difference is likely not clinically meaningful. A similar number of patients in all treatment groups received ondansetron for nausea.

Efficacy Results – Primary Endpoint and Key Secondary Endpoints

HTX-011 400 mg/12 mg and HTX-011 400 mg/12 + ropivacaine demonstrated statistically

significant reductions in mean AUC_{0-48} (primary efficacy endpoint) and mean AUC_{0-72} (key secondary efficacy endpoint) of NRS-R pain intensity scores compared to saline placebo. Mean NRS-R pain scores were lower for the HTX-011 400 mg/12 mg group compared to saline placebo at all timepoints through 72 hours. The posterior capsule injection with ropivacaine 0.5% 50 mg did appear to provide additional analgesia during the first eight hours. Table 11 summarizes the hierarchical testing results for the primary and key secondary endpoints.

Table 11: Results for Hierarchical Testing for the Primary and Key Secondary Endpoints, Study 209, Cohort 2 (wWOCF, ITT Population)

Treatment Group	N	Mean (SD)	p-value vs Saline Placebo
AUC_{0-48} of NRS-R (primary endpoint)			
HTX-011 400 mg/12 mg + low-dose ropivacaine	56	307.25 (127.674)	<0.0001
HTX-011 400 mg/12 mg	58	322.08 (99.669)	0.0002
Saline placebo	53	396.36 (77.468)	
AUC_{0-72} of NRS-R (key secondary endpoint)			
HTX-011 400 mg/12 mg + low-dose ropivacaine	56	452.54 (194.095)	<0.0001
HTX-011 400 mg/12 mg	58	471.19 (149.443)	0.0004
Saline placebo	53	577.93 (125.102)	

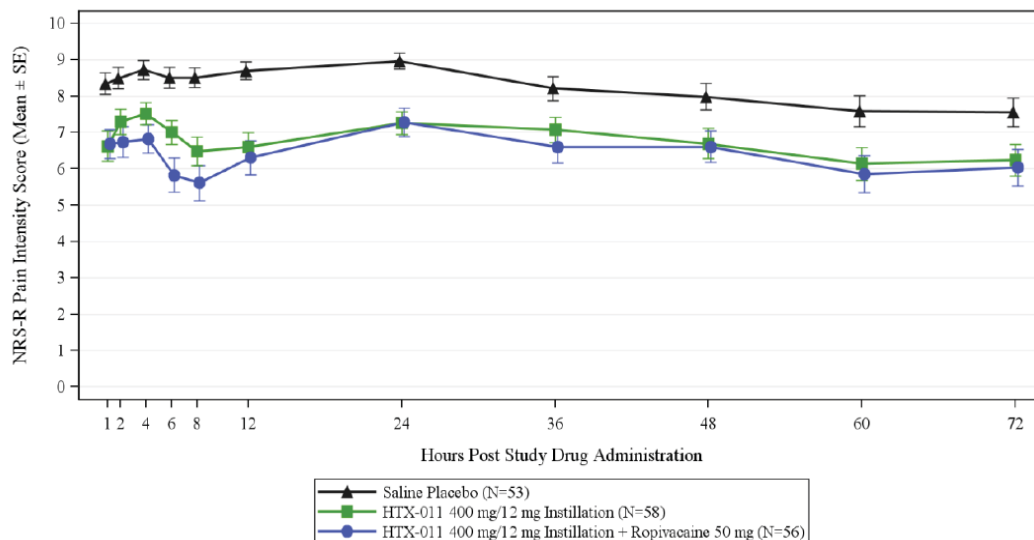
Abbreviations: AUC, area under the curve; ITT, Intent-to Treat; NRS-R, Numeric Rating Scale of pain intensity score at rest; wWOCF, windowed worst observation carried forward.

Notes: p-values reflect results of an analysis of variance (ANOVA) with randomized treatment as the main effect.

Source: HTX-011-209 Study Report Body, p. 104 (PDF), Applicant's submission, NDA 211988

Refer to the following figure for the pain intensity curves for each treatment group over 72 hours.

APPEARS THIS WAY ON ORIGINAL

Figure 5: Mean NRS-R Pain Intensity Scores Over Time for HTX-011 vs. Saline Placebo, Study 209, Cohort 2 (wWOCF, ITT Population)

Abbreviations: ITT, Intent-to-Treat; NRS-R, Numeric Rating Scale of pain intensity score at rest; wWOCF, windowed worst observation carried forward.

Source: HTX-011-209 Study Report Body, p. 103 (PDF), Applicant's submission, NDA 211988

The mean NRS-R pain intensity scores for the saline placebo group were consistently ≥ 7 throughout the 72-hour observation period. The maximum mean NRS-R pain score for this group was 9 at 24-hours postoperatively. The HTX-011 400 mg/12mg group had lower mean pain intensity scores compared with saline placebo at all time points through 72 hours. As indicated in the above figure, there is clear separation of the pain curves between the HTX-011 treatment and saline placebo groups. Maximum mean pain intensity scores for the HTX-011 400 mg/12 mg group was 7.5 at 4 hours. Pain scores increased slightly at 12 and 24 hours but then gradually declined through the remaining time period.

While Figure 5 indicates that the posterior capsule injection with ropivacaine appears to provide additional analgesic benefit for primarily the first eight hours postoperatively, review of the efficacy results for the other time intervals assessed suggests that the analgesic benefit of ropivacaine may extend far beyond the eight hours.

Data Quality and Integrity

Because this was a Phase 2 study, and the data will not be included in the final package insert, clinical study sites were not inspected, however, there was no indication during the clinical review of the study report that the results were not reliable.

Efficacy Results – Secondary and other relevant endpoints

HTX-011 400 mg/12 mg with or without ropivacaine statistically significantly reduced mean AUC_{0-24} of NRS-R pain scores and HTX-011 400 mg/12 mg with ropivacaine significantly reduced mean AUC_{0-48} and AUC_{0-72} of NRS-R pain scores compared with bupivacaine HCl. Refer to the

following table for a summary of the efficacy data for HTX-011 compared to bupivacaine HCl.

Table 12: Mean AUC₀₋₄₈ and AUC₀₋₇₂ of NRS-R Pain Intensity Scores for HTX-011 Compared with Bupivacaine HCl, Study 209, Cohort 2 (wWOCF, ITT Population)

Treatment Group	N	Mean (SD)	p-value vs Bupivacaine HCl
AUC₀₋₄₈ of NRS-R			
HTX-011 400 mg/12 mg + low-dose ropivacaine	56	307.25 (127.674)	0.0212
HTX-011 400 mg/12 mg	58	322.08 (99.669)	0.1160
Bupivacaine HCl 125 mg	55	352.74 (100.887)	
AUC₀₋₇₂ of NRS-R			
HTX-011 400 mg/12 mg + low-dose ropivacaine	56	452.54 (194.095)	0.0325
HTX-011 400 mg/12 mg	58	471.19 (149.443)	0.1246
Bupivacaine HCl 125 mg	55	516.93 (152.512)	

Abbreviations: AUC, area under the curve; ITT, Intent-to Treat; NRS-R, Numeric Rating Scale of pain intensity score at rest; wWOCF, windowed worst observation carried forward.

Notes: p-values reflect results of an analysis of variance (ANOVA) with randomized treatment as the main effect.

Source: HTX-011-209 Study Report Body, p. 105 (PDF), Applicant's submission, NDA 211988

Pain intensity with activity was also assessed and those results for the HTX-011 treatment groups were similar. Specifically, HTX-011 400 mg/12 mg with or without ropivacaine significantly reduced the mean AUC₀₋₂₄ and AUC₀₋₄₈ of NRS-A pain scores compared with saline placebo and bupivacaine HCl and over 72 hours compared to saline placebo. HTX-011 400 mg/12 mg + ropivacaine statistically significantly reduced mean AUC₀₋₇₂ of NRS-A pain scores compared to bupivacaine HCl.

Opioid consumption was statistically significantly lower in the HTX-011 400 mg/12 mg treatment group through 24 hours only when compared to saline placebo. There was no difference in opioid consumption through 24 hours between the HTX-011 400 mg/12 mg and bupivacaine HCl treatment groups. Additionally, opioid consumption between the HTX-011 400 mg/12 mg treatment group and the saline placebo or bupivacaine HCl treatment groups was not statistically significantly different at any other time points. All patients in the HTX-011 400 mg/12 mg treatment group received opioids during the 72-hour post-operative period.

Opioid consumption in the HTX-011 400 mg/12 mg + ropivacaine treatment group was statistically significantly lower over 24 hours compared to the bupivacaine HCl treatment group and over 24, 48, and 72 hours compared to the saline placebo treatment group. All but one patient in the HTX-011 400 mg/12 mg treatment group received opioids during the 72-hour post-operative period.

The efficacy results for HTX-011 treatment groups at various time intervals indicated the following:

- When compared to bupivacaine HCl treatment, patients treated with HTX-011 400 mg/12 mg alone had statistically significantly lower pain scores for only the mean AUC_{12-24} (p-value 0.017). The mean AUC_{0-24} was marginally significant with a p-value of 0.0497, which is rounded to 0.05.
- When compared to bupivacaine HCl treatment, patients treated with HTX-011 400 mg/12mg + ropivacaine had statistically significantly lower pain scores for mean AUC_{0-12} , AUC_{12-24} , and AUC_{0-24} .

These results taken together provide support for two conclusions. First, the posterior capsule injection with ropivacaine appears to play a larger role in analgesia than indicated by the Applicant and likely confers an analgesic benefit longer than the stated eight hours. This statement is also supported by the percentage of patients in each group who reported severe pain, defined as a pain intensity score of ≥ 7 at any time through 24, 48, and 72 hours. Statistically significant differences were observed only for the HTX-011 400 mg/12 mg + ropivacaine group through all timepoints when compared to both saline placebo and bupivacaine HCl. And second, for TKA, HTX-011 alone may offer no clinically meaningful analgesic benefit beyond bupivacaine HCl wound infiltration.

Proportion of Patients Pain-Free at Rest

The reported results for the proportion of patients who were pain-free at rest for each observed time point indicate that, in general, there was a higher percentage of patients in the HTX-011 treatment groups compared to those in either the saline placebo or bupivacaine HCl group who were pain-free. However, only a single time point, 72 hours, reached statistical significance for the HTX-011 400 mg/12 mg + ropivacaine versus saline placebo comparison. Furthermore, there was a higher percentage of patients treated with bupivacaine HCl who reported being pain-free compared to those treated with HTX-011 400 mg/12 mg alone at 72 hours. Refer to the following table for a summary of these results.

APPEAR THIS WAY ON ORIGINAL

Table 13: Proportion of Patients Pain-Free at Rest at Each Timepoint Using NRS-R, Study 209, Cohort 2 (wWOCF, ITT Population)

Timepoint	HTX-011			Control			% Difference Between Groups	95% CI Between Groups ^[2]	p-value ^[2]
	Treatment Group	n	% Pain-Free ^[1]	Treatment Group	n	% Pain-Free ^[1]			
24 Hours	HTX-011 400 mg/12 mg (13.7 mL) Instillation	58	1 (1.7%)	Saline Placebo (13.7 mL)	53	0	1.7%	-5.3%, 9.4%	>0.9999
				Bupivacaine HCl 125 mg (50 mL)	55	1 (1.8%)	-0.1%	-8.2%, 8.0%	>0.9999
	HTX-011 400 mg/12 mg (13.7 mL) Instillation + Ropivacaine 50 mg	56	5 (8.9%)	Saline Placebo (13.7 mL)	53	0	8.9%	1.3%, 19.6%	0.0573
				Bupivacaine HCl 125 mg (50 mL)	55	1 (1.8%)	7.1%	-2.2%, 18.4%	0.2060
48 Hours	HTX-011 400 mg/12 mg (13.7 mL) Instillation	58	7 (12.1%)	Saline Placebo (13.7 mL)	53	2 (3.8%)	8.3%	-2.9%, 20.1%	0.1657
				Bupivacaine HCl 125 mg (50 mL)	55	5 (9.1%)	3.0%	-9.7%, 15.4%	0.7626
	HTX-011 400 mg/12 mg (13.7 mL) Instillation + Ropivacaine 50 mg	56	7 (12.5%)	Saline Placebo (13.7 mL)	53	2 (3.8%)	8.7%	-2.4%, 20.7%	0.1628
				Bupivacaine HCl 125 mg (50 mL)	55	5 (9.1%)	3.4%	-9.6%, 16.7%	0.7613
72 Hours	HTX-011 400 mg/12 mg (13.7 mL) Instillation	58	6 (10.3%)	Saline Placebo (13.7 mL)	53	1 (1.9%)	8.5%	-1.2%, 19.5%	0.1158
				Bupivacaine HCl 125 mg (50 mL)	55	8 (14.5%)	-4.2%	-17.7%, 8.6%	0.5749
	HTX-011 400 mg/12 mg (13.7 mL) Instillation + Ropivacaine 50 mg	56	12 (21.4%)	Saline Placebo (13.7 mL)	53	1 (1.9%)	19.5%	7.8%, 32.9%	0.0020
				Bupivacaine HCl 125 mg (50 mL)	55	8 (14.5%)	6.9%	-7.9%, 21.9%	0.4599

Abbreviations: ITT, Intent-to-Treat; NRS-R, Numeric Rating Scale at Rest; wWOCF, windowed worst observation carried forward

^[1] Pain-free is defined as subjects with an NRS-R score of 0 or 1 at each assessed timepoint. NRS-R scores through 72 hours are constructed using wWOCF.

^[2] P-values from Fisher's exact test. Exact 95% CI is based on Farrington-Manning score statistics (Chan and Zhang, 1999).

Source: HTX-011-209 Study Report Body, p. 388 (PDF), Applicant's submission, NDA 211988

For those patients who reported no pain at rest at the 72-hour timepoint, a similar percentage of patients in all treatment groups, including saline placebo and bupivacaine HCl, reported a pain intensity score of < 4 on Days 10 and 28 postoperatively.

Pain Intensity Scores With Activity

As indicated in Table 14, pain intensity scores with activity through 72 hours were significantly lower for both HTX-011 treatment groups compared to saline placebo.

APPEARS THIS WAY ON ORIGINAL

Table 14: Mean AUC of NRS-A Pain Intensity Scores by Interval for HTX-011 Compared with Saline Placebo, Study 209, Cohort 2 (wWOCF, ITT Population)

Treatment Group	N	Mean (SD)	p-value vs Saline Placebo
AUC₀₋₂₄ of NRS-A			
HTX-011 400 mg/12 mg + low-dose ropivacaine	56	174.08 (51.237)	<0.0001
HTX-011 400 mg/12 mg	58	182.35 (44.346)	<0.0001
Saline placebo	53	212.81 (27.171)	
AUC₀₋₄₈ of NRS-A			
HTX-011 400 mg/12 mg + low-dose ropivacaine	56	359.88 (103.784)	<0.0001
HTX-011 400 mg/12 mg	58	378.61 (86.979)	0.0017
Saline placebo	53	427.88 (61.654)	
AUC₀₋₇₂ of NRS-A			
HTX-011 400 mg/12 mg + low-dose ropivacaine	56	536.77 (161.907)	0.0002
HTX-011 400 mg/12 mg	58	561.41 (136.923)	0.0058
Saline placebo	53	629.99 (99.888)	

Abbreviations: AUC, area under the curve; ITT, Intent-to Treat; NRS-A, Numeric Rating Scale of pain intensity score with activity; wWOCF, windowed worst observation carried forward.

Notes: p-values reflect results of an analysis of variance (ANOVA) with randomized treatment as the main effect.

Source: HTX-011-209 Study Report Body, p. 110 (PDF), Applicant's submission, NDA 211988

Clinically, the pain intensity scores with activity are more meaningful for this particular surgical procedure, where the expectation is early participation in physical therapy and rehabilitation. The following table summarizes the results of pain intensity scores with activity when compared to bupivacaine HCl.

Table 15: Mean AUC of NRS-A Pain Intensity Scores by Interval for HTX-011 Compared With Bupivacaine HCl, Study 209, Cohort 2 (wWOCF, ITT Population)

Treatment Group	N	Mean (SD)	p-value vs Bupivacaine HCl
AUC₀₋₂₄ of NRS-A			
HTX-011 400 mg/12 mg + low-dose ropivacaine	56	174.08 (51.237)	0.0002
HTX-011 400 mg/12 mg	58	182.35 (44.346)	0.0063
Bupivacaine HCl 125 mg	55	203.00 (30.250)	
AUC₀₋₄₈ of NRS-A			
HTX-011 400 mg/12 mg + low-dose ropivacaine	56	359.88 (103.784)	0.0012
HTX-011 400 mg/12 mg	58	378.61 (86.979)	0.0366
Bupivacaine HCl 125 mg	55	410.93 (65.577)	
AUC₀₋₇₂ of NRS-A			
HTX-011 400 mg/12 mg + low-dose ropivacaine	56	536.77 (161.907)	0.0104
HTX-011 400 mg/12 mg	58	561.41 (136.923)	0.1117
Bupivacaine HCl 125 mg	55	600.34 (107.816)	

Abbreviations: AUC, area under the curve; ITT, Intent-to Treat; NRS-A, Numeric Rating Scale of pain intensity score with activity; wWOCF, windowed worst observation carried forward.

Notes: p-values reflect results of an analysis of variance (ANOVA) with randomized treatment as the main effect.

NDA 211988
Bupivacaine and Meloxicam Extended-Release Solution

Source: HTX-011-209 Study Report Body, p. 112 (PDF), Applicant's submission, NDA 211988

Opioid Analgesia

Total postoperative opioid analgesia consumption was evaluated between the HTX-011 treatment groups and saline placebo and bupivacaine HCl. The results are summarized in Table 16. Briefly, patients treated with HTX-011 400 mg/12 mg alone had statistically significantly less opioid use through 24 hours only when compared to saline placebo. Opioid use through 48 and 72 hours was not statistically significantly different when compared to saline placebo. When compared to bupivacaine HCl, HTX-011 treatment did not result in statistically significantly less opioid use at any time point assessed. (b) (4)

Treatment with HTX-011 400 mg/12 mg + ropivacaine did result in less opioid use through 24, 48, and 72 hours when compared to saline placebo. However, when compared to bupivacaine HCl, HTX-011 resulted in statistically significantly less opioid use for 24 hours only.

Table 16: Total Postoperative Opioid Consumption From 0 Through 24, 48, and 72 Hours, Study 209, Cohort 2 (ITT Population)

	Saline Placebo (N=53)	Bupivacaine HCl 125 mg (N=55)	HTX-011 400 mg/12 mg (N=58)	HTX-011 400 mg/12 mg + low-dose ropivacaine (N=56)
Opioid consumption through 24 hours				
Mean (SD)	39.09 (19.215)	32.62 (15.232)	28.79 (14.031)	26.43 (14.191)
Median (min, max)	38.00 (5.0, 82.0)	30.00 (0.0, 71.0)	27.75 (2.5, 74.0)	26.00 (0.0, 66.0)
p-value vs saline placebo			0.0032	0.0003
p-value vs bupivacaine HCl			0.1584	0.0461
Opioid consumption through 48 hours				
Mean (SD)	58.45 (27.928)	52.56 (22.646)	48.75 (21.859)	45.41 (25.508)
Median (min, max)	56.00 (5.0, 114.0)	50.00 (0.0, 108.0)	48.50 (2.5, 105.0)	43.00 (0.0, 133.5)
p-value vs saline placebo			0.0532	0.0091
p-value vs bupivacaine HCl			0.4431	0.0611
Opioid consumption through 72 hours				
Mean (SD)	73.55 (34.448)	68.35 (29.169)	64.39 (27.889)	60.32 (34.949)
Median (min, max)	73.00 (10.0, 158.0)	70.00 (0.0, 147.5)	63.25 (2.5, 123.0)	60.25 (0.0, 188.5)
p-value vs saline placebo			0.1617	0.0253
p-value vs bupivacaine HCl			0.5560	0.1371

Abbreviations: ITT, Intent-to Treat; MME, morphine milligram equivalent.

Notes: Opioid rescue medications include hydrocodone, morphine, oxycodone, and pethidine. P-values were obtained using the Wilcoxon rank sum test.

Source: HTX-011-209 Study Report Body, p. 113 (PDF), Applicant's submission, NDA 211988

There was no statistically or clinically significant difference in time to first opioid rescue medication between the treatment groups. The median times ranged from 0.95 to 1.22 hours

for all groups. Additionally, there was no statistically or clinically significant difference in proportion of patients who were opioid-free over time between groups.

Patient Global Assessment

The proportion of patients who reported a PGA score of > 1 (defined as “good” or better pain control) was not statistically significant between the HTX-011 treatment groups and saline placebo and bupivacaine groups with the exception of HTX-011 400 mg/12 mg + ropivacaine compared to saline placebo at 24 hours and HTX-011 400 mg/12 mg compared to saline placebo at 72 hours.

Discharge Readiness

Treatment with HTX-011 did result in a statistically significantly higher percentage of patients reaching a score of ≥ 9 on the MPADSS when compared to saline placebo for 0-12 hours for HTX-011 400 mg/12 mg alone and for 0-24 hours for HTX-011 400 mg/12 mg + ropivacaine. Neither group reached statistical significance at any timepoint when compared to bupivacaine HCl. While the MPADSS seems acceptable as a general assessment tool for discharge readiness, it does not appear to be a validated tool for comparing treatment outcomes in clinical studies. Specifically, because it considers six different clinical criteria, including vital signs, ambulation, nausea/vomiting, pain, bleeding, and voiding, it is difficult to make definitive conclusions about the benefits of one analgesic regimen over another.

Rehabilitation and Ambulation

The proportion of patients who completed their first rehabilitation session by timepoint was similar across all treatment groups. The proportion of patients who were ambulatory at each timepoint was also similar across all timepoints.

Dose/Dose Response

For this study, a single dose of HTX-011 was administered, with and without a concomitant posterior capsule injection of ropivacaine 0.5% 50 mg. A dose response was, therefore, not observed.

Durability of Response

Administration of HTX-011 400 mg/12 mg did result in a statistically significant reduction in pain at rest through 72 hours and reduction in opioid analgesia use through 24 hours when compared to saline placebo.

6.2. A Phase 3, Randomized, Double-Blind, Saline Placebo- and Active-Controlled, Multicenter Study of HTX-011 via Local Administration for Postoperative Analgesia and Decreased Opioid Use Following Unilateral Simple Bunionectomy (Study 301)

6.2.1. Study Design

Overview and Objective

Study 301 was designed to evaluate the analgesic efficacy, safety, and pharmacokinetics of HTX-011 administered via instillation as a single dose into the surgical site compared with bupivacaine HCl (standard of care) and saline placebo in patients undergoing a primary unilateral, distal, first metatarsal bunionectomy with osteotomy and internal fixation (unilateral simple bunionectomy).

The study objectives (verbatim) were as follows:

- Primary objective - to compare the efficacy and duration of analgesia following local administration of HTX-011 with saline placebo during the first 72 hours following unilateral simple bunionectomy
- Secondary objectives –
 - to compare the efficacy and duration of analgesia for HTX-011 with bupivacaine HCl without epinephrine during the first 72 hours following surgery in this study population
 - to compare the effect of HTX-011 with saline placebo and bupivacaine HCl without epinephrine on opioid load during the first 72 hours following surgery in this study population
 - to assess the safety and tolerability of HTX-011 in this study population
 - to further establish the PK parameters of bupivacaine and meloxicam in HTX-011 in this study population.

Trial Design

This was a Phase 3, randomized, double-blind, saline placebo- and active-controlled, multicenter study to evaluate the analgesic efficacy, safety, and PK of HTX-011 administered via instillation into the surgical site in subjects undergoing unilateral simple bunionectomy under regional anesthesia (Mayo block performed with ≤ 20 mL of lidocaine 1%). Epidural or spinal anesthesia was not permitted.

Intraoperatively, patients received up to 4 mcg/kg of fentanyl IV, but administration of other opioid analgesics, non-opioid analgesics, local anesthetics, or anti-inflammatory medications were not permitted. Patients received sedation via IV Propofol. Near the completion of the surgery and after irrigation and suction were complete, a single dose of either HTX-011 60 mg/1.8 mg, saline placebo, or bupivacaine HCl 0.5% 50 mg was administered into the surgical site. HTX-011 and saline placebo were administered via instillation via a Luer-lock applicator.

Study drug was administered evenly to the proximal and distal ends of the wound, forming rings around the metatarsal. Study drug was not administered in the shallow subdermal layer. Bupivacaine HCl was administered via injection.

Postoperatively, patients received rescue medication only upon request, including oxycodone immediate-release oral (no more than 10 mg per four-hour period), morphine IV (no more than 10 mg in a two-hour period), and acetaminophen or paracetamol oral (no more than 1,000 mg in a six-hour period). They remained at the hospital or research facility through the 72-hour observation period, after which time patients were discharged with a daily diary for opioid medication use and pain data recording. Patients returned to the study site on Days 10 and 28 for follow-up assessments. A safety evaluation, including a postoperative x-ray, occurred on study Day 42.

Efficacy assessments included the following:

- evaluations of pain intensity using the Numeric Rating Scale (NRS) at rest and with activity (NRS-R and NRS-A, respectively)
 - the prescribed activity for NRS-A was sitting with the plantar surface of the ball of the surgically attended foot touching the floor (no weight-bearing)
- use of opioid analgesic medications
- discharge readiness as assessed via the Modified Postanesthetic Discharge Scoring System (MPADSS)
- Patient Global Assessment (PGA) of pain control

Safety assessments included the following:

- adverse event recording, local anesthetic systemic toxicity (LAST) assessments
- physical examinations, vital signs
- ECGs
- motor function assessments
- lab evaluations including hematology, chemistry
- wound healing assessments, bone x-rays

Pharmacokinetic assessments included scheduled blood sampling for bupivacaine and meloxicam PK analysis.

The schedule of assessments during this study is summarized in the following table.

Table 17: Schedule of Assessments, Study 301

Assessments	Time Window	Screening		Day 1		Time After Study Drug Administration*																		F/Up D42	ET ^a
						30 min	1h	1.5 h	2h	4h	8h	12h	18h	24h	36h	48h	60h	72h	D10	D28					
		≤28 days	≤1 day	Preop	OR	±5 min	±5 min	±10 min	±15 min	±15 min	±30 min	±30 min	±30 min	±1h	±2h	±2h	±4h	±4h	±3d	±4d	±7d				
Obtain informed consent		X																							
Urine drug screen ^b		X		X																					
Urine pregnancy test (WOCBP only) ^b		X		X																					
Assess/confirm eligibility		X		X																					
Medical history		X																							
Demographics		X																							
Physical examination		X ^c																X				X ^d			
Vital signs ^e		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X				X ^d			
12-lead ECG (triplicate) ^e		X							X			X	X		X		X					X ^d			
Subject training for pain assessments		X		X									X	X		X		X				X ^d			
Randomize subject ^f			X																						
Hematology and serum chemistry tests		X												X ^g			X	X				X ^d			
Surgery ^h					X																				
Administer study drug					X																				
LAST assessment						X	X		X	X			X	X			X					X ^d			
Pain intensity assessment (NRS-R) ⁱ							X ^j		X	X	X	X		X	X	X	X	X	X	X		X ^k			
Pain intensity assessment (NRS-A) ^j							X ^j		X	X	X	X		X	X	X	X	X	X	X		X ^k			
Record any rescue medication						←-----→																			
Record opioid use (Diary) ^m																			←-----→						
PGA of pain control															X		X		X		X	X ^k			
Discharge readiness per MPADSS ⁿ									X	X	X	X		X	X	X	X	X							
Wound healing assessment																		X	X	X	X	X			
Bone healing assessment (X-ray) ^o																				X	X	X ^p			
PK blood sample ^e										X			X	X		X									
Concomitant medications ^q		←-----→																				X			
Adverse events ^{a, r}		←-----→																				X			

Abbreviations: D, day; ECG, electrocardiogram; ET, Early Termination; F/Up, follow-up; h, hour; LAST, Local Anesthetic Systemic Toxicity; min, minutes; MPADSS, Modified Postanaesthetic Discharge Scoring System; NRS-A, Numeric Rating Scale of pain intensity score with activity; NRS-R, Numeric Rating Scale of pain intensity score at rest; OR, operating room; PGA, Patient Global Assessment; PK, pharmacokinetic; Preop, preoperative assessments; WOCBP, women of childbearing potential; D10, Day 10; D28, Day 28; D42, Day 42.

*The start of study drug administration was considered as Time 0 for all efficacy, safety, and PK assessments. For assessments at timepoints when the subject was asleep, an attempt was to be made to wake the subject. If there was no response, the assessments at these timepoints were to be recorded as "Not Done." Assessments that could be done without waking the subject (eg, blood collection for PK) were to be completed. When PK and NRS pain intensity assessments coincided, the NRS pain intensity assessments were to be conducted before the blood draw.

^a Subjects who withdrew from the study were asked to complete Early Termination procedures based on the timing of withdrawal (ie, prior to the Day 28 Visit, or after the Day 28 Visit and prior to the Safety Follow-Up on Day 42).

^b The urine drug screen and urine pregnancy tests were performed first. Results were to be confirmed negative prior to performing any additional assessments and prior to initiation of surgery. A subject who failed the drug test could have been rescreened at the discretion of the Investigator. Subjects with a positive drug screen who were taking an allowed, prescribed medication that is known to result in a positive drug test (eg, amphetamine and dextroamphetamine for attention deficit/hyperactivity disorder, benzodiazepine for anxiety disorder) may have been eligible for participation in the study. Subjects taking medical marijuana were not allowed to participate in the study.

^c Included height, weight, and body mass index calculation.

^d Only if subject withdrew prior to 72 hours.

^e If early neurological and cardiac signs and symptoms of LAST were observed, unscheduled vital sign measurements, 12-lead ECG, and blood sample collection for PK had to be performed.

^f Subjects who met the Screening eligibility criteria were randomized. Randomization could be done up to 1 business day prior to study drug administration. Subjects did not need to be present for randomization to occur.

^g Hematology only.

^h The length of the surgical incision was recorded.

ⁱ NRS-R was assessed while the subject is seated/recumbent with the surgically attended leg elevated or lying supine. Measurements were obtained after the subject was in the resting position for at least 5 minutes.

^j If a subject required rescue medication before the 1-hour pain intensity assessments, then an unscheduled NRS-R pain score followed by an NRS-A pain score was to be obtained before administering the first dose of rescue medication. These did not replace the 1-hour NRS-R and NRS-A assessments.

^k Only if subject withdrew prior to Day 28.

^l The prescribed activity for NRS-A was sitting with the plantar surface of the ball of the surgically attended foot touching the floor (no weight-bearing).

^m Subjects were to complete a daily diary from 72 hours through Day 28 to record if they took any opioid medication. Subject diary results were reviewed at each site visit up to and including the Day 28 Visit.

ⁿ This study instrument assessed a subject's potential readiness to be discharged and was repeated at all scheduled timepoints. It was not meant to be used to decide on whether or not to discharge a subject from the hospital/research facility.

^o An X-ray finding of delayed healing was followed with a repeat X-ray every 2 to 4 weeks until resolution (ie, signs of normal healing were evident).

^p Only if the subject withdrew from the study after 72 hours.

^q At the Screening Visit, the site was to ensure the subject was not taking any prohibited medications. All medications taken from the time the subject signed the Informed Consent Form (ICF) through the Safety Follow-Up on Day 42 were recorded.

^r Adverse events were collected from the time the subject signed the ICF through the Safety Follow-Up on Day 42.

Source: HTX-011-301 Study Report Body, p. 40 (PDF), Applicant's submission, NDA 211988.

Eligibility Criteria

Pertinent inclusion criteria include the following:

- adult male or female, at least 18 years of age
- scheduled to undergo primary unilateral, distal, first metatarsal bunionectomy with osteotomy and internal fixation under regional anesthesia
- ASA Physical Status three or less
- non-pregnant, non-lactating females

Pertinent exclusion criteria include the following:

- prior bunionectomy surgery in the past three months
- planned concurrent surgical procedure (e.g., bilateral bunionectomy)
- pre-existing concurrent acute or chronic painful condition requiring analgesic treatment in the post-operative period
- contraindication or known hypersensitivity to bupivacaine or other local anesthetics, meloxicam or other NSAIDs, oxycodone, morphine, or acetaminophen
- known or suspected daily opioid use for seven or more consecutive days in the preceding six months; had taken long-acting opioids within three days of surgery; had taken any opioids within 24 hours of surgery
- NSAID use within 10 days of surgery with the exception of low-dose aspirin (≤ 100 mg daily)
- received bupivacaine within five days of the surgery or any local anesthetic within 72 hours of surgery
- initiated any of the following medications to control pain within one month of surgery: selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin, or cyclooxygenase-2 (COX-2) inhibitors (if taking one of these medications not for pain control, must have been on a stable scheduled dose for at least one month)
- systemic steroids within five half-lives or 10 days prior to surgery (inhaled steroids excepted)
- medical condition that, in the opinion of the investigator, participating in the study would pose a health risk to the subject or confound the postoperative assessments, including the following:
 - myocardial infarction six months of signing the ICF, NY Heart Association Class three or higher, or clinically significant abnormalities of ECG or cardiac function
 - coronary artery bypass graft surgery within 12 months of signing ICF
 - severe liver function impairment (Child-Pugh Class C or higher, AST > three times upper limit of normal, ALT > three times upper limit of normal)
 - severe kidney function (creatinine clearance < 30 mL/min, on dialysis, and/or having serum creatinine > two times upper limit of normal)
 - coagulopathy or uncontrolled anticoagulation
 - loss of sensation in extremities or significant peripheral neuropathy

- history of Hepatitis B or C, human immunodeficiency virus (HIV)
- uncontrolled psychiatric or neurological disorder
- history of malignancy
- alcohol or substance abuse
- history of three or more surgeries in the 12 months prior to signing the ICF
- BMI > 39 kg/m²

Study Endpoints

The primary and key secondary efficacy endpoints were tested hierarchically, such that the first insignificant result would result in all subsequent endpoints being exploratory only.

- Primary efficacy endpoint – Mean AUC₀₋₇₂ of the NRS-A pain intensity scores for HTX-011 compared with saline placebo
- 1st key secondary efficacy endpoint – Mean AUC₀₋₇₂ of the NRS-A pain intensity scores for HTX-011 compared with bupivacaine HCl
- 2nd key secondary efficacy endpoint – Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with saline placebo
- 3rd key secondary efficacy endpoint – proportion of patients who are opioid-free through 72 hours for HTX-011 compared to bupivacaine HCl
- 4th key secondary efficacy endpoint – Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with bupivacaine HCl.
- Additional secondary efficacy endpoints –
 - Proportion of patients who are opioid-free through 72 hours compared with saline placebo
 - Proportion of patients who are opioid-free from 72 hours through Day 10 and Day 28
 - Median time in hours to first opioid rescue medication up to 72 hours
 - Mean AUC₀₋₇₂ of the NRS-R pain intensity scores
 - Integrated Rank Analysis of Silverman using the NRS-A pain intensity AUC scores and total opioid consumption through 72 hours
 - Proportion of patients who are pain-free with activity (defined as an NRS-A pain intensity score of 0 or 1) at each assessed timepoint through Day 28.
 - Proportion of patients with an NRS-A pain intensity score ≥4 at any timepoint through 72 hours
 - Proportion of patients with an NRS-A pain intensity score ≥7 at any timepoint through 72 hours.
 - Proportion of patients who first achieve an MPADSS score ≥9 at 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours
 - Proportion of patients achieving a score of “good” or better (>1) pain control based on PGA at 24, 48, 72 hours, and on Day 28.

Statistical Analysis Plan

Unless otherwise specified, statistical analyses were performed using a two-sided hypothesis test at the 5% level of significance. Continuous data are presented using descriptive statistics, including both the standard deviation and standard error. Categorical data are summarized by the number and percentage of patients. Confidence intervals are 95% and two-sided, unless otherwise specified.

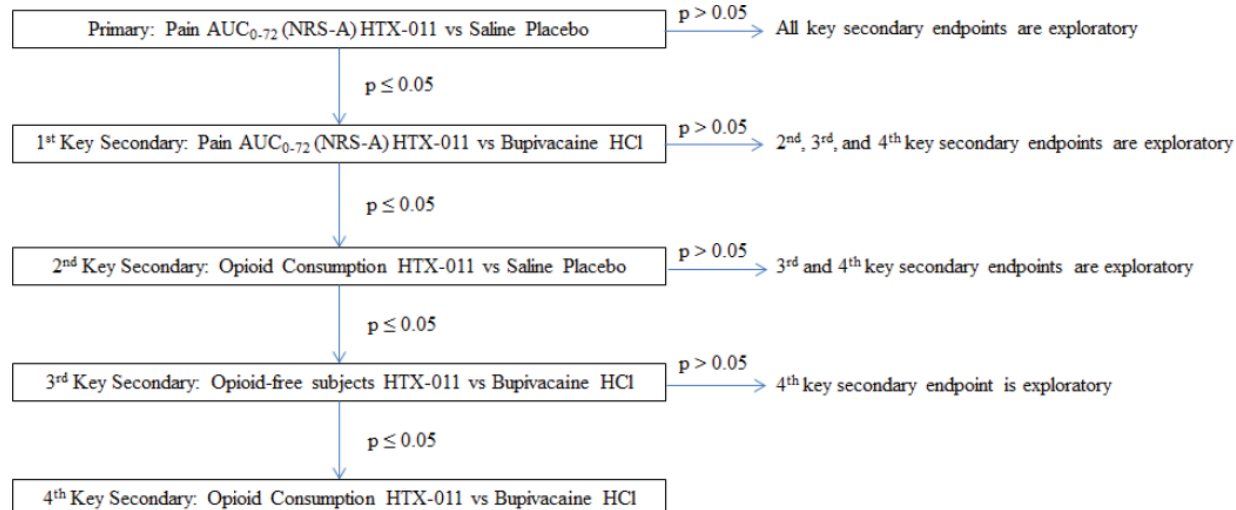
Baseline was defined as the last observed measurement collected, whether scheduled or unscheduled, prior to study drug administration. The 72-hour observation period was defined as the period of time from the start of study drug administration to the time of NRS-A pain intensity score at the nominal 72-hour timepoint.

The intent-to-treat (ITT) population consisted of all randomized patients who received study drug. This population was used for the primary analysis for all efficacy endpoints and patients were analyzed according to the randomized treatment assignment. Patients were excluded from the efficacy analyses if they received a prohibited rescue medication or had an important protocol violation prior to 72 hours. The per protocol (PP) population was all ITT patients who did not receive a prohibited rescue medication or who had no important protocol violations prior to 72 hours. The safety population was all patients who received study drug. This population was used for all summaries of safety data and the actual treatment was used for this analysis.

To account for multiple endpoint testing of the primary and four key secondary endpoints, a strict hierarchy was applied to control the study-wise alpha level at 0.05, as indicated in the figure below. Sequential testing continued until an endpoint failed to meet statistical significance, after which time all subsequent endpoint evaluations were considered exploratory.

APPEARS THIS WAY ON ORIGINAL

Figure 6: Hierarchical Test Procedure for Primary and Key Secondary Endpoints, Study 301



Abbreviations: AUC₀₋₇₂, area under the curve from Time 0 through 72 hours; NRS-A, Numeric Rating Scale of pain intensity score with activity.

Source: HTX-011-301 and HTX-011-302 Study Report Bodies, Applicant's submission, NDA 211988.

Missing NRS data was imputed via LOCF, in which the most recent post-dose nonmissing value was used for subsequent missing value. If there was no post-dose value available, median values from patients with observed values within the same treatment group at the same timepoint were used. For patients who withdrew prior to the 72-hour assessment, missing NRS scores were imputed using WOCF, in which the highest NRS pain intensity score prior to withdrawal was used for post-withdrawal values through 72 hours. Any missing NRS score prior to withdrawal were imputed via LOCF. For binary endpoints not involving the NRS-R or NRS-A, missing data was handled using the non-responder imputation.

Refer to the statistical review by Dr. Yan Zhou for additional information.

Protocol Amendments

The protocol was amended twice during the study before the first patient was dosed and two clarification memos were sent to investigative sites after the last amendment. The following is a high-level summary of the amendments and memos:

- Protocol Version 2, dated June 29, 2017 –
 - Revised key secondary efficacy endpoints and decreased the number of non-key secondary endpoints
 - Increased sample size in bupivacaine HCl treatment group from 100 to 150 patients
 - Revised instructions for administration of HTX-011
 - Acetaminophen added as a rescue medication
 - Discharge and post-operative pain management instructions revised

- Revised steroid exclusion criterion
 - Revised prescribed activity for NRS-A
 - ITT population to include all randomized patients who received study drug and removed mITT population
 - Revised use of LOCF for interval censored pain scores and WOCF for right-censored pain scores
- Protocol Version 3, dated September 24, 2017 –
 - LAST toxicity assessments, body temperature measurement, and additional vital sign timepoints added to the protocol based on feedback from FDA
 - Bone healing x-rays assessments added to the protocol
 - Abnormal wound healing to be followed until resolution and wound healing questionnaire revised
 - Route of administration for acetaminophen clarified
 - Intra-operative safety monitoring consistent with ASA standards
 - Stopping criteria clarified
 - Additional safety follow-up visit on Day 42
- Clarification memo, dated October 25, 2017 –
 - Clinical trial material staff, clinical observers, and bioanalytical staff are not blinded to the study treatment assignments
- Clarification memo, dated December 15, 2017 –
 - Inhalational anesthetic agents are not permitted during this study

6.2.2. Study Results

Compliance with Good Clinical Practices

Per the Study Report Body for Study 301, *“This study was conducted in compliance with the protocol and all applicable regulatory requirements in accordance with International Council for Harmonisation (ICH)/Good Clinical Practice (GCP) and in general conformity with the most recent version of the Declaration of Helsinki.”*

Financial Disclosure

Robert E. Hoffman, Chief Financial Officer and Senior Vice President, Finance, signed FDA form 3454 on October 19, 2018, certifying that he has not entered into any financial arrangement with any of the listed clinical investigators. He further certified that none of the individual investigators has a proprietary interest in this drug product or a significant equity in the Sponsor per 21 CFR 54.2(b) or received payments in excess of what is permitted per 21 CFR 54.2(f).

Patient Disposition

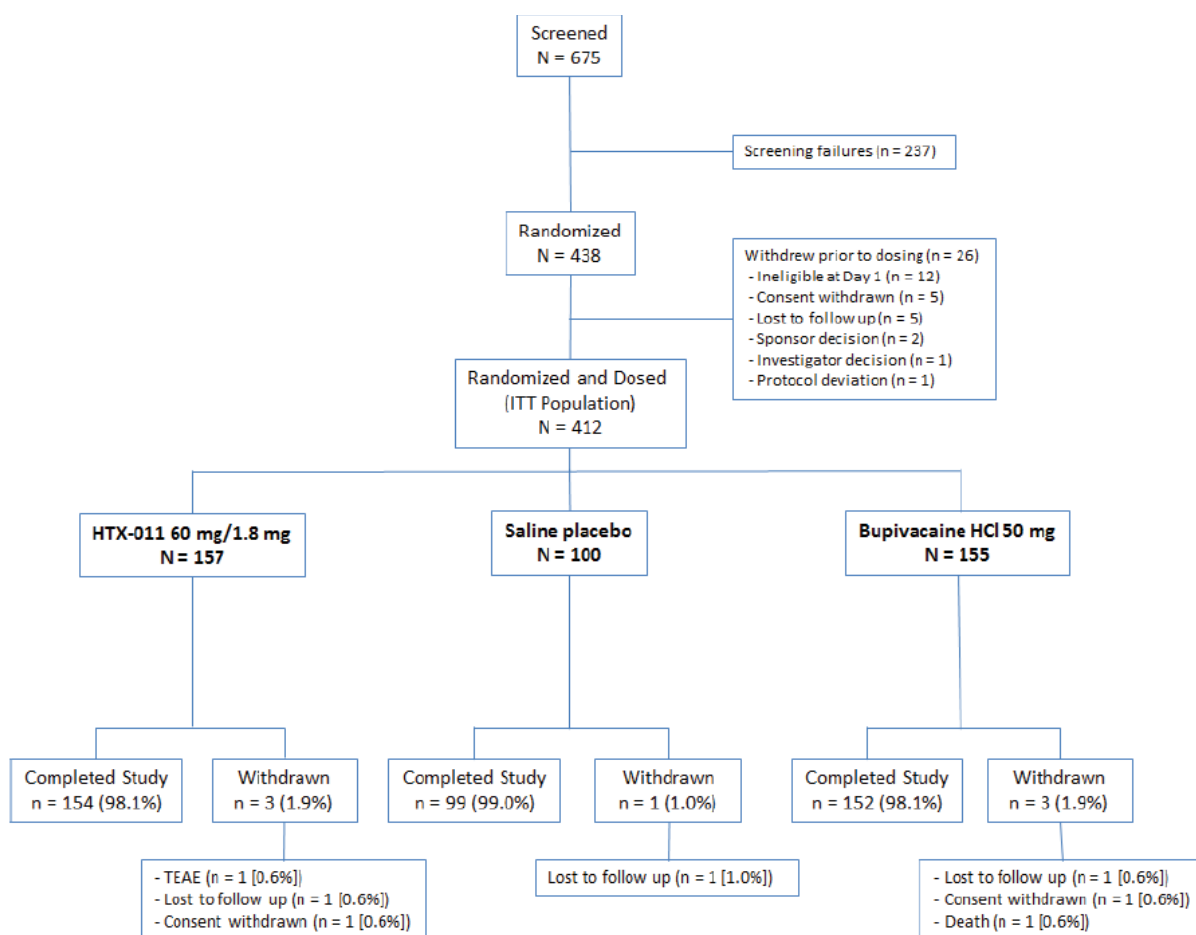
A total of 438 patients were randomized in a 3:3:2 ratio and 412 received a study drug as follows:

- 157 patients received HTX-011 60 mg/1.8 mg

- 100 patients received saline placebo
- 155 patients received bupivacaine HCl 0.5% 50 mg (one patient was randomized to this group but received saline placebo)

Refer to the following figure for additional disposition information.

Figure 7: Patient Disposition, Study 301



Abbreviations: ITT, Intent-to Treat; TEAE, treatment-emergent adverse event.

Notes: Screened was defined as signing an informed consent form. Completed the study was defined as completing the Day 42 Safety Follow-Up Visit. One subject randomized to the bupivacaine HCl group was misdosed; the subject received saline placebo instead of bupivacaine HCl.

Source: HTX-011-301 Study Report Body, p. 61 (PDF), Applicant's submission, NDA 211988

Protocol Violations/Deviations

Protocol deviations were categorized as follows: informed consent procedures, eligibility criteria, prohibited concomitant medication/therapy, laboratory assessments, study procedures, safety reporting, randomization/blinding, study drug dosing/administration, visit schedule/windows, and other. A total of 328 patients (80%) had at least one protocol violation,

the most common being visit schedule/windows (60%), study procedures (46%), and prohibited medication (19%).

Patients with important protocol deviations were excluded from the Per Protocol Population. These were considered deviations that could significantly impact the accuracy of the efficacy results and included the following:

- Patient did not meet inclusion criterion of needing the required surgical procedure.
- Patient did not meet the following exclusion criteria:
 - contralateral bunionectomy in the preceding three months
 - planned concurrent procedure
 - pre-existing concurrent acute or chronic painful condition requiring analgesic treatment in the post-operative period
 - known or suspected daily opioid use for seven or more days in the preceding six months; had taken long-acting opioids within three days of surgery; had taken any opioids within 24 hours of surgery
 - received bupivacaine within five days of the surgery
 - Informed consent not signed
 - prohibited medication with the 72-hour post-operative period
 - opioid rescue prior to first NRS-A pain assessment
 - unblinding by rating assessor or patient
 - study drug that was different than randomization assignment

The following table summarizes the important protocol deviations for this study.

Table 18: Incidence of Important Protocol Deviations, Study 301 (ITT Population)

	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=100)	Bupivacaine HCl 50 mg (N=155)	Total (N=412)
Any Important Protocol Deviation	15 (9.6%)	17 (17.0%)	17 (11.0%)	49 (11.9%)
Received prohibited pain medication during surgery or within 72-hour postoperative period ^a	13 (8.3%)	16 (16.0%)	14 (9.0%)	43 (10.4%)
Did not meet key eligibility criteria ^b	1 (0.6%)	1 (1.0%)	1 (0.6%)	3 (0.7%)
Study drug dosing deviation ^c	1 (0.6%)	0	2 (1.3%)	3 (0.7%)
Study procedure deviation related to pain assessments ^d	0	1 (1.0%)	0	1 (0.2%)

Abbreviations: ITT, Intent-to-Treat; NRS-A, Numeric Rating Scale of pain intensity score with activity.

^a Includes subjects who received a prohibited pain medication and subjects who received too much of a permitted rescue medication during the requisite periods specified in the protocol (Section 9.4.7.4).

^b Key eligibility criteria are listed in Section 9.7.2. Three subjects met exclusion criterion 1 (had a contralateral foot bunionectomy in the past 3 months).

^c Two subjects were administered study drug incorrectly (at beginning of surgery instead of the end of surgery), and 1 subject received study drug that was different from her randomized treatment assignment.

^d One subject was administered rescue pain medication prior to the first NRS-A pain assessment.

Source: HTX-011-301 Study Report Body, p. 62 (PDF), Applicant's submission, NDA 211988.

At discharge, patients were provided a daily diary to record opioid rescue analgesic use from 72 hours to Day 28. Two investigative sites distributed the diary only to patients who received an opioid prescription at discharge. A total of 64 patients, therefore, did not receive a diary from these sites; 46 patients from Site 013 and 18 patients from Site 020. The determination of opioid use and proportion of opioid-free patients was made based on concomitant medication data. The Applicant did not provide additional information regarding the treatment groups for these patients. An additional site-specific deviation is two sites, Site 005 and Site 020, used the incorrect wound healing assessment tool for 19 patients (five patients in the HTX-011 group, four patients in the saline placebo group, and ten patients in the bupivacaine HCl group) at 36 timepoints. The Applicant has indicated that while the wound healing questionnaire results were recorded as “Not Done” in the database, any clinically significant wound healing issues were documented as adverse events, such that the likelihood the reported results for the sites underestimated the incidence of wound issues is low.

Demographic and Baseline Characteristics

Demographic and other baseline characteristics are presented in in the following table. Briefly, the majority of patients were female (86%), White (82%), not Hispanic or Latino (69%), and the mean age was 47 years. Based on the disease process, the older aged population is expected. In general, there no meaningful differences in demographic characteristics across the treatment and placebo groups. Refer to the following table for additional demographic information.

APPEARS THIS WAY ON ORIGINAL

Table 19: Summary of Demographic and Baseline Characteristics, Study 301 (ITT Population)

	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=100)	Bupivacaine HCl 50 mg (N=155)	Total (N=412)
Age (years)^a				
Mean (SD)	48.0 (14.47)	47.3 (12.83)	45.5 (14.79)	46.9 (14.22)
Median	50.0	49.0	45.0	48.0
Min, Max	18, 77	19, 77	18, 77	18, 77
Sex, n (%)				
Male	19 (12.1%)	14 (14.0%)	23 (14.8%)	56 (13.6%)
Female	138 (87.9%)	86 (86.0%)	132 (85.2%)	356 (86.4%)
Ethnicity, n (%)				
Hispanic or Latino	47 (29.9%)	32 (32.0%)	49 (31.6%)	128 (31.1%)
Not Hispanic or Latino	110 (70.1%)	68 (68.0%)	106 (68.4%)	284 (68.9%)
Race, n (%)				
American Indian or Alaska Native	1 (0.6%)	0	2 (1.3%)	3 (0.7%)
Asian	8 (5.1%)	2 (2.0%)	1 (0.6%)	11 (2.7%)
Black or African Descent	24 (15.3%)	12 (12.0%)	22 (14.2%)	58 (14.1%)
Native Hawaiian or Other Pacific Islander	0	0	1 (0.6%)	1 (0.2%)
White	123 (78.3%)	86 (86.0%)	128 (82.6%)	337 (81.8%)
Multiple	1 (0.6%) ^b	0	1 (0.6%) ^c	2 (0.5%)
BMI (kg/m²)				
Mean (SD)	27.31 (4.793)	27.91 (5.050)	27.15 (4.376)	27.39 (4.704)
Median	26.81	27.27	26.74	26.91
Min, Max	18.3, 38.6	17.5, 38.4	17.3, 38.5	17.3, 38.6

Abbreviations: BMI, body mass index; ITT, Intent-to-Treat.

^a Age was calculated relative to the date of informed consent.^b Asian and White.^c Black or African Descent and White.

Source: HTX-011-301 Study Report Body, p. 64 (PDF), Applicant's submission, NDA 211988

Other Baseline Characteristics

The majority of patients in this study had no history of prior contralateral bunion surgery. The most common past medical history included seasonal allergy, headache, history of bunion surgery, and history of hysterectomy. The majority of women were premenopausal. There did not appear to be large differences in medical history incidences between groups that could have impacted the reported safety or efficacy results.

Prior medication use was reported for approximately 40% of the overall study population. The most commonly reported prior medications included vitamins (14%), anti-inflammatory and antirheumatic medications (9%), and analgesics (7%). The prior analgesic medication used most

frequently was paracetamol. Prior opioid analgesic medication use was reportedly very low and use was limited pre-operatively as described Section 6.2.1. Study Design, Eligibility Criteria.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study drug compliance was 100% for patients who received study drug.

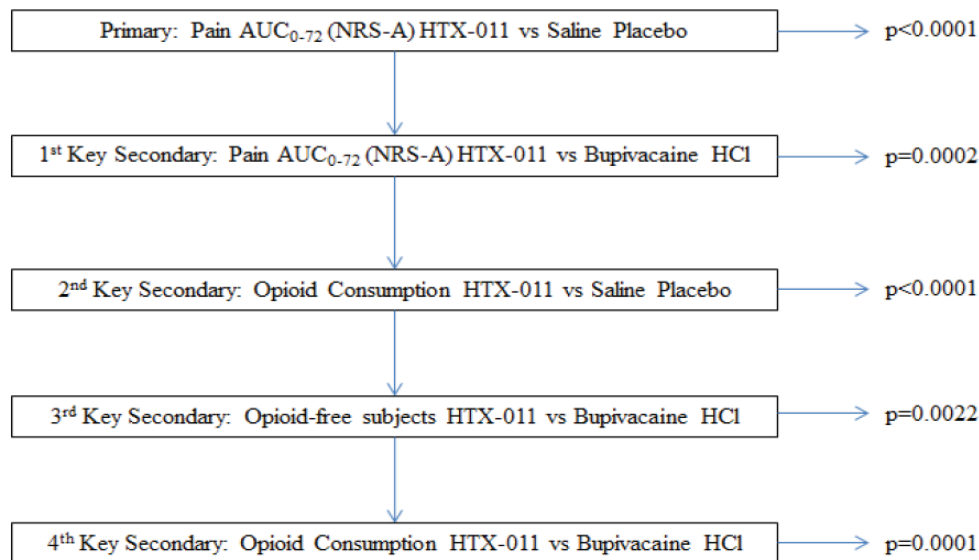
The majority of concomitant medications administered during the study were sedatives, analgesics, or antibiotics for infection prophylaxis. The majority of patients did not receive emesis prophylaxis or medications to treat constipation.

Permitted rescue medication included IV morphine, oral immediate-release oxycodone, and oral acetaminophen during the 72-hour observation period. Upon discharge, patients were permitted immediate-release oxycodone and acetaminophen. No other analgesics, including NSAIDs, were permitted. The overall use across different treatment groups is described throughout this review, as pertinent to efficacy data.

Efficacy Results – Primary Endpoint and Key Secondary Endpoints

The results for the primary and all four key secondary efficacy endpoints were statistically significant, as indicated in the following figure:

Figure 8: Summary of Hierarchical Testing Results for the Primary and Key Secondary Efficacy Endpoints, Study 301

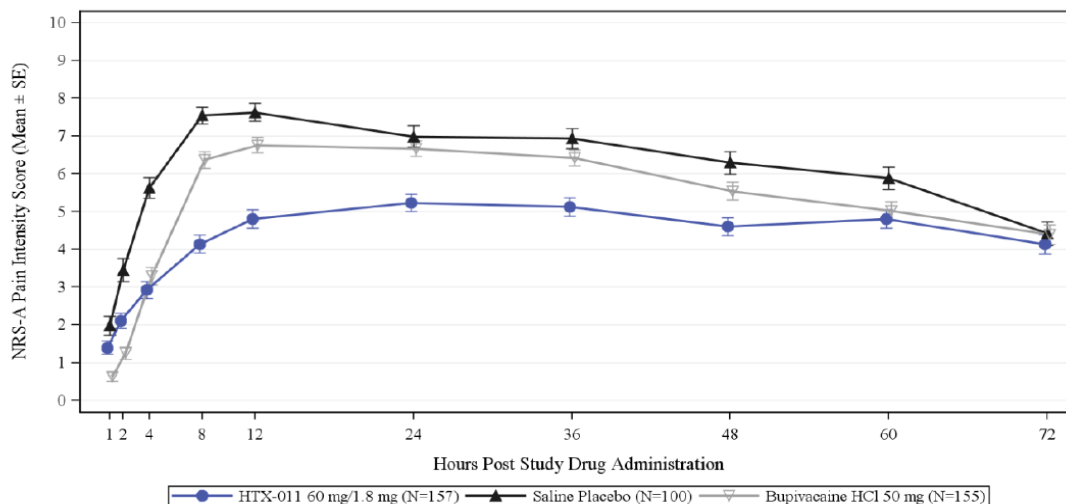


Abbreviations: AUC₀₋₇₂, area under the curve from Time 0 through 72 hours; NRS-A, Numeric Rating Scale of pain intensity score with activity.

Source: HTX-011-301 Study Report Body, p. 69 (PDF), Applicant's submission, NDA 211988

The following figure depicts the mean NRS-A pain intensity curves for each treatment group:

Figure 9: Mean NRS-A Pain Intensity Scores Over Time, Study 301 (wWOCF, ITT Population)



Abbreviations: ITT, Intent-to-Treat; NRS-A, Numeric Rating Scale of pain intensity score with activity; wWOCF, windowed worst observation carried forward.

Source: HTX-011-301 Study Report Body, p. 70 (PDF), Applicant's submission, NDA 211988

The pain curve data indicates overall lower scores for the HTX-011 treatment group compared to both saline placebo and bupivacaine HCl treatment. However, in the first two hours postoperatively, the bupivacaine HCl treatment group had lower NRS-A pain intensity scores compared to the HTX-011 and saline placebo groups (Table 14.2.7, Mean NRS-A Pain Intensity Scores at Each Timepoint Using wWOCF ITT Population, p. 249 PDF, Applicant's submission). Additionally, it appears that at 60 hours and beyond postoperatively, there was no difference in pain scores between the HTX-011 and bupivacaine treatment groups. When compared to saline placebo, there was no difference in observed NRS-A pain scores in the HTX-011 group at 72 hours and beyond postoperatively. These results suggest that the analgesic benefit of HTX-011 over bupivacaine HCl standard of care after bunionectomy appears to be from 2 to 60 hours post-operatively.

The primary and 1st key secondary efficacy findings support the Applicant's claim that for bunionectomy surgery, HTX-011 appears to offer superior pain control compared to saline placebo or bupivacaine HCl through 72 hours postoperatively. It is worth mentioning, however, that the prescribed activity for NRS-A was sitting with the plantar surface of the ball of the surgically attended foot touching the floor, non-weight-bearing. This seems like a relatively benign activity that would not result in significant discomfort beyond the resting position.

With respect to the 2nd and 4th key secondary efficacy findings, review of specific time intervals indicates that the greatest reduction in opioid use between the treatment group and the saline placebo or bupivacaine HCl groups was observed early in the postoperative period, specifically the 0 to 24-hour interval. This early difference likely drove the statistical significance for the 0

to 72-hour interval. The following table summarizes the opioid consumption by treatment group and time interval.

Table 20: Mean Total Postoperative Opioid Consumption in Morphine Equivalents, Study 301 (ITT Population)

Mean Opioid Consumption by Time Interval	HTX-011 60 mg/1.8 mg (n=157)	Saline Placebo, 2.1 mL (n=100)	Bupivacaine HCl 0.5%, 50 mg (n=155)
0-24h	7.38	14.12	11.81
– p-value vs. saline pbo	<0.0001		
– p-value vs. bupiv	<0.0001		
24-48h	6.42	9.88	8.19
– p-value vs. saline pbo	<0.0009		
– p-value vs. bupiv	0.0728		
48-72h	5	6	5
– p-value vs. saline pbo	0.0316		
– p-value vs. bupiv	0.6182		
0-72h	18.8	30	25
– p-value vs. saline pbo*	<0.0001		
– p-value vs. bupiv [#]	0.0022		

*2nd key secondary efficacy endpoint; [#]4th key secondary efficacy endpoint

Source: Adapted from HTX-011-301 Study Report Body, p. 227-229 (PDF), Applicant's submission, NDA 211988

The Agency's current thinking is that while a demonstrable decrease in opioid analgesic use is clinically meaningful, a corresponding decrease in opioid-related adverse events would be more informative, relevant, and beneficial to surgical patients. The following table summarizes the opioid-related adverse events for all treatment groups.

Table 21: Incidence of Opioid-Related Treatment-Emergent Adverse Events (TEAE) by Preferred Term, Study 301 (Safety Population)

Preferred Term ^[1]	HTX-011 60 mg/1.8 mg (2.1 mL) (N=157)	Saline Placebo (2.1 mL) (N=101)	Bupivacaine HCl 50 mg (10 mL) (N=154)
Subjects Reporting at Least One Opioid-related TEAE	69 (43.9%)	54 (53.5%)	78 (50.6%)
Nausea	59 (37.6%)	44 (43.6%)	70 (45.5%)
Vomiting	23 (14.6%)	19 (18.8%)	33 (21.4%)
Constipation	9 (5.7%)	7 (6.9%)	18 (11.7%)
Pruritus	8 (5.1%)	6 (5.9%)	1 (0.6%)
Pruritus generalised	4 (2.5%)	4 (4.0%)	8 (5.2%)
Somnolence	1 (0.6%)	0	1 (0.6%)

[1] Adverse events are coded to Preferred Term using MedDRA, version 19.1

Source: HTX-011-301 Study Report Body, p. 330 (PDF), Applicant's submission, NDA 211988

In general, it does appear that treatment with HTX-011 reduces the incidence of opioid-related adverse events compared to saline placebo and bupivacaine HCl.

The Applicant evaluated the percentage of patients in the HTX-011 treatment group compared to those in the bupivacaine treatment group who are opioid-free through 72 hours, the 3rd key secondary efficacy endpoint. Those results are not formally presented here but do indicate a statistically significant difference in the percentage of patients treated with HTX-011 who were opioid-free compared to those treated with bupivacaine HCl. Post-hoc analyses demonstrated that the majority of patients in all treatment groups who were opioid-free at 72 hours, remained opioid-free through the end of the study, Day 28. Refer to the following table for additional information.

Table 22: Proportion of Patients Who Are Opioid-Free Through Day 10 or 28, Study 301 (ITT Population)

	HTX-011 60 mg/1.8 mg	Saline Placebo	Bupivacaine HCl 50 mg
All subjects	N=157	N=100	N=155
Opioid-free through Day 10	41 (26.1%)	2 (2.0%)	15 (9.7%)
Difference (95% CI) vs saline placebo	24.1% (16.0%, 32.0%)		
p-value vs saline placebo	<0.0001		
Difference (95% CI) vs bupivacaine HCl	16.4% (7.4%, 25.1%)		
p-value vs bupivacaine HCl	0.0002		
Opioid-free through Day 28	37 (23.6%)	2 (2.0%)	14 (9.0%)
Difference (95% CI) vs saline placebo	21.6% (13.8%, 29.3%)		
p-value vs saline placebo	<0.0001		
Difference (95% CI) vs bupivacaine HCl	14.5% (5.9%, 22.9%)		
p-value vs bupivacaine HCl	0.0007		
Subjects who are opioid-free through 72 hours	n=45	n=2	n=17
Remained opioid-free through Day 10	41/45 (91.1%)	2/2 (100.0%)	15/17 (88.2%)
Remained opioid-free through Day 28	37/45 (82.2%)	2/2 (100.0%)	14/17 (82.4%)

Abbreviation: ITT, Intent-to-Treat.

Notes: Opioid-free through 72 hours is defined as having total morphine milligram equivalent (MME) opioid dose = 0 during the 72-hour on-site postoperative period, based on concomitant medication data. Opioid-free through Day 10 is defined as MME = 0 through 72 hours and answering "No" to the diary question "Did you take any opioid medication?" every day from 72 hours through Day 10. Opioid-free through Day 28 is defined similarly. Subjects who answered "Yes" or had a missing answer on any day during the period, or withdrew from the study during the period, were not considered opioid-free. A total of 64 subjects from 2 sites did not receive a diary upon discharge; concomitant medication data was used for these 64 subjects for opioid-free analyses through Day 10 and Day 28. 95% CIs are based on Farrington-Manning score statistics. P-values from Fisher's exact test.

Source: HTX-011-301 Study Report Body, p. 79 (PDF), Applicant's submission, NDA 211988

In summary, while there are nuances to interpretation of the data, as discussed, the results for the primary and key secondary efficacy endpoints, in combination with the decreased incidence of opioid-related adverse events, support the Applicant's claim that HTX-011 administration during simple bunionectomy surgery improves postoperative pain control and decreases opioid consumption for 72 hours compared to either saline placebo or bupivacaine HCl standard of care.

Data Quality and Integrity

The Applicant reported that two investigative sites did not distribute the daily diary, for patient recording of opioid pain medication use, to patients who did not receive an opioid prescription at discharge. This was reported as a protocol deviation and involved 64 treated patients. Efficacy analyses for opioid use and proportion of patients opioid-free for these 64 patients was based on concomitant medication data.

On March 5, 2019, the Agency was notified of the closure of investigative Site (b) (6) with Principal Investigator (b) (6) who participated in Study (b) (6). Heron stated they were notified on February 1, 2019, that the facility closed (b) (6) due financial instability. Patient records were relocated to a public storage facility. Phone and email contact information (b) (6) has not changed. Based on the number of enrolled patients from Site (b) (6) additional sensitivity analyses were performed to determine the impact of data from study Site (b) (6) on overall study results. Excluding data from Site (b) (6) additional analyses determined that all primary and key secondary endpoints maintained statistical significance.

Additionally, (b) (6) did receive significant payments of other sorts from the Applicant, totaling \$29,100.00, between March 31, 2017, and June 15, 2018. FDA Form 3455 was completed with a description of steps taken to minimize potential bias.

Efficacy Results – Secondary and other relevant endpoints

The results for additional secondary endpoints are as follows:

- The proportion of patients who were opioid-free through 24, 48, and 72 hours was statistically significantly higher in the HTX-011 treatment group compared with the saline placebo treatment group.
- The median time to first opioid rescue medication during the 72-hour post-operative period was statistically significantly longer in the HTX-011 treatment group (12 hours) compared to saline placebo (5 hours) and bupivacaine HCl (8 hours) treatment.
- The Integrated Rank of Silverman (IRS) scores based on NRS-A were significantly lower in the HTX-011 treatment group when compared to the saline placebo and bupivacaine HCl treatment groups over 24, 48, and 72 hours. These results suggest the patients treated with HTX-011 had less pain despite using less opioid rescue analgesia. Similar results were reported for IRS scores based on NRS-R.
- The proportion of patients with both an NRS-A pain intensity score < 4 at 72 hours and no opioid rescue medication through 72 hours was statistically significantly higher in the HTX-011 treatment group compared to saline placebo and bupivacaine HCl treatment groups.
- MPADSS score was evaluated at 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours post-operatively and a score ≥ 9 indicates discharge readiness, which was used as an overall assessment

tool in this study since all patients remained at the hospital or research facility for 72 hours. At 2 hours, the bupivacaine HCl treatment group had the highest proportion of patients with a score ≥ 9 . At 8 hours, the proportion of patients with a score ≥ 9 was highest in the HTX-011 treatment group and the treatment effect was statistically significant compared to saline placebo only. The proportion of patients with a score ≥ 9 was similar for both HTX-011 and bupivacaine HCl treatment groups.

- When asked how well post-operative pain was controlled at 24, 48, and 72 hours and on Day 28, a higher proportion of patients in the HTX-011 treatment group reported “good” or “better” pain control when compared to saline placebo and bupivacaine HCl at 24 hours only. A similar proportion of patients in all treatment groups reported good pain control at all other timepoints assessed.

Dose/Dose Response

For this study, a single dose of HTX-011 was administered. A dose response was, therefore, not observed.

Durability of Response

Administration of HTX-011 60 mg/1.8 mg did result in a statistically significant reduction in pain with activity and reduction in opioid analgesia use through 72 hours when compared to saline placebo and bupivacaine HCl wound infiltration.

6.3. A Phase 3, Randomized, Double-Blind, Saline Placebo- and Active-Controlled, Multicenter Study of HTX-011 via Local Administration for Postoperative Analgesia and Decreased Opioid Use Following Unilateral Open Inguinal Herniorrhaphy (Study 302)

6.3.1. Study Design

Overview and Objective

Study 302 was designed to evaluate the analgesic efficacy, safety, and pharmacokinetics of HTX-011 administered via instillation as a single dose into the surgical site compared with bupivacaine HCl (standard of care) and saline placebo in subjects undergoing unilateral open inguinal herniorrhaphy with mesh.

The study objectives (verbatim) were as follows:

- Primary objective – to compare the efficacy and duration of analgesia following local administration of HTX-011 with saline placebo during the first 72 hours following unilateral open inguinal herniorrhaphy
- Secondary objectives –
 - to compare the efficacy and duration of analgesia for HTX-011 with bupivacaine HCl without epinephrine during the first 72 hours following surgery in this study population

- to compare the effect of HTX-011 with saline placebo and bupivacaine HCl without epinephrine on opioid load during the first 72 hours following surgery in this study population
- to assess the safety and tolerability of HTX-011 in this study population
- to further establish the PK parameters of bupivacaine and meloxicam in HTX-011 in this study population.

Trial Design

This was a Phase 3, randomized, double-blind, saline placebo- and active-controlled, multicenter study to evaluate the analgesic efficacy, safety, and PK of HTX-011 administered via instillation into the surgical site in subjects undergoing unilateral open inguinal herniorrhaphy with mesh under general anesthesia. Spinal, epidural, or regional anesthesia was not permitted.

Intraoperatively patients received up to 4 mcg/kg of fentanyl and just prior to the end of surgery, an additional 50 mcg of fentanyl IV was administered. Intraoperative administration of other opioids, non-opioid analgesics, local anesthetics, or anti-inflammatory medications was not permitted. Near the completion of the surgery and after irrigation and suction were complete, a single dose of either HTX-011 300 mg/9 mg, saline placebo, or bupivacaine HCl 0.25% 75 mg was administered into the surgical site. HTX-011 and saline placebo were administered via instillation using a Luer lock applicator. Study drug was administered at the level below and the level above the fascial plane. Study drug was not administered in the shallow subdermal layer. Bupivacaine HCl was administered via injection.

Postoperatively, patients received rescue medication only upon request, including oxycodone immediate-release oral (no more than 10 mg per four-hour period), morphine IV (no more than 10 mg in a two-hour period), and acetaminophen or paracetamol oral (no more than 1,000 mg in a six-hour period). They remained at the hospital or research facility through the 72-hour observation period, after which time patients were discharged with a daily diary for opioid medication use and pain data recording. Patients returned to the study site on Days 10 and 28 for follow-up assessments.

Efficacy assessments included the following:

- evaluations of pain intensity using the Numeric Rating Scale (NRS) at rest and with activity (NRS-R and NRS-A, respectively)
 - the prescribed activity for NRS-A was sitting up from a supine position
- use of opioid analgesic medications
- discharge readiness as assessed via the Modified Postanesthetic Discharge Scoring System (MPADSS)
- Patient Global Assessment (PGA) of pain control

Safety assessments included the following:

- adverse event recording, local anesthetic systemic toxicity (LAST) assessments
- physical examinations, vital signs
- ECGs
- motor function assessments
- lab evaluations including hematology, chemistry
- wound healing assessments

Pharmacokinetic assessments included scheduled blood sampling for bupivacaine and meloxicam PK analysis.

The schedule of assessments during this study is summarized in the following table.

APPEARS THIS WAY ON ORIGINAL

Table 23: Schedule of Assessments, Study 302

Assessments	Time Window	Time After Study Drug Administration*																			
		Screening		Day 1																	
		≤28 days	≤1 day	Preop	OR	±5 min	±5 min	±10 min	±15 min	±15 min	±30 min	±30 min	±30 min	±1h	±2h	±2h	±4h	±4h	±3d	±4d	ET ^a
Obtain informed consent		X																			
Urine drug screen ^b		X		X																	
Urine pregnancy test (WOCBP only) ^b		X		X																	
Assess/confirm eligibility		X		X																	
Medical history		X																			
Demographics		X																			
Physical examination		X ^c																X			X ^d
Vital signs ^e		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X			X ^d
12-lead ECG (triplicate) ^e		X							X				X	X		X		X			X ^d
Subject training for pain assessments		X		X																	
Randomize subject ^f			X																		
Hematology and serum chemistry tests		X												X ^g				X	X		X ^d
Surgery ^h					X																
Administer study drug					X																
LAST assessment						X	X		X	X			X	X				X			X ^d
Pain intensity assessment (NRS-R) ⁱ							X ^j		X	X	X	X		X	X	X	X	X	X	X	X
Pain intensity assessment (NRS-A) ^k							X ^j		X	X	X	X		X	X	X	X	X	X	X	X
PGA of pain control														X		X		X		X	X
Record any rescue medication						←-----→															
Record opioid use (Diary) ^l																			←-----→		
Discharge readiness per MPADSS ^m									X	X	X	X		X	X	X	X	X			
Wound healing assessment																		X	X	X	X
PK blood sample ^e										X				X	X		X				
Concomitant medications ⁿ		←-----→																			X
Adverse events ^{e, o}		←-----→																			X

Abbreviations: d, day; ECG, electrocardiogram; ET, Early Termination; h, hour; min, minutes; LAST, Local Anesthetic Systemic Toxicity; MPADSS, Modified Postanaesthetic Discharge Scoring System; NRS-A, Numeric Rating Scale of pain intensity score with activity; NRS-R, Numeric Rating Scale of pain intensity score at rest; OR, operating room; PGA, Patient Global Assessment; PK, pharmacokinetic; Preop, preoperative assessments; WOCBP, women of childbearing potential; D10, Day 10; D28, Day 28.

* The start of study drug administration was considered as Time 0 for all efficacy, safety, and PK assessments. For assessments at timepoints when the subject was asleep, an attempt was to be made to wake the subject. If there was no response, the assessments at these timepoints were to be recorded as "Not Done." Assessments that could be done without waking the subject (eg, blood collection for PK) were to be completed. When PK and NRS pain intensity assessments coincided, the NRS pain intensity assessments were to be conducted before the blood draw.

^a Subjects who withdrew from the study before their Day 28 Visit were asked to complete Early Termination procedures.

^b The urine drug screen and urine pregnancy test were performed first. Results were to be confirmed negative prior to performing any additional assessments and prior to initiation of surgery. A subject who failed the drug test could have been rescreened at the discretion of the Investigator. Subjects with a positive drug screen who were taking an allowed, prescribed medication that is known to result in a positive drug test (eg, amphetamine and dextroamphetamine for attention-deficit/hyperactivity disorder, benzodiazepine for anxiety disorder) may have been eligible for participation in the study. Subjects taking medical marijuana were not allowed to participate in the study.

^c Included height, weight, and body mass index calculation.

^d Only if subject withdrew prior to 72 hours.

^e If early neurological and cardiac signs and symptoms of LAST were observed, unscheduled vital sign measurements, 12-lead ECG, and blood sample collection for PK had to be performed.

^f Subjects who met the Screening eligibility criteria were randomized. Randomization could be done up to 1 business day prior to study drug administration. Subjects did not need to be present for randomization to occur.

^g Hematology only.

^h The length of the surgical incision was recorded.

ⁱ NRS-R was assessed while the subject was recumbent or lying supine. Measurements were obtained after the subject was in the resting position for at least 5 minutes.

^j If a subject required rescue medication before the 1-hour pain intensity assessments, then an unscheduled NRS-R pain score followed by an NRS-A pain score was to be obtained before administering the first dose of rescue medication. These did not replace the 1-hour NRS-R and NRS-A assessments.

^k For NRS-A assessments, subjects were recumbent or lying supine and instructed to sit up. Measurements were obtained as soon as the subject sat up from the resting position.

^l Subjects completed a daily diary from 72 hours through Day 28 to record if they took any opioid medication. Subject diary results were reviewed at each site visit.

^m This study instrument assessed a subject's potential readiness to be discharged and was repeated at all scheduled timepoints. It was not meant to be used to decide on whether or not to discharge a subject from the study.

ⁿ At the Screening Visit, the site was to ensure the subject was not taking any prohibited medications. All medications taken from the time the subject signed the Informed Consent Form (ICF) through Day 28 were recorded.

^o Adverse events were collected from the time the subject signed the ICF through Day 28.

Source: HTX-011-302 Study Report Body, p. 41 (PDF), Applicant's submission, NDA 211988

Eligibility Criteria

Pertinent inclusion criteria include the following:

- adult male or female, at least 18 years of age
- scheduled to undergo unilateral open inguinal hernia repair with mesh under general anesthesia
- ASA Physical Status three or less
- non-pregnant, non-lactating females

Pertinent exclusion criteria include the following:

- prior inguinal hernia repair, except as a child of less than six years of age
- planned concurrent surgical procedure (e.g., bilateral herniorrhaphy)
- pre-existing concurrent acute or chronic painful condition requiring analgesic treatment in the post-operative period
- contraindication or known hypersensitivity to bupivacaine or other local anesthetics, meloxicam or other NSAIDs, oxycodone, morphine, acetaminophen/paracetamol, or fentanyl
- known or suspected daily opioid use for seven or more consecutive days in the preceding six months; had taken long-acting opioids within three days of surgery; had taken any opioids within 24 hours of surgery
- NSAID use within 10 days of surgery with the exception of low-dose aspirin (≤ 100 mg daily)
- received bupivacaine within five days of the surgery or any local anesthetic within 72 hours of surgery
- initiated any of the following medications to control pain within one month of surgery: selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin, or cyclooxygenase-2 (COX-2) inhibitors (if taking one of these medications not for pain control, must have been on a stable scheduled dose for at least one month)
- systemic steroids within five half-lives or 10 days prior to surgery (inhaled steroids excepted)
- medical condition that, in the opinion of the investigator, participating in the study would pose a health risk to the subject or confound the postoperative assessments, including the following:
 - myocardial infarction six months of signing the ICF, NY Heart Association Class three or higher, or clinically significant abnormalities of ECG or cardiac function
 - coronary artery bypass graft surgery within 12 months of signing ICF
 - severe liver function impairment (Child-Pugh Class C or higher, AST > three times upper limit of normal, ALT > three times upper limit of normal)
 - severe kidney function (creatinine clearance < 30 mL/min, on dialysis, and/or having serum creatinine > two times upper limit of normal)
 - coagulopathy or uncontrolled anticoagulation

- loss of sensation in extremities or significant peripheral neuropathy
- history of Hepatitis B or C, human immunodeficiency virus (HIV)
- uncontrolled psychiatric or neurological disorder
- history of malignancy
- alcohol or substance abuse
- history of three or more surgeries in the 12 months prior to signing the ICF
- BMI > 39 kg/m²

Study Endpoints

The primary and key secondary efficacy endpoints were tested hierarchically, such that the first insignificant result would result in all subsequent endpoints being exploratory only.

- Primary efficacy endpoint – Mean AUC₀₋₇₂ of the NRS-A pain intensity scores for HTX-011 compared with saline placebo
- 1st key secondary efficacy endpoint – Mean AUC₀₋₇₂ of the NRS-A pain intensity scores for HTX-011 compared with bupivacaine HCl
- 2nd key secondary efficacy endpoint – Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with saline placebo
- 3rd key secondary efficacy endpoint – proportion of patients who are opioid-free through 72 hours for HTX-011 compared to bupivacaine HCl
- 4th key secondary efficacy endpoint – Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with bupivacaine HCl.
- Additional secondary efficacy endpoints –
 - Proportion of subjects who are opioid-free through 72 hours compared with saline placebo
 - Proportion of subjects who are opioid-free from 72 hours through Day 10 and Day 28
 - Median time in hours to first opioid rescue medication up to 72 hours
 - Mean AUC₀₋₇₂ of the NRS-R pain intensity scores
 - Integrated Rank Analysis of Silverman using the NRS-A pain intensity AUC scores and total opioid consumption through 72 hours
 - Proportion of subjects who are pain-free with activity (defined as an NRS-A pain intensity score of 0 or 1) at each assessed timepoint through Day 28.
 - Proportion of subjects with an NRS-A pain intensity score ≥4 at any timepoint through 72 hours
 - Proportion of subjects with an NRS-A pain intensity score ≥7 at any timepoint through 72 hours.
 - Proportion of subjects who first achieve an MPADSS score ≥9 at 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours
 - Proportion of subjects achieving a score of “good” or better (>1) pain control based on PGA at 24, 48, 72 hours, and on Day 28.

Statistical Analysis Plan

Unless otherwise specified, all statistical analyses were performed using a two-sided hypothesis test at the 5% significance level. Continuous data are presented using descriptive statistics, including both the standard deviation and standard error. Categorical data are summarized by the number and percentage of patients. Two-sided 95% confidence intervals were provided.

Baseline was defined as the last observed measurement collected, whether scheduled or unscheduled, prior to the start of study drug administration. The 72-hour postoperative period was defined as the period of time from the start of study drug administration to the time of NRS-A pain score assessment at the 72-hour postoperative timepoint.

The intent-to-treat population consisted of all randomized patients who received study drug. This population was used for the primary analyses and patients were analyzed according to the assigned treatment at randomization. The per protocol population was all ITT patients who did not receive a prohibited rescue medication prior to the 72-hour timepoint and had no important protocol violations. This population was used for sensitivity analyses of the primary and key secondary endpoints.

To account for multiple endpoint testing of the primary and four key secondary endpoints, a strict hierarchy was applied to control the study-wise alpha level at 0.05, as indicated in Figure 6. Sequential testing continued until an endpoint failed to meet statistical significance, after which time all subsequent endpoint evaluations were considered exploratory.

Missing NRS data was imputed via LOCF, in which the most recent post-dose nonmissing value was used for subsequent missing value. If there was no post-dose value available, median values from patients with observed values within the same treatment group at the same timepoint were used. For patients who withdrew prior to the 72-hour assessment, missing NRS scores were imputed using WOCF, in which the highest NRS pain intensity score prior to withdrawal was used for post-withdrawal values through 72 hours. Any missing NRS score prior to withdrawal were imputed via LOCF. For binary endpoints not involving the NRS-R or NRS-A, missing data was handled using the non-responder imputation.

Refer to the statistical review by Dr. Yan Zhou for additional information.

Protocol Amendments

The protocol was amended twice during the study before the first patient was dosed and two clarification memos were sent to the investigative sites after the last amendment. The following is a high-level summary of the amendments and memos:

- Protocol Version 2, dated June 29, 2017
- Protocol Version 3, dated July 30, 2017
- Clarification memo, dated August 23, 2017

- Clarification memo, dated October 25, 2017

6.3.2. Study Results

Compliance with Good Clinical Practices

Per the Study Report Body for Study 302, *“This study was conducted in compliance with the protocol and all applicable regulatory requirements in accordance with International Council for Harmonisation (ICH)/Good Clinical Practice (GCP) and in general conformity with the most recent version of the Declaration of Helsinki.”*

Financial Disclosure

Robert E. Hoffman, Chief Financial Officer and Senior Vice President, Finance, signed FDA form 3454 on October 19, 2018, certifying that he has not entered into any financial arrangement with any of the listed clinical investigators. He further certified that none of the individual investigators has a proprietary interest in this drug product or a significant equity in the Sponsor per 21 CFR 54.2(b) or received payments in excess of what is permitted per 21 CFR 54.2(f).

Patient Disposition

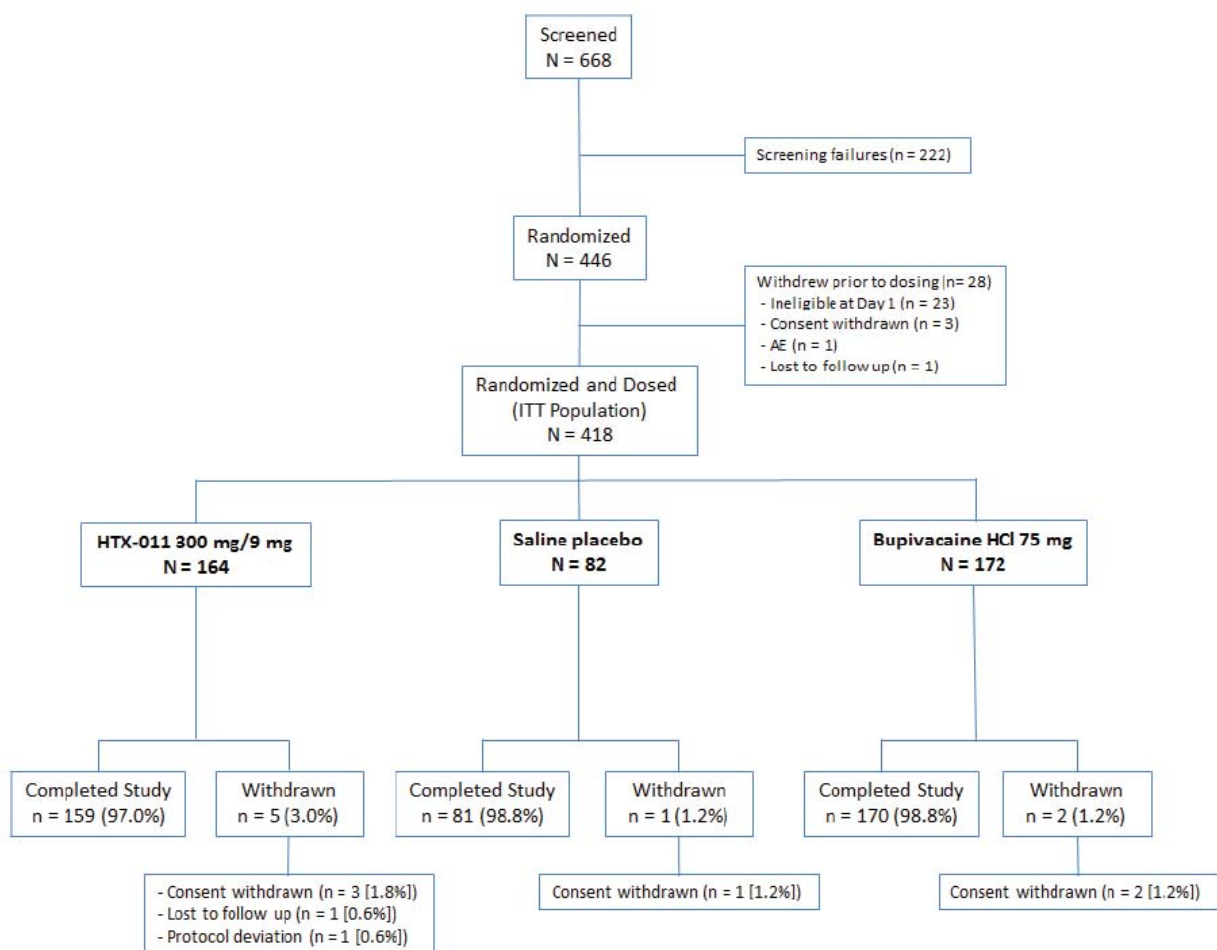
A total of 446 patients were randomized in a 2:2:1 ratio and 418 received study drug as follows:

- 164 patients received HTX-011 300 mg/9 mg
- 82 patients received saline placebo
- 172 patients received bupivacaine 0.25% 75 mg

Four patients were treated at an investigative site in Belgium. One patient was randomized to the HTX-011 group received bupivacaine HCl. Twenty-eight patients were randomized but withdrew prior to study drug administration due to ineligibility, withdrawn consent, pretreatment adverse event, or no return for surgery. The majority of patients who received treatment completed the study, $\geq 97\%$ in each treatment group.

Refer to the following figure for additional patient disposition information.

Figure 10: Patient Disposition, Study 302



Abbreviations: AE, adverse event; ITT, Intent-to Treat.

Notes: Screened was defined as signing an informed consent form. Completed the study was defined as completing the Day 28 Visit. One subject randomized to the HTX-011 group was misdosed; the subject received bupivacaine HCl instead of HTX-011.

Source: HTX-011-302 Study Report Body, p. 61 (PDF), Applicant's submission, NDA 211988

Protocol Violations/Deviations

A total of 262 patients, 63%, had at least one protocol deviation. The most common deviations across all treatment groups were associated with study procedures, visit/schedule windows, or use of prohibited medication. Patients with important protocol deviations were excluded from the Per Protocol Population. These were considered deviations that could significantly impact the accuracy of the efficacy results and included the following:

- Patient did not meet the following exclusion criteria:
 - any prior inguinal hernia repair except as a child (defined as less than six years of age)
 - planned concurrent surgical procedure

- pre-existing concurrent acute or chronic painful condition requiring analgesic treatment in the post-operative period
- known or suspected daily opioid use for seven or more days in the preceding six months; had taken long-acting opioids within three days of surgery; had taken any opioids within 24 hours of surgery
- received bupivacaine within five days of the surgery
- Informed consent not signed
- prohibited medication with intra-operatively or within the 72-hour post-operative period
- 50 µg IV fentanyl not administered at the end of surgery
- opioid rescue prior to first NRS-A pain assessment
- unblinding by rating assessor or patient
- study drug that was different than randomization assignment

The following table summarizes the important protocol deviations that were reported for this study.

Table 24: Incidence of Important Protocol Deviations, Study 302 (ITT Population)

	HTX-011 300 mg/9 mg (N=164)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=172)	Total (N=418)
Any Important Protocol Deviation	19 (11.6%)	11 (13.4%)	24 (14.0%)	54 (12.9%)
Received prohibited pain medication during surgery or within 72-hour postoperative period ^a	13 (7.9%)	7 (8.5%)	19 (11.0%)	39 (9.3%)
Study procedure deviation related to pain assessments ^b	4 (2.4%)	3 (3.7%)	2 (1.2%)	9 (2.2%)
Study drug dosing/administration deviation ^c	2 (1.2%)	1 (1.2%)	0	3 (0.7%)
Did not meet key eligibility criteria ^d	1 (0.6%)	0	3 (1.7%)	4 (1.0%)
Other (site closed due to noncompliance) ^e	0	0	3 (1.7%)	3 (0.7%)

Abbreviations: ITT, Intent-to-Treat; NRS-A, Numeric Rating Scale of pain intensity score with activity.

^a Includes subjects who received a prohibited pain medication, subjects who received too much of a permitted pain medication during the requisite periods specified in the protocol, and subjects who received a permitted rescue medication by a prohibited route of administration (Section 9.4.7.4). Two subjects received protocol-required fentanyl after the last suture and were incorrectly categorized as important protocol deviations.

^b Six subjects were administered rescue pain medication prior to the first NRS-A pain assessment, 2 subjects were assessed using an NRS questionnaire that was not IRB-approved, and 1 subject was not administered fentanyl at the end of surgery.

^c One subject received study drug that was different from his randomized assignment, and 2 subjects were administered study drug incorrectly (1 was administered study drug without a Luer lock applicator and 1 was administered study drug only below fascia area instead of evenly distributing the dose on each layer of the fascia).

^d Key eligibility criteria are listed in Section 9.3.2. Three subjects met exclusion criterion 1, and 1 subject met exclusion criterion 3.

^e Site 037 was closed due to noncompliance. The 3 subjects dosed at this site were excluded from the Per Protocol Population (Section 9.6).

Source: HTX-011-302 Study Report Body, p. 62 (PDF), Applicant's submission, NDA 211988

Demographic and Baseline Characteristics

Demographic and other baseline characteristics are presented in the following table. Briefly, the majority of patients were male (95%), White (89%), not Hispanic or Latino (70%), and the mean age was 49 years. Based on the disease process, the predominant male population is expected. In general, there no meaningful differences in demographic characteristics across the treatment and placebo groups. Refer to the following table for additional demographic information.

Table 25: Summary of Demographic and Baseline Characteristics, Study 302 (ITT Population)

	HTX-011 300 mg/9 mg (N=164)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=172)	Total (N=418)
Age (years)^a				
Mean (SD)	48.9 (13.29)	48.0 (14.59)	49.4 (11.26)	48.9 (12.75)
Median	50.0	50.5	51.0	51.0
Min, Max	22, 83	19, 82	18, 69	18, 83
Sex, n (%)				
Male	152 (92.7%)	79 (96.3%)	164 (95.3%)	395 (94.5%)
Female	12 (7.3%)	3 (3.7%)	8 (4.7%)	23 (5.5%)
Ethnicity, n (%)				
Hispanic or Latino	43 (26.2%)	30 (36.6%)	51 (29.7%)	124 (29.7%)
Not Hispanic or Latino	121 (73.8%)	52 (63.4%)	121 (70.3%)	294 (70.3%)
Race, n (%)				
American Indian or Alaska Native	2 (1.2%)	0	0	2 (0.5%)
Asian	2 (1.2%)	1 (1.2%)	2 (1.2%)	5 (1.2%)
Black or African Descent	17 (10.4%)	3 (3.7%)	16 (9.3%)	36 (8.6%)
Native Hawaiian or Other Pacific Islander	4 (2.4%)	0	1 (0.6%)	5 (1.2%)
White	139 (84.8%)	78 (95.1%)	153 (89.0%)	370 (88.5%)
BMI (kg/m²)				
Mean (SD)	27.14 (4.386)	28.12 (4.232)	26.86 (3.578)	27.21 (4.058)
Median	26.90	27.99	26.44	26.75
Min, Max	17.9, 38.5	17.6, 38.5	19.4, 37.9	17.6, 38.5

Abbreviations: BMI, body mass index; ITT, Intent-to-Treat.

^a Age was calculated relative to the date of informed consent.

Source: HTX-011-302 Study Report Body, p. 64 (PDF), Applicant's submission, NDA 211988

Other Baseline Characteristics

All patients had a non-incarcerated inguinal hernia (there was a single patient whose inguinal hernia was miscoded as incarcerated). The most common past medical history included seasonal allergy, hypertension, and wisdom teeth extraction. There did not appear to be large

differences in medical history incidences between groups that could have impacted the reported safety or efficacy results.

Prior medication use was reported for approximately 14% of the overall study population. The most commonly reported prior medications included vitamins (4%) and anti-inflammatory and antirheumatic medications (4%).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study drug compliance was 100% for patients who received study drug.

The majority of concomitant medications administered during the study were anesthetics, analgesics, antibiotics for infection prophylaxis, and psycholeptics (sedatives). The majority of patients did not receive emesis prophylaxis or medications to treat constipation.

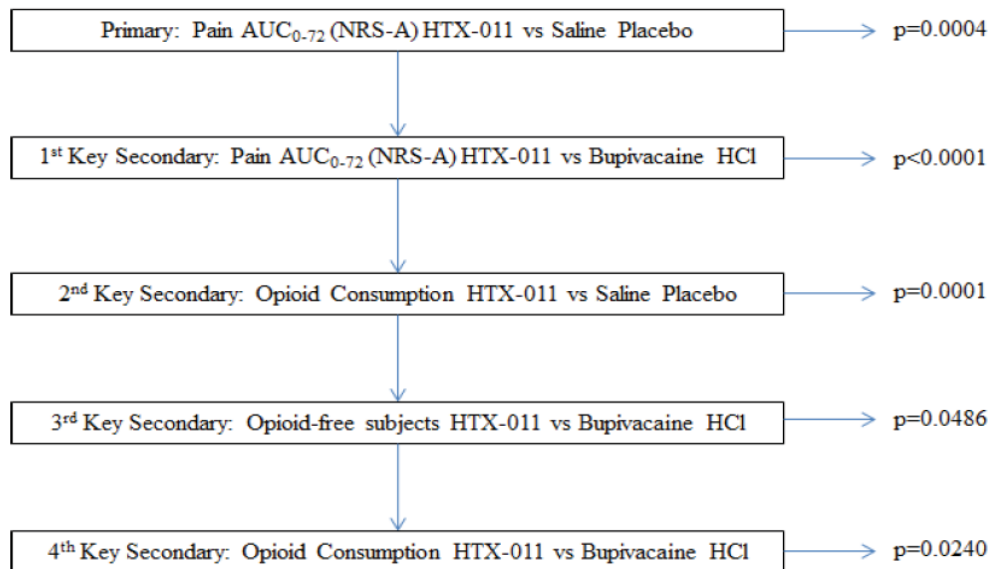
Permitted rescue medication included oral immediate-release oxycodone, IV morphine, and or acetaminophen or paracetamol during the 72-hour observation period. Upon discharge, patients were permitted immediate-release oxycodone and paracetamol or acetaminophen. No other analgesics, including NSAIDs, were permitted. The overall use across different treatment groups is described throughout this review, as pertinent to efficacy data.

Efficacy Results – Primary Endpoint and Key Secondary Endpoints

The results for the primary and all four key secondary efficacy endpoints were statistically significant, as indicated in the following figure:

APPEARS THIS WAY ON ORIGINAL

Figure 11: Summary of Hierarchical Testing Results for the Primary and Key Secondary Efficacy Endpoints, Study 302

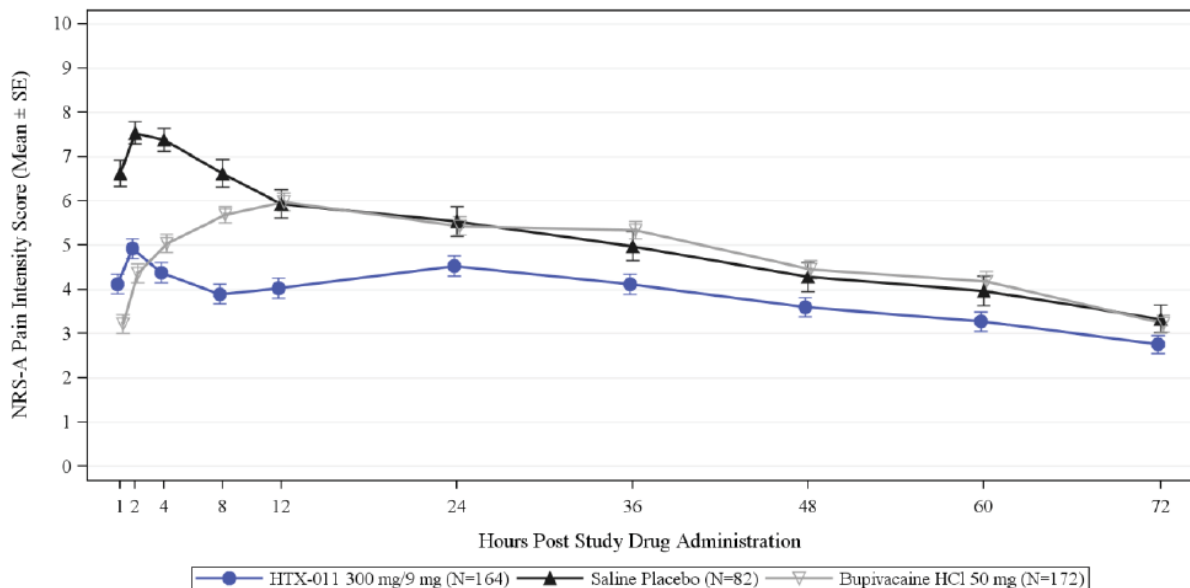


Abbreviations: AUC₀₋₇₂, area under the curve from Time 0 through 72 hours; NRS-A, Numeric Rating Scale of pain intensity score with activity.

Source: HTX-011-302 Study Report Body, p. 69 (PDF), Applicant's submission, NDA 211988

The following figure depicts the mean NRS-A pain intensity curves for each treatment group.

Figure 12: Mean NRS-A Pain Intensity Scores Over Time, Study 302 (wWOCF, ITT Population)



Abbreviations: ITT, Intent-to-Treat; NRS-A, Numeric Rating Scale of pain intensity score with activity; wWOCF, windowed worst observation carried forward.

Source: HTX-011-302 Study Report Body, p. 70 (PDF), Applicant's submission, NDA 211988

The pain curve data indicates overall lower scores for the HTX-011 treatment group compared to both saline placebo and bupivacaine HCl treatment. However, similar to the results for Study 301, in the first two hours postoperatively, the bupivacaine HCl treatment group had lower mean AUC of NRS-A pain intensity scores compared to the HTX-011 and saline placebo groups (Table 14.2.7, Mean NRS-A Pain Intensity Scores at Each Timepoint Using wWOCF ITT Population, p. 227 PDF, Applicant's submission). Interestingly, at the 36, 48, and 72-hour timepoints, the saline placebo treatment group had lower mean pain intensity scores than the bupivacaine HCl treatment group. The pain curves appear to converge at 72 hours.

In general, the primary and 1st key secondary efficacy findings support the Applicant's claim that for inguinal hernia surgery, HTX-011 appears to offer superior pain control compared to saline placebo or bupivacaine HCl up to 72 hours postoperatively. And unlike the arguably benign activity in Study 301 of placing the operative foot flat on the floor, sitting up from a supine position in this study would clearly generate some discomfort in the postoperative period.

With respect to the 2nd and 4th key secondary efficacy findings, review of specific time intervals indicates that the greatest reduction in opioid use between the treatment group and the saline placebo or bupivacaine HCl groups was observed early in the postoperative period, specifically the 0 to 24-hour interval. This early difference likely drove the statistical significance for the 0 to 72-hour interval. Interestingly, for the 24 to 48-hour and 48 to 72-hour time points, the saline placebo group received less opioid rescue than the bupivacaine HCl treatment group. The following table summarizes the opioid consumption by treatment group and time interval.

Table 26: Mean Total Postoperative Opioid Consumption in Morphine Equivalents, Study 302 (ITT Population)

Mean Opioid Consumption by Time Interval	HTX-011 300 mg/9 mg (n=164)	Saline Placebo, 10.3 mL (n=82)	Bupivacaine HCl 0.25%, 75 mg (n=172)
0-24h	5.23	11.65	7.27
– p-value vs. saline pbo	<0.0001		
– p-value vs. bupiv	0.0073		
24-48h	3.48	3.61	4.60
– p-value vs. saline pbo	0.4445		
– p-value vs. bupiv	0.0172		
48-72h	2.13	2.27	2.64
– p-value vs. saline pbo	0.3166		
– p-value vs. bupiv	0.0267		
0-72h	10.85	17.53	14.51
– p-value vs. saline pbo*	<0.0001		
– p-value vs. bupiv [#]	0.0240		

*2nd key secondary efficacy endpoint; [#]4th key secondary efficacy endpoint

Source: Adapted from HTX-011-302 Study Report Body, p. 205-207 (PDF), Applicant's submission, NDA 211988

As previously discussed in Section 6.2.2. Study Results for Study 301, the Agency's current thinking is that a reduction in postoperative opioid use is more clinically relevant if there is a corresponding decrease in opioid-related adverse events. The following table summarizes the opioid-related adverse events for all treatment groups.

Table 27: Incidence of Opioid-Related Treatment-Emergent Adverse Events (TEAE) by Preferred Term, Study 302 (Safety Population)

Preferred Term ^[1]	HTX-011 300 mg/9 mg (10.3 mL) (N=163)	Saline Placebo (10.3 mL) (N=82)	Bupivacaine HCl 75 mg (30 mL) (N=173)
Subjects Reporting at Least One Opioid-related TEAE	53 (32.5%)	36 (43.9%)	73 (42.2%)
Nausea	30 (18.4%)	28 (34.1%)	37 (21.4%)
Constipation	28 (17.2%)	15 (18.3%)	41 (23.7%)
Vomiting	7 (4.3%)	4 (4.9%)	12 (6.9%)
Pruritus generalised	2 (1.2%)	1 (1.2%)	1 (0.6%)
Urinary retention	1 (0.6%)	1 (1.2%)	3 (1.7%)
Pruritus	0	0	3 (1.7%)

[1] Adverse events are coded to Preferred Term using MedDRA, version 19.1

Source: HTX-011-302 Study Report Body, p. 304 (PDF), Applicant's submission, NDA 211988

It appears that there is a lower incidence of nausea, constipation, and vomiting in the HTX-011 treatment group when compared to the saline placebo and bupivacaine HCl groups. With the exception of nausea, however, the differences are small and potentially not clinically meaningful.

With respect to the 3rd key efficacy endpoint, the proportion of opioid-free patients in the HTX-011 treatment group compared to those in the bupivacaine HCl treatment through 72 hours, the results are closely insignificant, with a p-value of 0.0486. The percentage of opioid-free patients in the HTX-011 group at the various time intervals was as follows: at 0 to 24 hours, there were 58% of treated patients who were opioid-free; at 0-48 hours, there were 52% of treated patients who were opioid-free; and at 0 to 72 hours, there were 51% of treated patients who were opioid-free. On Days 10 and 28, the percentage of patients who are opioid-free was statistically significantly higher in the HTX-011 treatment group compared to the saline placebo group. The percentage was higher when compared to the bupivacaine HCl treatment group as well, but was not statistically significant. Furthermore, the percentage of patients who were opioid-free through 72 hours and remained opioid-free through Days 10 and 28, was higher in the saline placebo and bupivacaine groups. The following table summarizes the proportion of patients in each treatment group who were opioid-free through Day 28.

Table 28: Proportion of Patients Who Are Opioid-Free Through Day 10 or 28, Study 302 (ITT Population)

	HTX-011 300 mg/9 mg	Saline Placebo	Bupivacaine HCl 75 mg
All subjects	N=164	N=82	N=172
Opioid-free through Day 10	80 (48.8%)	18 (22.0%)	67 (39.0%)
Difference (95% CI) vs saline placebo	26.8% (12.6%, 38.1%)		
p-value vs saline placebo	<0.0001		
Difference (95% CI) vs bupivacaine HCl	9.8% (-0.9%, 20.5%)		
p-value vs bupivacaine HCl	0.0787		
Opioid-free through Day 28	71 (43.3%)	17 (20.7%)	60 (34.9%)
Difference (95% CI) vs saline placebo	22.6% (8.7%, 33.8%)		
p-value vs saline placebo	0.0007		
Difference (95% CI) vs bupivacaine HCl	8.4% (-2.3%, 18.8%)		
p-value vs bupivacaine HCl	0.1189		
Subjects who are opioid-free through 72 hours	n=84	n=18	n=69
Remained opioid-free through Day 10	80/84 (95.2%)	18/18 (100.0%)	67/69 (97.1%)
Remained opioid-free through Day 28	71/84 (84.5%)	17/18 (94.4%)	60/69 (87.0%)

Abbreviation: ITT, Intent-to-Treat.

Notes: Opioid-free through 72 hours is defined as having total morphine milligram equivalent (MME) opioid dose = 0 during the 72-hour on-site postoperative period, based on concomitant medication data. Opioid-free through Day 10 is defined as MME = 0 through 72 hours and answering "No" to the diary question "Did you take any opioid medication?" every day from 72 hours through Day 10. Opioid-free through Day 28 is defined similarly. Subjects who answered "Yes" or had a missing answer on any day during the period, or withdrew from the study during the period, were not considered opioid-free. 95% CIs are based on Farrington-Manning score statistics. P-values from Fisher's exact test.

Source: HTX-011-302 Study Report Body, p. 80 (PDF), Applicant's submission, NDA 211988

In summary, while there are nuances to interpretation of the data, as discussed, the results for the primary and key secondary efficacy endpoints, in combination with the decreased incidence of opioid-related adverse events, support the Applicant's claim that HTX-011 administration during inguinal hernia repair improves postoperative pain control and decreases opioid consumption for 72 hours compared to either saline placebo or bupivacaine HCl standard of care.

Data Quality and Integrity

As discussed in Section 6.2.2. Study Results for Study 301, the Agency was notified of the closure of investigative Site (b) (6)

Based on the number of enrolled patients from Site (b) (6) additional sensitivity analyses were performed to determine the impact of data from study Site (b) (6) on overall study results. Excluding data from Site (b) (6) additional analyses determined that all primary and key secondary endpoints maintained statistical significance, with the exception of the 3rd key secondary endpoint, proportion of patients who are opioid-free through 72 hours for HTX-011 compared to bupivacaine HCl. The p-value is 0.0717 and the proportion of opioid-free subjects was numerically higher in the HTX-011

treatment group (55%) compared to the bupivacaine group (44%). Therefore, it does not appear that the data from Site (b) (6) had a large impact on the overall reported efficacy.

Additionally, (b) (6) received significant payments of other sorts from the Applicant, totaling \$29,100.00, between March 31, 2017, and June 15, 2018. FDA Form 3455 was completed with a description of steps taken to minimize potential bias.

Efficacy Results – Secondary and other relevant endpoints

The results for additional secondary endpoints are as follows:

- The proportion of patients who were opioid-free through 24, 48, and 72 hours was statistically significantly higher in the HTX-011 treatment group compared with the saline placebo treatment group.
- The median time to first opioid rescue medication during the 72-hour post-operative period was statistically significantly longer in the HTX-011 treatment group (> 72 hours) compared to saline placebo (2 hours) and bupivacaine HCl (12 hours) treatment.
- The Integrated Rank of Silverman (IRS) scores based on NRS-A were significantly lower in the HTX-011 treatment group when compared to the saline placebo and bupivacaine HCl treatment groups over 24, 48, and 72 hours. These results suggest the patients treated with HTX-011 had less pain despite using less opioid rescue analgesia. Similar results were reported for IRS scores based on NRS-R.
- The proportion of patients with both an NRS-A pain intensity score < 4 at 72 hours and no opioid rescue medication through 72 hours was statistically significantly higher in the HTX-011 treatment group compared to saline placebo and bupivacaine HCl treatment groups.
- MPADSS score was evaluated at 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours post-operatively and a score ≥ 9 indicates discharge readiness, which was used as an overall assessment tool in this study since all patients remained at the hospital or research facility for 72 hours. The proportion of patients who first achieved a score ≥ 9 was significantly higher in the HTX-011 treatment group compared to the saline placebo group beginning at 2 hours. At 8 hours, 85% of patients in the HTX-011 and 70% of patients in the saline placebo groups had scores ≥ 9 .
- When asked how well post-operative pain was controlled at 24, 48, and 72 hours and on Day 28, a similar proportion of patients across all treatment groups reported “good” or “better” pain control. A higher proportion of patients treated with HTX-011 reported excellent pain control at 24, 48, and 72 hour compared to patients treated with saline placebo and bupivacaine.

Dose/Dose Response

For this study, a single dose of HTX-011 was administered. A dose response was, therefore, not observed.

Durability of Response

Administration of HTX-011 300 mg/9 mg did result in a statistically significant reduction in pain with activity and reduction in opioid analgesia use through 72 hours when compared to saline placebo and bupivacaine HCl wound infiltration.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Fixed Combination Product Classification

The following discussion relies on information provided in Dr. Alla Bazini's *Consult Response on Citizen Petition Regarding Approval Requirements for New Drug Applications for a Fixed-Dose Combination of Bupivacaine and Meloxicam*, in draft form at the time of this review.

According to the Proposed Rule on Fixed-Combination and Co-Packaged Drugs: Applications for Approval and Combinations of Active Ingredients Under Consideration for Inclusion in an Over-the-Counter Monograph issued by FDA on December 23, 2015, HTX-011 is defined as a Combination 2 drug product, defined as, "One Active Ingredient Is Intended To Provide a Direct Effect That Enhances the Safety or Effectiveness of Another Active Ingredient". The Applicant has described HTX-011 as,

"an extended-release, fixed-ratio combination product that contains 2 APIs, bupivacaine as the disease-active ingredient and low-dose meloxicam to enhance the effectiveness of bupivacaine..." (End-of-Phase 2 Meeting background materials submitted by Heron on April 14, 2017).

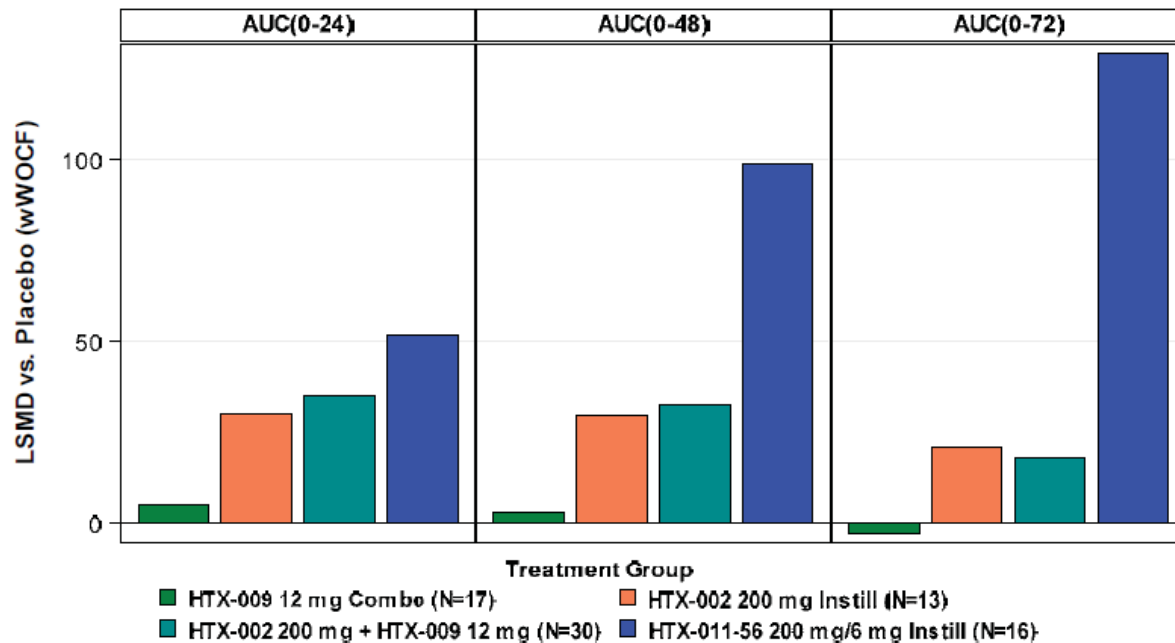
The Applicant conducted two Phase 2 studies, Study 202 and 208, to assess the contribution of bupivacaine and meloxicam to the activity of the fixed-ratio combination product. According to the Proposed Rule for Combination 2 products, *"...a clinical trial comparing the combination to the disease-active ingredient alone would usually be necessary to demonstrate the contribution of each active ingredient. The study would have to establish enhanced safety or effectiveness of the combination versus the disease-active ingredient alone. This would be true whether or not the disease-active ingredient has already been proven to be effective"*. As described in more detail below, both studies demonstrated meloxicam treatment alone resulted in the same efficacy as placebo, supporting the Applicant's position that bupivacaine is the disease-active component in HTX-011.

In Study 202, patients undergoing unilateral open inguinal herniorrhaphy were randomized to one of four treatment groups; HTX-011-56 (various doses in the to be marketed formulation), HTX-002 (bupivacaine only in the to be marketed formulation), HTX-009 (meloxicam only in the

to be marketed formulation), bupivacaine HCl, and saline placebo. The results are as follows (and pictured in the figure below):

- the mean differences of the AUC values compared with saline placebo showed that HTX-011-56 reduced pain more effectively than the sum of each comparator alone, demonstrating a synergistic effect for the combination of meloxicam and bupivacaine in HTX-011-56
- HTX-009 (meloxicam only) was not differentiated from saline placebo in pain intensity scores
- HTX-011-56 400 mg/12 mg significantly reduced the total amount of opioids consumed through 24 and 48 hours and significantly increased the number of patients who were opioid free through 72 hours compared with saline placebo
- A review of treatment-emergent adverse events for HTX-011-56, HTX-002, and HTX-009 did not reveal added toxicity for the fixed-ratio combination product compared with the two individual components.

Figure 13: Contribution of HTX-011-56 Components to the Reduction in Mean AUC of Pain Intensity Scores Following Herniorrhaphy, Study 202 (wWOCF, Preliminary Data)

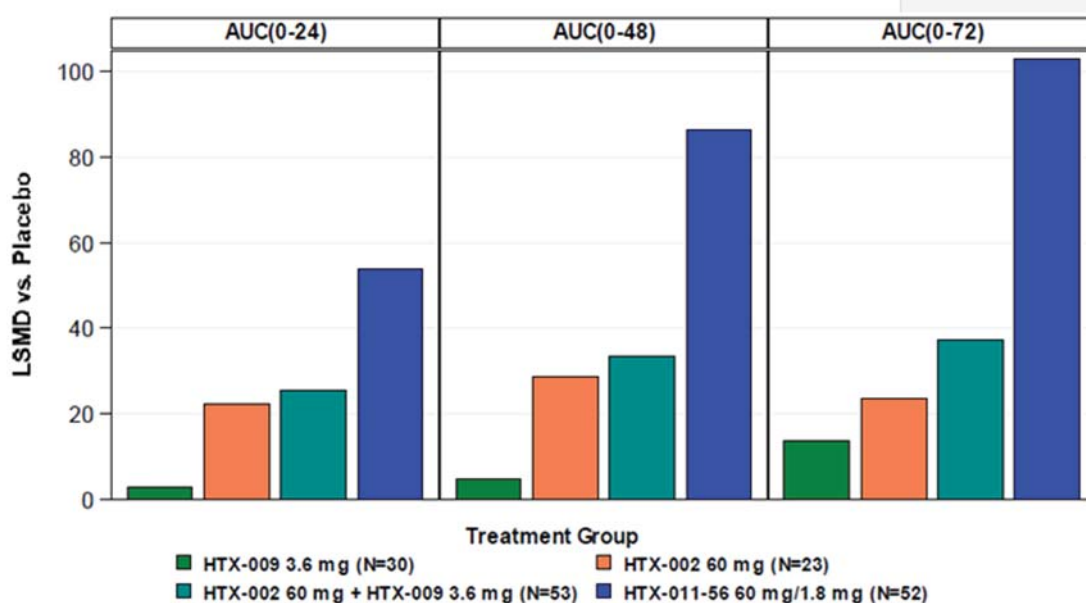


Abbreviations: AUC0-24, area under the curve through 24 hours; AUC0-48, area under the curve through 48 hours; AUC0-72, area under the curve through 72 hours LSMD, least square mean difference; wWOCF; windowed worst observation carried forward. Note: HTX-002 and HTX-009 have similar compositions to HTX-011-56 except HTX-002 contains only bupivacaine as the active pharmaceutical ingredient (API) and HTX-009 contains only meloxicam as the API. HTX-009 6 mg, a dose equivalent to HTX-011-56 200 mg/6 mg, was not evaluated in Study 202; therefore, a higher dose of HTX-009, 12 mg, was used in this analysis as it is a more conservative dose. wWOCF is used for adjusting opioid rescue medication duration effect. Source: Applicant's End-of-Phase 2 Meeting Background Materials, Table 16, April 14, 2017.

In Study 208, patients undergoing unilateral, simple bunionectomy were randomized to one of four treatment groups; HTX-011-56 (various doses), HTX-002, HTX-009, bupivacaine HCl and saline placebo. The results are as follows (and pictured below):

- the combination of bupivacaine and meloxicam in HTX-011-56 provided a greater analgesic effect over 72 hours after surgery than either component alone (HTX-002 or HTX-009) or the sum of the 2 components
- the mean differences of the AUC values compared with saline placebo showed that HTX-011-56 reduced pain more effectively than the sum of each comparator alone, indicating a possible synergistic effect for the combination of meloxicam and bupivacaine in HTX-011-56

Figure 14: Contribution of HTX-011-56 Components to the Reduction in Mean AUC of Pain Intensity Scores Following Bunionectomy, Study 208 (wWOFCF, Preliminary Data)



Abbreviations: AUC0-24, area under the curve through 24 hours; AUC0-48, area under the curve through 48 hours; AUC0-72, area under the curve through 72 hours LSMD, least square mean difference; wWOFCF; windowed worst observation carried forward. Note: HTX-002 and HTX-009 have similar compositions to HTX-011-56 except HTX-002 contains only bupivacaine as the active pharmaceutical ingredient (API) and HTX-009 contains only meloxicam as the API. HTX-009 1.8 mg, a dose equivalent to HTX-011-56 60 mg/1.8 mg, was not evaluated in Study 208; therefore, a higher dose of HTX-009, 3.6 mg, was used in this analysis as it is a more conservative dose. wWOFCF is used for adjusting opioid rescue medication duration effect. Source: Applicant's End-of-Phase 2 Meeting Background Materials, Table 16, April 14, 2017.

In summary, both Study 202 and 208 demonstrated that treatment with meloxicam alone (HTX-009) resulted in similar efficacy as placebo, thereby supporting the claim that bupivacaine is the disease-active component and the most appropriate comparator to satisfy the combination product requirements. Based on these findings, the Applicant's Phase 3 clinical program was designed to include endpoints intended to demonstrate superiority of HTX-011-56 over bupivacaine HCl infiltration for reduction in pain intensity.

7.1.2. Primary Endpoints

Study 209, Cohort 2, Study 301, and Study 302 were adequate and well-controlled studies designed to support the proposed indications and dosing of HTX-011. All three studies demonstrated statistical significance on the primary efficacy endpoints, mean AUC of pain intensity scores after treatment with HTX-011 compared to saline placebo. The clinical significance, however, of lower pain intensity scores after treatment with HTX-011 compared to saline placebo is questionable. As will be discussed in the following Section, 7.1.3. Secondary and Other Endpoints, the Phase 3 studies also demonstrated statistical significance on the secondary endpoints, which included mean AUC of pain intensity score comparisons to bupivacaine HCl wound infiltration. The following table summarizes the efficacy endpoint results for the Phase 3 studies.

Table 29: Results for the Primary and Key Secondary Endpoints in Study 301 and Study 302 (ITT Populations)

	Study 301 (Bunionectomy)			Study 302 (Herniorrhaphy)		
	Saline Placebo (N=100)	Bupivacaine HCl 50 mg (N=155)	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=172)	HTX-011 300 mg/9 mg (N=164)
AUC₀₋₇₂ of the NRS-A (wWOCF)						
Mean (SD)	445.34 (155.792)	393.45 (153.756)	323.29 (182.641)	350.82 (171.224)	341.88 (158.303)	269.39 (173.719)
Primary endpoint: p-value ^a vs saline placebo			<0.0001			0.0004
1 st key secondary endpoint: p-value ^a vs bupivacaine HCl			0.0002			<0.0001
Total Opioid Consumption 0-72 Hours (MME)						
Mean (SD)	30.06 (21.016)	25.09 (21.553)	18.80 (19.801)	17.53 (18.908)	14.51 (18.185)	10.85 (17.062)
Median (Min, Max)	25.00 (0.0, 80.0)	17.50 (0.0, 92.5)	12.50 (0.0, 83.0)	11.25 (0.0, 73.5)	7.25 (0.0, 87.5)	0.00 (0.0, 103.0)
2 nd key secondary endpoint: p-value ^b vs saline placebo			<0.0001			0.0001
4 th key secondary endpoint: p-value ^b vs bupivacaine HCl			0.0022			0.0240
Opioid-Free 0-72 Hours						
n (%)	2 (2.0%)	17 (11.0%)	45 (28.7%)	18 (22.0%)	69 (40.1%)	84 (51.2%)
Other secondary endpoint: p-value ^c vs saline placebo			<0.0001			<0.0001
3 rd key secondary endpoint: p-value ^c vs bupivacaine HCl			0.0001			0.0486

Abbreviations: AUC, area under the curve; ITT, Intent-to-Treat; MME, milligram morphine equivalents; NRS-A, Numeric Rating Scale of pain intensity score with activity; wWOCF, windowed worst observation carried forward.

Notes: HTX-011 (also referred to as HTX-011-56) is the intended commercial formulation.

^a p-values reflect results of an analysis of variance (ANOVA) with randomized treatment as the main effect.

^b p-values were obtained using the Wilcoxon rank sum test.

^c p-values from Fisher's exact test.

Source: Summary of Clinical Efficacy, p. 62 (PDF), Applicant's submission, NDA 211988.

An additional issue is the primary efficacy endpoint for Study 209, Cohort 2. Specifically, mean AUC₀₋₄₈ of pain intensity scores at rest may not be clinically relevant for a procedure requiring early mobilization and ambulation. Based on a variety of clinical outcome assessments as well as financial incentives, patients are encouraged to begin physical therapy and rehabilitation early in the post-operative course, many on the day of surgery. Participation requires adequate analgesia, which is not likely accurately assessed using pain intensity scores at rest. Table 11, in Section 6.1.2. Study Results, summarizes the primary and key secondary efficacy results for

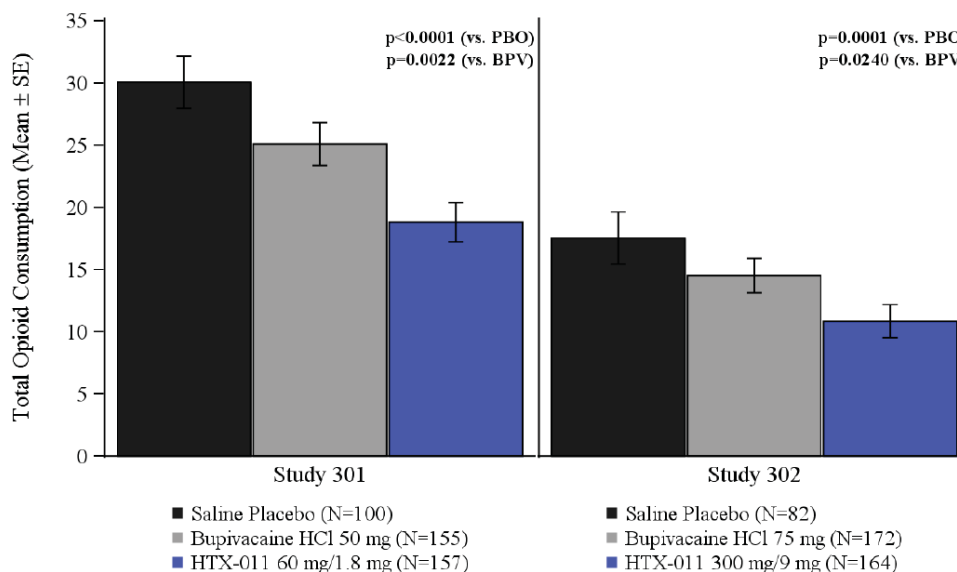
Study 209, Cohort 2.

Despite the limitations of the interpretation of the primary efficacy results, HTX-011 did demonstrate a significant reduction in post-operative pain after bunionectomy and open inguinal hernia repair with mesh, and can be approved on that basis.

7.1.3. Secondary and Other Endpoints

Study 301 and Study 302 demonstrated statistical significance on all key secondary efficacy endpoints (refer to Table 29 above). As previously mentioned, while demonstrating a statistically significant difference between HTX-011 and saline placebo may be acceptable from a regulatory perspective, this type of evaluation is not clinically useful, particularly because intra-operative administration of local anesthesia, via some route, is universal unless an absolute contraindication exists. In the Phase 3 studies, the results did demonstrate a statistically significant difference in mean AUC of pain intensity scores with activity through 72 hours in patients treated with HTX-011 compared to bupivacaine HCl (key secondary efficacy endpoint). Additionally, treatment with HTX-011 was shown to decrease post-operative opioid use, as indicated in the figure below.

Figure 15: Total Post-Operative Opioid Consumption (MME) from 0 Through 72 Hours – Study 301 and Study 302 (ITT Population)



Abbreviations: BPV; bupivacaine HCl; ITT, Intent-to-Treat; MME, morphine milligram equivalent; PBO, saline placebo.
Notes: HTX-011 (also referred to as HTX-011-56) is the intended commercial formulation. Doses of opioid rescue medication are expressed as intravenous milligram morphine equivalents. P-values were obtained using the Wilcoxon rank sum test.
Source: Summary of Clinical Efficacy, p. 70 (PDF), Applicant's submission, NDA 211988.

There are limitations to the interpretation of the opioid use data, including early differences in opioid use potentially driving the statistical significance for all subsequent timepoints. However, it is worth noting that a lower percentage of patients treated with HTX-011 required

IV morphine compared to the other treatment groups. The results are most impressive for Study 301, as indicated in the table below.

Table 30: Summary of Rescue Medication Use Through 72 Hours – Study 301 and Study 302 (ITT Population)

	Study 301			Study 302		
	Saline Placebo (N=100)	Bupivacaine HCl 50 mg (N=155)	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=172)	HTX-011 300 mg/9 mg (N=164)
Opioid rescue medications						
Oxycodone/oxycodone hydrochloride ^a	98 (98.0%)	138 (89.0%)	112 (71.3%)	62 (75.6%)	100 (58.1%)	76 (46.3%)
Morphine/morphine sulfate ^b	54 (54.0%)	68 (43.9%)	42 (26.8%)	41 (50.0%)	42 (24.4%)	38 (23.2%)
Fentanyl ^c	0	0	0	0	1 (0.6%)	2 (1.2%)
Hydrocodone ^c	0	0	0	0	0	1 (0.6%)
Non-opioid rescue medications						
Paracetamol/acetaminophen	85 (85.0%)	127 (81.9%)	122 (77.7%)	50 (61.0%)	104 (60.5%)	82 (50.0%)

Abbreviation: ITT, Intent-to-Treat.

Notes: HTX-011 (also referred to as HTX-011-56) is the intended commercial formulation. Medications are coded to generic drug names using the World Health Organization (WHO) Drug dictionary, Version 01 September 2016. At each level of summarization (any medication, generic drug name), subjects reporting use of more than one medication are counted only once.

^a Subjects taking oxycodone and/or oxycodone hydrochloride were pooled.

^b Subjects taking morphine and/or morphine sulfate were pooled.

^c Protocol deviation.

Source: Summary of Clinical Efficacy, p. 71 (PDF), Applicant's submission, NDA 211988.

This is clinically significant based on the opioid prescribing order generally used for post-operative pain management. Specifically, moderate to severe pain is generally treated with IV opioids and mild to moderate pain generally treated with oral opioids, unless the patient is not tolerating oral intake. Less IV morphine administration compared to the other treatment groups is clinically meaningful and provides additional support for the efficacy claims made by the Applicant.

An additional efficacy endpoint which the Applicant has emphasized throughout development and in particular during the EOP2 meeting discussions, is the number of patients opioid-free through 72 hours. The Applicant has stated that while reductions in opioid use and opioid-related AEs is clinically relevant, the number of opioid-free patients through 72 hours may be more meaningful. As indicated in Table 31, the percentage of opioid-free patients in the Phase 3 studies was statistically significantly higher in the HTX-011 treatment group when compared to both saline placebo and bupivacaine HCl treatment groups. During the EOP2 meeting, the Division stated that while the percentage of opioid-free patients through 72 hours is relevant, it is also important to consider opioid consumption after 72 hours. Specifically, if a higher percentage of HTX-011-treated patients remain opioid-free beyond 72 hours, that is relevant clinical information for consideration as labeling language. The following table summarizes the opioid-free data for the Phase 3 studies.

Table 31: Proportion of Patients Who Were Opioid-Free Through Day 10 or Through Day 28 in Study 301 and Study 302 (ITT Population)

	Study 301			Study 302		
	Saline Placebo (N=100)	Bupivacaine HCl 50 mg (N=155)	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=172)	HTX-011 300 mg/9 mg (N=164)
All Subjects						
Opioid-free through Day 10	2 (2.0%)	15 (9.7%)	41 (26.1%)	18 (22.0%)	67 (39.0%)	80 (48.8%)
p-value vs PBO			<0.0001			<0.0001
p-value vs BPV			0.0002			0.0787
Opioid-free through Day 28	2 (2.0%)	14 (9.0%)	37 (23.6%)	17 (20.7%)	60 (34.9%)	71 (43.3%)
p-value vs PBO			<0.0001			0.0007
p-value vs BPV			0.0007			0.1189
Subjects who were opioid-free through 72 hours						
N	2	17	45	18	69	84
Remained opioid-free through Day 10	2/2 (100.0%)	15/17 (88.2%)	41/45 (91.1%)	18/18 (100.0%)	67/69 (97.1%)	80/84 (95.2%)
Remained opioid-free through Day 28	2/2 (100.0%)	14/17 (82.4%)	37/45 (82.2%)	17/18 (94.4%)	60/69 (87.0%)	71/84 (84.5%)

Abbreviations: BPV, bupivacaine HCl; ITT, Intent-to-Treat; PBO, saline placebo.

Notes: HTX-011 (also referred to as HTX-011-56) is the intended commercial formulation. Opioid-free through 72 hours was defined as having total morphine milligram equivalent (MME) opioid dose = 0 during the 72-hour postoperative period, based on concomitant medication data. Opioid-free through Day 10 was defined as MME = 0 through 72 hours and answering "No" to the diary question "Did you take any opioid medication?" every day from 72 hours through Day 10. Opioid-free through Day 28 was defined similarly. Subjects who answered "Yes" or had a missing answer on any day during the period, or withdrew from the study during the period, were not considered opioid-free. A total of 64 subjects in Study 301 did not receive a diary upon discharge; concomitant medication data was used for these 64 subjects for opioid-free analyses through Day 10 and Day 28.

P-values from Fisher's exact test.

Source: Summary of Clinical Efficacy, p. 73 (PDF), Applicant's submission, NDA 211988.

The above table indicates for Study 301, a statistically significantly higher percentage of patients treated with HTX-011 were opioid-free at Days 10 and 28 when compared to patients treated with either saline placebo or bupivacaine HCl. For Study 302, statistical significance was reached only for the HTX-011 versus saline placebo treatment group comparison. Additionally, there was a higher percentage of patients in the saline placebo treatment group who were opioid-free through 72 hours and remained opioid-free through Days 10 and 28 when compared to the HTX-011 and bupivacaine HCl treatment groups, albeit the number of patients was low. Furthermore, for Study 302, it appears that the HTX-011 treatment group had the smallest percentage of patients remain opioid-free through Days 10 and 28 who were initially opioid-free through 72 hours.

For Study 209, Cohort 2, a secondary efficacy endpoint included an evaluation of mean AUC of pain intensity scores with activity, described as a straight leg raise in the supine position. The pain associated with this activity may be more clinically meaningful than one observed at rest, however, physical therapy often begins with standing and/or walking, exercises that would

result in more discomfort than a straight leg raise. An additional limitation of the efficacy results from this study is the measurable clinical benefit from the posterior capsule injection with ropivacaine 50 mg. The HTX-011 + ropivacaine treatment group consistently demonstrated improved efficacy/analgesia over HTX-011 administration alone. This is concerning for two reasons. First, HTX-011 will not be marketed with ropivacaine and in fact, the label will include recommendations to avoid additional local anesthetic administration for a prolonged period of time, at least through mean T_{max} . And second, HTX-011 alone did not demonstrate improved analgesia over 48 hours when compared to bupivacaine HCl, suggesting it does not offer any additional benefit over standard of care unless the posterior capsule injection is also administered.

Regarding opioid consumption in Study 209, Cohort 2, the only statistically significant difference between the HTX-011 and saline placebo group was through 24 hours. The difference in opioid consumption at all other timepoints was not statistically significant. Furthermore, there were no timepoints when the opioid consumption was statistically significantly less in the HTX-011 treatment group when compared to the bupivacaine HCl treatment group and all patients in the HTX-011 required opioids during the 72-hour post-operative period, further supporting the conclusion that HTX-011 alone does not offer additional efficacy benefit over bupivacaine HCl in the management of post-TKA pain.

As previously mentioned, the proportion of patients who completed the first rehabilitation session and the proportion of ambulatory patients at specific timepoints was not significantly different between treatment groups. While these were only additional secondary efficacy endpoints, they may be considered among the most clinically relevant based on the post-operative goals set by the orthopedic surgery team. Early rehabilitation and ambulation have been shown to improve long-term strength and mobility of the operative leg after TKA and some studies suggest there is a measurable decrease in post-operative complications, including DVT. Admittedly, TKA is a challenging surgical model to evaluate. It is considered among the most painful surgical procedures performed and the goals of post-operative pain management often conflict with the goals of early rehabilitation and ambulation.

7.1.4. Subpopulations

The efficacy results from the Phase 3 studies for primary and key secondary endpoints were evaluated to identify potential differences in treatment effect across the subgroups of age, sex, race, and ethnicity. Not surprisingly, the distribution of sex was dependent on the procedure performed, such that there was a larger proportion of female patients (> 85%) undergoing bunionectomy and a larger proportion of male patients (> 90%) undergoing open IHR. The following subgroups had less than 20 patients and were, therefore, pooled with other subgroups in each study:

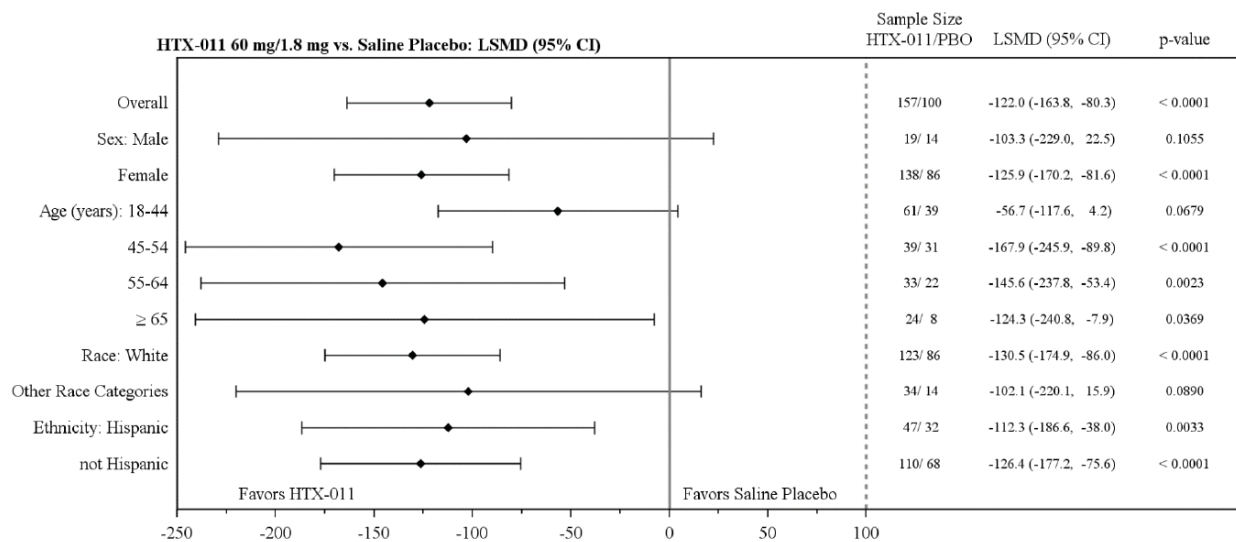
- Age categories of 65 to 74, 75 to 84, and ≥ 85 years pooled as a ≥ 65 years of age subgroup.

- All races other than White were pooled as an 'Other Race Categories' subgroup.

In general, the subgroup analyses were all consistent with the overall study population results demonstrating that HTX-011 treatment reduced the mean AUC₀₋₇₂ of pain intensity scores with activity compared to saline placebo and bupivacaine HCl treatment. In the subgroup analysis in which the confidence intervals crossed the null, the overall number of treated patients was low.

The following figures summarize the subgroup analysis results for the primary efficacy endpoint for Study 301 and Study 301.

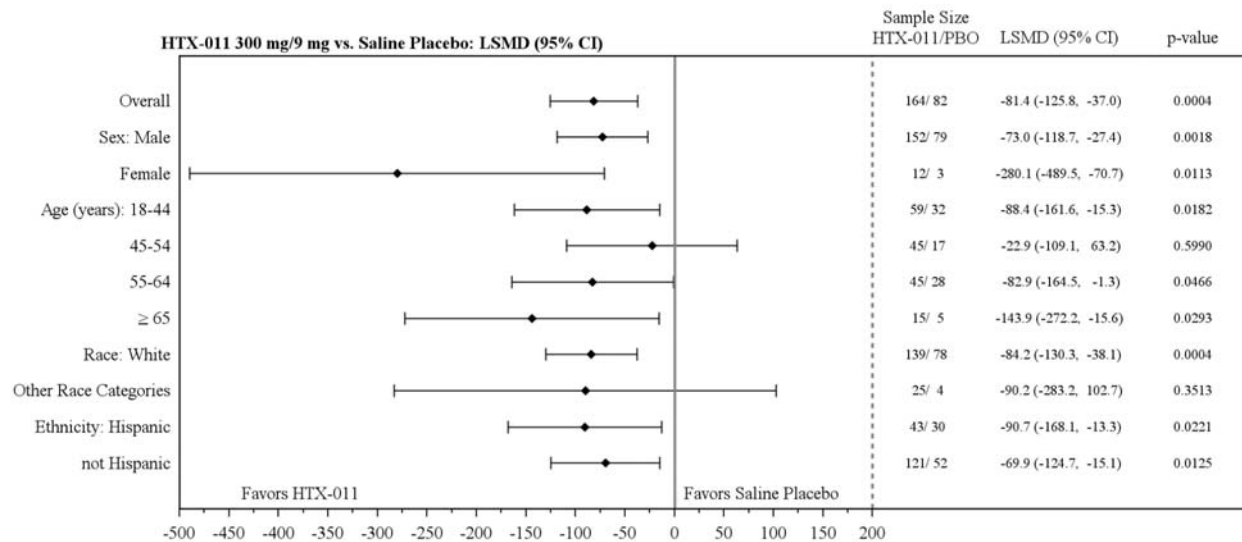
Figure 16: Subgroup Analysis for Mean AUC₀₋₇₂ of the NRS-A Pain Intensity Scores for HTX-011 vs. Saline Placebo, Study 301 (wWOFC, ITT Population)



Abbreviations: ANOVA, analysis of variance; AUC, area under the curve; ITT, Intent-to-Treat; LSMD, least squares mean difference; NRS-A, Numeric Rating Scale of pain intensity score with activity; PBO, saline placebo; wWOFC, windowed worst observation carried forward.
Notes: HTX-011 (also referred to as HTX-011-56) is the intended commercial formulation. LSMD and 95% CI reflect results of an ANOVA with randomized treatment as the main effect; LSMD is for HTX-011 minus control (saline placebo or bupivacaine HCl) difference.

Source: Summary of Clinical Efficacy, p. 94 (PDF), Applicant's submission, NDA 211988.

Figure 17: Subgroup Analysis for Mean AUC₀₋₇₂ of the NRS-A Pain Intensity Scores for HTX-011 vs. Saline Placebo, Study 302 (wWOCF, ITT Population)



Abbreviations: ANOVA, analysis of variance; AUC, area under the curve; ITT, Intent-to-Treat; LSMD, least squares mean difference; NRS-A, Numeric Rating Scale of pain intensity score with activity; PBO, saline placebo; wWOCF, windowed worst observation carried forward.

Notes: HTX-011 (also referred to as HTX-011-56) is the intended commercial formulation. LSMD and 95% CI reflect results of an ANOVA with randomized treatment as the main effect; LSMD is for HTX-011 minus control (saline placebo or bupivacaine HCl) difference.

Source: Summary of Clinical Efficacy, p. 95 (PDF), Applicant's submission, NDA 211988.

With respect to subgroup analysis of the secondary efficacy endpoints (results not shown), there were no differences in the efficacy of HTX-011 treatment in the demographic subgroups evaluated.

7.1.5. Dose and Dose-Response

There were several doses of HTX-011, ranging from 60 mg/1.8 mg to 600 mg/18 mg, evaluated for efficacy in the Applicant's drug development program. In the Phase 3 studies, only a single dose administered as a single instillation was evaluated in two different surgical populations, such that a dose-response was not appreciated.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

There are currently no FDA-approved bupivacaine products that are labeled for extended-release and while it is not clear if HTX-011 will be labeled as such, it is an additional bupivacaine product administered via a novel route that clearly has some clinical benefit. Approval of this product would offer clinicians an additional treatment option for managing acute postsurgical pain after unilateral bunionectomy and open inguinal hernia repair, relatively common surgical

procedures, with the potential to have a positive impact on a large number of patient outcomes.

The post-marketing surveillance reporting will provide usage data, guiding general conclusions regarding the utility of this product and the feasibility of other drug product delivery via this novel route of administration.

7.3. Integrated Assessment of Effectiveness

(b) (4)

The Applicant conducted a diverse and extensive evaluation of the efficacy of HTX-011, which included a variety of surgical procedures, both boney and soft tissue models. The Phase 3 studies demonstrated a statistically significant difference between the HTX-011 and saline placebo group on the primary efficacy endpoints. Additionally, all key secondary efficacy endpoints reached statistical significance, including lower mean AUC of pain intensity scores with activity when compared to bupivacaine HCl and decreased post-operative opioid consumption when compared to both saline placebo and bupivacaine HCl through 72 hours.

(b) (4)

(b) (4)

With respect to the opioid consumption data, incidence of opioid-related adverse events, and

the percentage of opioid-free patients, the Applicant demonstrated statistically significant differences between the HTX-011 treatment group and the saline placebo and bupivacaine HCl treatment groups on many of the endpoints. The nuances in the interpretation of the data have been previously discussed, but it is worth mentioning that while the decreases in opioid consumption were statistically significant, they may not translate into a significant clinical benefit. For example, in Study 302, the incidence of nausea was approximately 18% in the HTX-011 treatment group and 21% in the bupivacaine HCl treatment group, a difference that represents three out of 100 hundred treated patients.

The endpoint that may be more clinically meaningful is the proportion of opioid-free patients, specifically through Day 28. For both Phase 3 studies, more patients treated with HTX-011 remained opioid-free through Day 28 when compared to patients treated with bupivacaine HCl. Although the results were not statistically significant for Study 302, the use of opioid rescue in this study was higher in the bupivacaine HCl treatment group than the saline placebo treatment group for two timepoints, clearly an unexpected finding that likely led to the lack of statistical significance for the bupivacaine HCl treatment group.

For Study 209, Cohort 2, the efficacy data is not supportive of the Applicant's claim that treatment with HTX-011 results in a clinically meaningful decrease in opioid consumption, a decrease in opioid-related adverse events, and a larger proportion of opioid-free patients. Additionally, the median time to first opioid rescue for the HTX-011 treatment group was shorter than for either the saline placebo or bupivacaine HCl treatment groups.

In summary, the Phase 3 studies conducted by the Applicant did demonstrate a statistically and clinically significant difference between the HTX-011 treatment group and the saline placebo and bupivacaine HCl treatment groups on the primary and all key secondary efficacy endpoints. The reported results support approval of this marketing application with revisions to the product label. Specifically, I recommend the indicated surgical populations include only those evaluated in the Phase 3 studies, unilateral bunionectomy and open inguinal hernia repair with mesh, at the HTX-011 doses evaluated. (b) (4)

8. Review of Safety

8.1. Safety Review Approach

This application is a 505(b)(2), thus the Applicant is relying on the Agency's previous findings of safety and efficacy for Marcaine™ 0.25%, approved under NDA 016964 and Mobic® (meloxicam) tablets, approved under NDA 020938, and information in the published literature. Additionally, the Applicant has completed an extensive clinical development program to

support the safe use of HTX-011.

The evaluation of the safety profile for HTX-011 involved a comprehensive review of adverse events suspected to be related to the drug products, bupivacaine and meloxicam, and those suspected to be related to the novel Biochronomer® formulation or excipients in the formulation. The Applicant included agreed-upon prespecified preferred terms for adverse events thought to be most concerning with administration of this product. Relevant adverse events have been loosely categorized according to the potential causal factor, drug or Biochronomer® formulation. Refer to Section 8.3.2. Categorization of Adverse Events for additional information.

The potential safety issue of greatest concern with administration of bupivacaine is LAST. Like all local anesthetics, bupivacaine binds the Na⁺ channel in the inactivated state slowing the rate of neuronal depolarization. Electrophysiological studies, however, suggest that bupivacaine results in more profound depolarization changes, which in combination with its high degree of protein binding, leads to the marked toxicity observed with inadvertent intravascular injection or overdose (Morgan *et al*, 2002). The proposed maximum recommended dose of HTX-011, 400 mg/12 mg, adds a level of concern for the development of LAST. Refer to Section 8.8.4. Overdose, for additional information regarding symptomatology associated with LAST.

The safety issues of greatest concern with administration of meloxicam are the associated risks of cardiovascular thrombosis and gastrointestinal bleeding, ulceration, and perforation as indicated in the Mobic® boxed label warnings. The Applicant has provided supportive data that the systemic exposure, the main determinant of systemic toxicity, to meloxicam after administration of HTX-011 is much lower than that observed after oral meloxicam administration, and therefore, the product label for HTX-011 does not have to include the boxed warnings. While a final determination regarding the need for the boxed warnings has not been made at the time of this review, in general, all NSAID-containing products must contain the boxed warnings, including topically administered products used in the treatment of arthritic pain.

The safety issue of greatest concern during review of this NDA is the potential increased risk of wound-related adverse events and local tissue toxicity, particularly observed in Study 301, in patients undergoing bunionectomy. Wound-related adverse events most concerning from a clinical perspective include wound dehiscence, cellulitis, infection, and bony changes in the case of orthopedic procedures. The novel Biochronomer® formulation is used in the manufacture of HTX-011, as well as the extended-release formulation of grisetron (Sustol®), an antiemetic marketed by Heron and approved for chemotherapy-induced nausea and vomiting. There was concern that the Biochronomer® formulation may have an adverse impact on surgical wound healing, prompting review of the Sustol® label, which indicates that injection site reactions (ISRs), including infection, bleeding, pain, nodules, swelling, and induration, were commonly reported adverse events in the supportive clinical studies. Specifically, in Study 1, ISRs (any) were reported in 37% of patients who received Sustol® compared to 15% of patients

who received saline control. In Study 2, 62% of patients who received Sustol® experienced an adverse event of ISR (the data for the Sustol®-matched control consisting of the vehicle polymer was not shown). The ISR most commonly reported in both studies was bruising/hematoma (Sustol® [package insert]. Redwood City, CA: Heron Therapeutics, Inc.; 2016). While it appears that the Biochronomer® formulation and its metabolites are implicated in adverse wound healing, meloxicam may play a role as well.

Opioid-related adverse events will be discussed briefly, but will not be emphasized during the safety review. (b) (4)

8.2. Review of the Safety Database

8.2.1. Overall Exposure

A total of 1077 patients were administered a single dose of HTX-011, ranging from 30 mg/0.9 mg to 600 mg/18 mg, in the clinical development program (data from recently submitted Phase 2 studies, 215 and 218, are not included due to incomplete final study reports). With the exception of ten healthy volunteers in Study 102, a Phase 1 study, all patients received HTX-011 during a surgical procedure. The Applicant conducted the following eight clinical studies using the intended commercial formulation:

- One Phase 1
- Three Phase 2a
- Two Phase 2b
- Two Phase 3

Two additional studies were conducted by the Applicant using earlier formulations of HTX-011.

The clinical studies evaluated postsurgical analgesia after representative boney and soft tissue surgical procedures utilizing a variety of administration routes. Evaluated surgical procedures did capture diverse anatomic spaces with varying degrees of vascularity and resultant post-operative pain and included simple bunionectomy, unilateral open herniorrhaphy, unilateral total knee replacement, bilateral augmentation mammoplasty, and mini- or complete abdominoplasty. Evaluated routes of administration included subcutaneous injection, wound infiltration, nerve block injection, and wound instillation. A total of 448 patients received the intended commercial formulation of HTX-011 via the intended route of administration, currently described as instillation using a unique applicator without a needle, in the two Phase 2b and two Phase 3 studies. The following table provides an overview of the Phase 2b and Phase 3 Studies contributing to the pooled assessment of safety. Review of data from the Phase 3 studies will primarily inform the safety assessment for HTX-011, however, the Phase 2b studies will provide information regarding the maximum proposed dose, HTX-011 400 mg/12 mg.

Table 32: Phase 3 and Phase 2b Study Safety Population

Study (Region)	Study Design	Surgery	Treatment Group (Number of Subjects)
301 (US)	Phase 3, randomized, double-blind, placebo- and active-controlled efficacy and safety study	Unilateral simple bunionectomy	- HTX-011 60 mg/1.8 mg via instillation (157) - Bupivacaine HCl 0.5% 50 mg via injection (154) - Saline placebo via instillation (101)
302 (US and Belgium)	Phase 3, randomized, double-blind, placebo- and active-controlled efficacy and safety study	Unilateral open inguinal herniorrhaphy	- HTX-011 300 mg/9 mg via instillation (163) - Bupivacaine HCl 0.25% 75 mg via injection (173) - Saline placebo via instillation (82)
209 (US)	Phase 2b, randomized, double-blind, placebo- and active-controlled efficacy, safety, and PK study	Total knee arthroplasty	- HTX-011 200 mg/6 mg via periarticular instillation (20) - HTX-011 400 mg/12 mg via periarticular instillation and ropivacaine 50 mg via periarticular injection (56) - HTX-011 400 mg/12 mg via periarticular instillation (58) - Bupivacaine HCl 0.25% 125 mg via periarticular injection (65) - Saline placebo via periarticular injection (64)
211 ^a (US) Cohort 4	Phase 2b, randomized, double-blind, placebo- and active-controlled efficacy, safety, and PK study	Bilateral augmentation mammoplasty	HTX-011 400 mg/12 mg (200 mg/6 mg per side) via instillation administered in each of the surgical incision lines (50)

Abbreviations: PK, pharmacokinetics; US, United States.

Note: the number of subjects in each treatment group is based on the Safety Population.

^a Study 211 included additional cohorts to evaluate HTX-011 administered by nerve block. These cohorts are not included in the integrated analysis of safety. Saline placebo and bupivacaine HCl are also not included because they were administered by nerve block. Because only 200 mg/6 mg of HTX-011 was administered into each incision, local safety in this study was assessed at a 200 mg/6 mg dose and systemic safety at a 400 mg/12 mg dose.

Source: ISS, p. 21 (PDF), Applicant's submission, NDA 211988.

The following table summarizes disposition of the safety population by treatment group.

Table 33: Overall Disposition of Patients in Phase 2b and Phase 3 Studies (All Enrolled Patients)

	Saline Placebo	Bupivacaine HCl				HTX-011				
		50 mg	75 mg	125 mg	Total	60 mg/ 1.8 mg	200 mg/ 6 mg	300 mg/ 9 mg	400 mg/ 12 mg	Total
Subjects randomized	266	165	179	69	413	164	21	178	168	531
Subjects in Safety Population ^a	247 (92.9%)	154 (93.3%)	173 (96.6%)	65 (94.2%)	392 (94.9%)	157 (95.7%)	20 (95.2%)	163 (91.6%)	164 (97.6%)	504 (94.9%)
Completed the 72-hour period ^b	242 (98.0%)	153 (99.4%)	171 (98.8%)	65 (100%)	389 (99.2%)	155 (98.7%)	20 (100%)	161 (98.8%)	161 (98.2%)	497 (98.6%)
Completed the study	243 (98.4%)	151 (98.1%)	171 (98.8%)	65 (100%)	387 (98.7%)	154 (98.1%)	20 (100%)	158 (96.9%)	158 (96.3%)	490 (97.2%)
Primary reasons for study withdrawal after dosing										
Adverse event	1 (0.4%)	0	0	0	0	1 (0.6%)	0	0	2 (1.2%)	3 (0.6%)
Lost to follow-up	1 (0.4%)	1 (0.6%)	0	0	1 (0.3%)	1 (0.6%)	0	1 (0.6%)	4 (2.4%)	6 (1.2%)
Protocol deviation	0	0	0	0	0	0	0	1 (0.6%)	0	1 (0.2%)
Withdrawal by subject	2 (0.8%)	1 (0.6%)	2 (1.2%)	0	3 (0.8%)	1 (0.6%)	0	3 (1.8%)	0	4 (0.8%)
Death	0	1 (0.6%)	0	0	1 (0.3%)	0	0	0	0	0

^a Safety Population includes all subjects who received study drug.

^b Subjects who had reported a numeric rating scale (NRS) pain intensity score at the nominal 72-hour postoperative timepoint were considered as completing the 72-hour postoperative observation period.

Source: ISS, p. 57 (PDF), Applicant's submission, NDA 211988.

8.2.2. Relevant characteristics of the safety population:

The majority of patients undergoing bunionectomy and all patients undergoing augmentation mammoplasty were female, while the majority of patients undergoing inguinal herniorrhaphy were male. In general, patients undergoing TKA were older than those undergoing other evaluated procedures.

Patients in the Phase 3 studies were permitted both opioid and non-opioid analgesics, acetaminophen and paracetamol, while patients in the Phase 2b studies were permitted opioid analgesics alone. NSAID use was not permitted during any clinical study and was an exclusion criterion. All studies were conducted in the United States, with the exception of a single foreign investigative site for Study 302, which enrolled four patients all in the HTX-011 treatment group.

8.2.3. Adequacy of the safety database:

The totality of the safety database is adequate for the revised indication as described in Section 9. Labeling Recommendations. (b) (4)

[Redacted text block]

(b) (4)

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There were no issues regarding the data integrity or the overall quality of the submission. The information provided was organized and easy to locate. Unlike the Summary of Clinical Efficacy in Module 2.7.3 as a substitute for an ISE, the Applicant submitted an ISS in Module 5, in addition to the Summary of Clinical Safety in Module 2.

8.3.2. Categorization of Adverse Events

The adverse events of most clinical significance with administration of HTX-011 include LAST-related adverse events, cardiovascular thrombotic and gastrointestinal adverse events, and wound-related adverse events, and are loosely categorized by likely causal factor as follows:

- Bupivacaine
 - LAST-related adverse events
- Meloxicam
 - Cardiovascular thrombotic adverse events (Mobic® box warning)
 - Gastrointestinal adverse events (Mobic® boxed warning)
- Biochronomer® formulation or excipients
 - Local inflammatory adverse events (also referred to as wound-related adverse events in this review)
 - Other observed local toxicities, including those observed in nonclinical studies and those included in the Sustol® label

Throughout the clinical development program, patients were regularly evaluated for neurological and cardiac signs and symptoms consistent with LAST. In the Phase 3 studies, this evaluation included a questionnaire used during the in-patient admission and continued after discharge (pictured below). Any event possibly attributed to LAST triggered additional safety assessments, including vital sign measurements, 12-lead ECG monitoring, and PK blood sampling, and was recorded as an adverse event.

Figure 18: LAST Questionnaire, Phase 3 Studies

Metallic/strange taste	Present ☒	Absent ☒
Perioral tingling	Present ☒	Absent ☒
Ringing in ears	Present ☒	Absent ☒
Visual disturbance	Present ☒	Absent ☒
Tremors	Present ☒	Absent ☒
Muscle twitching	Present ☒	Absent ☒
Dizziness/lightheadedness	Present ☒	Absent ☒
Convulsion/seizure	Present ☒	Absent ☒
Bradycardia	Present ☒	Absent ☒
Arrhythmia	Present ☒	Absent ☒
Hypotension	Present ☒	Absent ☒
Cardiac arrest	Present ☒	Absent ☒
Respiratory arrest	Present ☒	Absent ☒

Reference: Vasques, F., A.U. Behr, G. Weinberg, C. Ori, G. Di Gregorio (2015). "A Review of Local Anesthetic Systemic Toxicity Cases Since Publication of the American Society of Regional Anesthesia Recommendations: To Whom It May Concern." *Reg Anesth Pain Med* 40(6): 698-705.

Source: HTX-011-301 Protocol or Amendment, Appendix H, p. 175 (PDF), and HTX-011-302 Protocol or Amendment, p. 169 (PDF), Applicant's submission, NDA 211988

Additionally, the Applicant searched the Phase 3 clinical databases for a prespecified list of preferred terms possibly related to LAST, shown below.

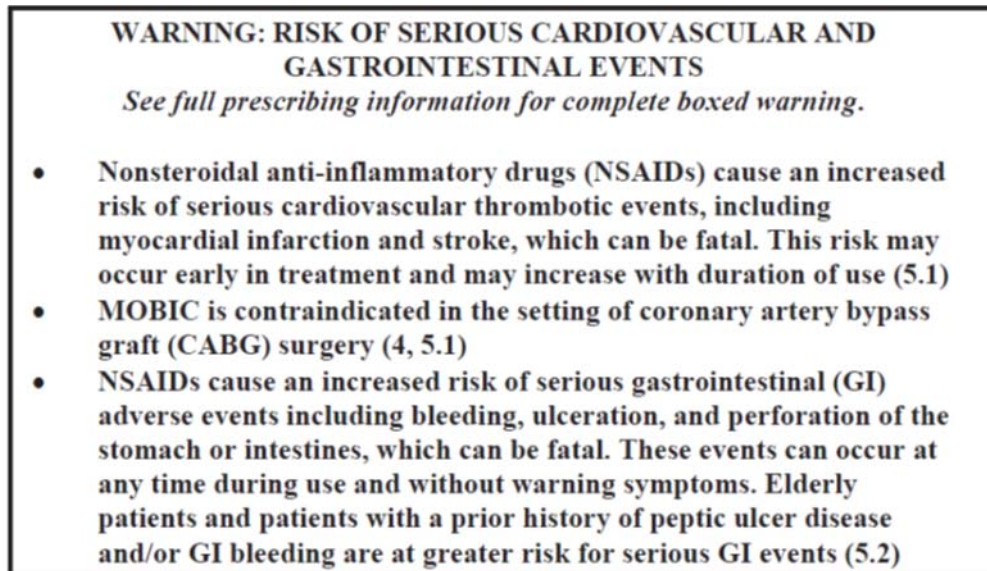
- Any PT that includes "arrhythmia"^a - Any PT that includes "bradycardia"^a - Cardiac arrest - Dizziness - Dysguesia	- Hypotension - Muscle twitching - Paraesthesia^a - Paraesthesia oral - Respiratory arrest	- Seizure - Tinnitus - Tremor - Vision blurred^a - Visual impairment
---	--	--

^a The PTs of arrhythmia and bradycardia were updated and the PTs of paraesthesia and vision blurred were added following a blinded review of safety data after the SAP was finalized, but before database lock, for a more comprehensive list.

Source: HTX-011-301 and HTX-011-302 Study Report Bodies, Applicant's submission, NDA 211988.

There were no specific assessments in the clinical studies for capture of meloxicam-related cardiovascular thrombotic or gastrointestinal adverse events described in the boxed warning in the Mobic® package insert, pictured below.

Figure 19: Boxed Warning, Mobic® Package Insert



Source: Mobic® package insert (Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2016.)

The Applicant argued that the safety issues identified and included in the boxed warnings for Mobic® are not relevant to administration of HTX-011 and should not be required as boxed warnings in the product label. A comprehensive review of preferred terms in the Cardiac Disorders, Gastrointestinal Disorders, and Investigations system organ class was performed to assess the incidence and potential risk of these adverse events with administration of HTX-011.

Based on discussions with the Agency, the Applicant conducted a search of the clinical study databases for local inflammatory treatment-emergent adverse events using a prespecified, comprehensive list of preferred terms (PTs) in an attempt to further characterize any potential increased risk in wound-healing or wound-related adverse events associated with HTX-011 treatment. The following PTs were searched:

• Blister	• Incision site haemorrhage	• Postoperative wound infection
• Blood blister	• Incision site infection	• Post procedural cellulitis
• Cellulitis	• Incision site oedema ^a	• Purulent discharge
• Erythema	• Incision site rash ^a	• Wound complication
• Impaired healing	• Incision site swelling ^a	• Wound dehiscence
• Incision site cellulitis	• Incision site vesicles	• Wound infection
• Incision site complication	• Infection	• Wound secretion ^a
• Incision site erythema	• Postoperative wound complication	

Source: Clinical Study Report Bodies, Applicant's submission, NDA 211988.

The Applicant also extensively evaluated opioid-related adverse events to support the claim

that administration of HTX-011 results in a clinically meaningful reduction in post-operative opioid use, demonstrated by a measurable decrease in opioid-related adverse events. Those adverse events will be discussed briefly, but in general do not appear to impact the overall safety profile of HTX-011.

8.3.3. Safety Assessments and Evaluations

The clinical evaluations performed in the Phase 2b and Phase 3 studies included the following.

Table 34: Safety Assessments and Evaluation Timepoints for Phase 2b and Phase 3 Studies Included in the Applicant's Pooled Analysis

Safety Assessment	Studies Pooled	Evaluation Timepoint
TEAEs	301, 302, 209, 211	Continuous evaluation
Hematology	301, 302, 209, 211	Screening, Baseline ^a ; 24 and 72 hours; Day 10
Serum chemistry	301, 302, 209, 211	Screening, Baseline ^a , 72 hours, Day 10
Vital signs	301, 302, 209, 211	- Studies 209 and 211: Screening; Baseline^a; 24, 48, and 72 hours - Studies 301 and 302: Screening; Baseline^a; 30 minutes; 1, 1.5, 2, 4, 8, 12, 18, 24, 36, 48, 60, and 72 hours
Surgical wound healing - Southampton Wound Scoring System	302, 209, 211 ^b	72 hours; Days 10 and 28
LAST assessment questionnaire	301, 302 ^c	30 minutes; 1, 2, 4, 18, 24, and 72 hours

Abbreviations: LAST, local anesthetic systemic toxicity; TEAE, treatment-emergent adverse event.

^a Baseline for clinical laboratory evaluations is the last value observed prior to administration of study drug.

^b Study 301 used a different surgical wound healing assessment and was not pooled for analysis of wound healing (Section 1.1.4.1.2.8).

^c LAST assessment questionnaire was not included in Studies 209 and 211.

Source: ISS, p. 26 (PDF), Applicant's submission, NDA 211988.

The following table summarizes the safety assessments and evaluations performed during the Phase 2b and Phase 3 studies that were not included in the Applicant's pooled analysis due to differences in evaluation(s) between studies.

Table 35: Safety Assessments and Evaluation Timepoints for Phase 2b and Phase 3 Studies Not Included in the Applicant's Pooled Analysis

Safety Assessment	Evaluation Timepoint
Physical examinations	Screening; 72 hours
ECGs	12-lead ECG in Studies 301 and 302: Screening; 4, 18, 24, 48, and 72 hours 12-lead ECG in Studies 209 and 211: Screening - Holter monitoring in Studies 209 and 211: -24 to 72 hours
Bone healing for Study 301	Days 28 and 42
Surgical wound healing for Study 301	72 hours, Days 10 and Day 28, and Day 42 at the Safety Follow-Up

Abbreviation: ECG, electrocardiogram.

Source: ISS, p. 27 (PDF), Applicant's submission, NDA 211988.

8.4. Safety Results

8.4.1. Deaths

No patient administered HTX-011 died during the clinical development program. A single male patient in Study 301 received bupivacaine HCl for unilateral bunionectomy and died on Day 17. The patient (subject id. number (b) (6)) was a 62-year-old African American male with a past medical history of hypercholesterolemia and asthma. He had a total knee arthroplasty in (b) (6). His daily medications included

Pre-operative ECG was read as normal. There were no reported intra- or post-operative complications. The patient was discharged on Day 4, as per the study protocol. He was not prescribed opioids upon discharge and it does not appear he had access to them otherwise. He returned on study Day 6 for a postoperative assessment and was without significant complaints. The surgical site was noted to be mildly edematous and mildly painful upon palpation. X-ray of the operative foot showed normal bone healing and was documented as, "healing as expected". He returned to the site on study Day 12 and was noted to have unremarkable healing and a pain score of one on a NRS of 0 to 10.

On study Day 17, the patient was found dead in his bed by family members. His daughter reported that he had died of "natural causes". No autopsy was performed and no additional information was provided.

8.4.2. Serious Adverse Events (SAEs)

In the Phase 1 and Phase 2a studies, there were a total of eight SAEs in eight patients; four SAEs in four patients treated with HTX-011, two SAEs in two patients treated with bupivacaine HCl, and two SAEs in two patients treated with saline placebo. None of the SAEs reported during these studies were in patients treated with HTX-011 via instillation. Of the eight SAEs reported, three were severe, three were moderate, and two were mild in severity. There were two SAEs

either possibly or probably related to study drug and included wound dehiscence in Study 203 and impaired healing in Study 208. A brief summary of SAEs reported in the Phase 1 and Phase 2a studies is as follows:

- Study 202
 - HTX-011 treatment group: presyncope, DVT
 - Bupivacaine HCl treatment group: scrotal hematoma, wound dehiscence
 - Saline placebo treatment group: non-cardiac chest pain, cellulitis of male external genital organ
- Study 203
 - HTX-011 treatment group: wound dehiscence
 - Bupivacaine HCl treatment group: wound dehiscence
- Study 208
 - HTX-011 treatment group: impaired healing

In the Phase 2b and Phase 3 studies, there were a total of 30 SAEs; 14 SAEs in 11 patients (2%) treated with HTX-011, 8 SAEs in 7 patients (2%) treated with bupivacaine HCl, and 8 SAEs in 5 patients (2%) treated with saline placebo. Of the 30 SAEs, 14 were severe, 14 were moderate, and 2 were mild in severity, and 29 were considered unlikely related to study drug. The single SAE reported as possibly related to study drug was for a patient in Study 209, Cohort 2, who received HTX-011 400 mg/12 mg and developed post-procedural cellulitis. The operative knee was aspirated and the patient was treated with antibiotics. The SAE resolved, with normal healing with mild erythema reported on Day 16, and normal healing reported on Day 33.

A brief summary of SAEs reported in the Phase 2b studies is as follows:

- Study 209
 - HTX-011 treatment group: atrial fibrillation, pulmonary embolism, urinary retention, respiratory failure, respiratory depression, post-procedural cellulitis
 - Bupivacaine HCl treatment group: syncope, pulmonary embolism, hypoxia
 - Saline placebo treatment group: hematoma, hyponatremia, visual hallucination, cholecystitis
- Study 211
 - HTX-011 treatment group: left silicone breast implant rupture

A high-level summary of the SAEs reported in the Phase 3 studies is as follows:

Study 301

HTX-011 Treatment Group

- 42-year-old White male with no significant past medical history developed venous thrombosis (DVT) of right peroneal vein, operative side. He returned for follow-up visit

on Study Day 31, with complains of swelling and pain in his right calf. A Doppler ultrasound performed on Day 34 revealed a venous thrombosis of the right peroneal vein. The patient was started on rivaroxaban. On Day 84, the SAE was considered resolved.

- 68-year-old White female with past medical history of hypothyroidism, osteoporosis, chronic kidney disease, hypercholesteremia, and prior lumbar vertebral fracture, thyroidectomy, mitral valve replacement, and hysterectomy, presented to the Emergency Room (ER) on Day 30 complaints of a syncopal episode and fall. She had been feeling ill in the weeks leading up to the fall. Myocardial infarction and cerebrovascular accident were ruled out. Work up revealed thoracic (T11) vertebral fracture and urinary tract infection. She was hospitalized and fracture was treated with a brace. She was discharged on Study Day 33 and all events were resolved. She returned for a post-operative follow-up on Study Day 52, no complaints were noted.

Saline Placebo Treatment Group

- 53-year-old White female with past medical history of anemia and hot flash and prior oophorectomy, hysterectomy, and instrumentation and subsequent removal of left humerus and left fibula presented on Study Day 7 with complaints of pain in the right calf (operative side). Doppler ultrasound was positive for DVT of soleal vein. Patient was started on rivaroxaban. On Study Day 8, the patient reported worsening symptoms and new tingling and throbbing in the foot. Evaluation in the ER revealed similar findings as previous day in addition to large right popliteal fossa cyst, measuring 9.2 x 3.4 x 1.2 cm. Coagulation studies were within normal limits and patient was advised to continue anticoagulation medication. Multiple repeat Doppler evaluations were performed with ultimate resolution on Study Day 71.

Bupivacaine HCl Treatment Group

- 64-year-old White male with past medical history of hypertension, pericardial effusion, COPD, asthma, chronic low thyroid-stimulating hormone, blood testosterone decreased, blood cholesterol increased, and previous ablation developed atrial fibrillation with rapid ventricular response on Study Day 2. He was evaluated in the ER, with a documented heart rate of approximately 145 beats per minute. He was not experiencing chest pain, dizziness, diaphoresis, or shortness of breath. He was treated with a diltiazem infusion and cardioversion (single synchronous biphasic shock at 150 Joules) with successful conversion to normal sinus rhythm. SAE resolved and at follow-up visit on Study Day 9, patient was without complaints.
- 34-year-old White female with no significant past medical history developed DVT in the left (operative side) tibial, popliteal, and superficial femoral veins with extension as high as the saphenofemoral junction, without common femoral vein involvement on Study Day 16. She was evaluated in the ER, given a prescription for rivaroxaban, and discharged home. On the following day, she developed shortness of breath and returned to the ER where she was diagnosed with a pulmonary embolism. On Study Day

43, the SAE of pulmonary embolism was considered resolved, SAE of DVT was ongoing, and she was otherwise doing well without complaints.

Study 302

HTX-011 Treatment Group

- 23-year-old White female with past medical history of appendicitis with previous appendectomy developed a hematoma in the area of the right inguinal hernia repair approximately 14 hours post-operatively. No drainage was noted. On Study Day 2, she returned to the operating room for incision and drainage of the hematoma, at which time approximately 180 mL of clotted blood was removed. Inspection of the wound identified multiple small oozing vessels but no single arterial or venous source. Electrocautery was used for hemostasis. The event was considered resolved and the patient was discharged on Study Day 4 without additional complications.
- 67-year-old White male with past medical history of advanced COPD (emphysema) and a prior left lower lobe infiltrate, coccidiomycosis, and previous right knee surgery experienced worsening shortness of breath and productive cough on Study Day 5. The patient presented to the ER and was noted to be diaphoretic. A CAT scan of the chest was negative for pulmonary embolism but significant for emphysematous changes, calcified granuloma in left upper lung, and atherosclerotic calcification. Laboratory elevation revealed slight elevation in Troponin-I levels and ECG demonstrated sinus tachycardia, negative for ischemic changes. Cardiology consultation recommended no acute intervention and future ischemic work-up once COPD exacerbation resolves. The patient was treated with nebulized albuterol and ipratropium, steroids, and antibiotics. On Study Day 9, the SAE of acute exacerbation was considered resolved and patient was discharged to a rehabilitation facility.

Saline Placebo Treatment Group

- 80-year-old White male with past medical history of hypertension, hypercholesterolemia, tinnitus, gastroesophageal reflux disease, and Crohn's disease with previous right IHR, right leg surgery, gastric bypass surgery, and right and left TKA experienced recurrence of left inguinal hernia, cellulitis of male genital organ, and post-operative wound infection. On Study Day 6, the patient presented to the ER with scrotal pain and swelling. CAT scan and scrotal ultrasound revealed possible bowel or fatty tissue herniation into the scrotum. On Study Day 8, patient returned to the OR for repair of recurrent left inguinal hernia with mesh. The SAE of recurrent inguinal hernia was considered resolved and patient was discharged. On Study Day 10, the patient returned to the ER with complaints of feeling ill and feverish. Physical examination revealed cellulitis. CAT scan demonstrated fluid collection in left groin. Patient also had urinary tract infection. He was treated with antibiotics and SAE of cellulitis and postoperative wound infection were considered resolved on Study Day 17.

Bupivacaine HCl Treatment Group

- 46-year-old White male with past medical history of hypertension and hypertriglyceridemia developed fever of unknown origin on Study Day 2. His body temperature ranged from 37.6°C to 39.5°C. He also experienced diarrhea and hypokalemia. He was treated with antibiotics. On Study Day 3, his temperature ranged from 36.9°C to 39.6°C with a white blood cell count of $11.7 \times 10^3/\mu\text{L}$. The patient underwent testing and laboratory evaluations that did not reveal a cause for the fever. He was discharged on Study Day 6 with ongoing antibiotic treatment.

The SAEs reported in the Phase 3 studies appear unlikely related to study drug treatment, but more likely related to the surgical procedure, perioperative stress response, or exacerbation of underlying medical conditions. Specifically, there did not appear to be a causal relationship between the reported SAEs and administration of HTX-011 in either Phase 3 study.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In the Phase 3 studies, there was a single patient in the HTX-011 treatment group who had an SAE that led to study withdrawal. The patient was a 51-year-old White female with a past medical history of gastric ulcer, cholelithiasis status post cholecystectomy, and GERD who experienced abdominal and upper back pain and vomiting six hours post-bunionectomy. Ultrasound evaluation revealed distended common bile duct and laboratory evaluation demonstrated elevated liver enzymes. The patient was transferred to nearby hospital and ultimately diagnosed with choledocholithiasis. She underwent surgical removal of the bile duct stone via endoscopic retrograde cholangiopancreatography (ERCP) and discharged on Study Day 4. She was readmitted to the hospital on Study Day 5 with bowel perforation and pneumoperitoneum secondary to ERCP complications. She underwent exploratory laparotomy and placement of feeding jejunostomy tube. with placement of percutaneous endoscopic jejunostomy tube. The patient had an extended and complicated hospital course and was ultimately discharged on Study 47.

In Study 209, Cohort 2, there were two patients treated with HTX-011 400 mg/12 mg + ropivacaine who were discontinued due to an SAE.

- A 67-year-old White male with a past medical history of Type 2 diabetes mellitus, benign prostatic hyperplasia, hypertension, urinary tract infection, chronic intermittent poor urinary stream following catheter insertion, and lower urinary tract syndrome developed urinary retention on Day 1 following TKA. Foley catheter insertion was unsuccessful, patient was transferred to another facility, and was discontinued from the study. The SAE was reported as unlikely related to study drug administration and resolved approximately three months after the start date.
- A 66-year-old White male with a past medical history of asthma, obesity, hypertension, snoring, gout, pneumonia, bronchitis, sinus polyps, and low testosterone experienced

intra-operative hypotension and shortness of breath, dizziness, and palpitation post-operatively. He developed hypoxemic respiratory failure, was transferred to another facility, and treated for pulmonary emboli. He was withdrawn from the study. The SAEs of respiratory failure and pulmonary emboli were reported as unlikely related to study drug administration. The SAE of respiratory failure was considered resolved on Day 9. Treatment for the pulmonary emboli, anticoagulation, was ongoing.

8.4.4. Study Pregnancy

There were two documented pregnancies across the drug development program. In Study 211, a patient received HTX-011 240 mg/7.2 mg as a nerve block during bilateral augmentation mammoplasty. Her urine pregnancy test at screening and on the day of surgery was negative, but was pregnant on Day 21. On Day 25, the patient had a spontaneous abortion, which was classified as an SAE. The investigator felt the pregnancy loss was unlikely related to study drug administration. No additional follow-up was provided.

In Study 301, a 26-year-old patient with a past medical history of three prior pregnancy miscarriages, abnormal cervical Pap smear, iron deficiency anemia, and morbid obesity had a positive urine pregnancy test on Day 21. Her urine pregnancy tests at screening and on the day of surgery were negative. She was evaluated in the ER secondary to vaginal bleeding and abdominal pain. She admitted to unprotected intercourse in the weeks preceding the bunionectomy surgery. A transvaginal ultrasound revealed a single, viable intrauterine pregnancy of approximately six weeks gestation. The last follow-up occurred on Study Day 63, at which time the patient was felt to have a normal first trimester pregnancy. No additional follow-up is available despite attempts by the investigator.

8.4.5. Treatment-Emergent Adverse Events (TEAEs)

Review of adverse events in this section will focus on those observed in the two Phase 3 clinical studies, and the doses likely to gain approval. All adverse events were coded using MedDRA, Version 19.1.

Study 301

A total of 412 patients received a single dose of study drug and are included in the safety population for this study. A brief summary of TEAEs is included in the following table.

Table 36: Overall Summary of TEAEs, Study 301 (Safety Population)

TEAE Categories	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=101)	Bupivacaine HCl 50 mg (N=154)
Any TEAEs	131 (83.4%)	79 (78.2%)	131 (85.1%)
TEAEs Possibly Related to Study Drug	29 (18.5%)	21 (20.8%)	35 (22.7%)
Severe TEAEs	5 (3.2%)	3 (3.0%)	7 (4.5%)
ORAEs	69 (43.9%)	54 (53.5%)	78 (50.6%)
Local Inflammatory TEAEs	45 (28.7%)	20 (19.8%)	34 (22.1%)
Potential LAST-Related TEAEs	55 (35.0%)	34 (33.7%)	64 (41.6%)
TEAEs Leading to Study Withdrawal	1 (0.6%)	0	0
SAEs	3 (1.9%)	1 (1.0%)	3 (1.9%)
SAEs Possibly Related to Study Drug	0	0	0
Fatal TEAE	0	0	1 (0.6%)

Abbreviations: LAST, local anesthetic systemic toxicity; ORAE, opioid-related adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Source: HTX-011-301 Study Report Body, p. 93 (PDF), Applicant's submission, NDA 211988.

In general, the proportion of patients who experienced a TEAE and the severity of TEAEs was similar across all treatment groups. The exception, which will be discussed in detail in Section 8.5.3. Wound-Related Adverse Events, is the increased incidence of local inflammatory TEAEs in the HTX-011 treatment group. There was one patient who experienced an SAE resulting in withdrawal from the study and one patient death, both previously described.

TEAEs were most commonly reported in the Gastrointestinal Disorders, Nervous System Disorders, and Injury, Poisoning, and Procedural Complications system order classes (SOCs). The incidence of TEAEs within each SOC was similar across all treatment groups. In the Injury, Poisoning, and Procedural Complications SOC, the incidence of TEAEs was higher in both the HTX-011 (29%) and bupivacaine HCl (29%) treatment groups when compared to the saline placebo group (20%). The most common TEAEs by preferred term (PT) are summarized in the following table.

Table 37: Incidence of Most Common Treatment-Emergent Adverse Events by Preferred Term, Study 301 (Safety Population)

	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=101)	Bupivacaine HCl 50 mg (N=154)
Any TEAE	131 (83.4%)	79 (78.2%)	131 (85.1%)
Nausea	59 (37.6%)	44 (43.6%)	70 (45.5%)
Dizziness	34 (21.7%)	18 (17.8%)	36 (23.4%)
Incision site oedema	27 (17.2%)	13 (12.9%)	22 (14.3%)
Vomiting	23 (14.6%)	19 (18.8%)	33 (21.4%)
Headache	22 (14.0%)	10 (9.9%)	20 (13.0%)
Incision site erythema	20 (12.7%)	8 (7.9%)	18 (11.7%)
Post procedural contusion	19 (12.1%)	13 (12.9%)	18 (11.7%)
Bradycardia	12 (7.6%)	6 (5.9%)	12 (7.8%)
Impaired healing	10 (6.4%)	1 (1.0%)	6 (3.9%)
Constipation	9 (5.7%)	7 (6.9%)	18 (11.7%)
Muscle twitching	9 (5.7%)	5 (5.0%)	8 (5.2%)
Pruritus	8 (5.1%)	6 (5.9%)	1 (0.6%)
Sinus arrhythmia	6 (3.8%)	6 (5.9%)	10 (6.5%)
Dysgeusia	4 (2.5%)	6 (5.9%)	6 (3.9%)
Pruritus generalised	4 (2.5%)	4 (4.0%)	8 (5.2%)
Tinnitus	2 (1.3%)	2 (2.0%)	8 (5.2%)

Abbreviation: TEAE, treatment-emergent adverse event.

Notes: Most common was defined as $\geq 5\%$ of subjects in any treatment group. TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.1. For each Preferred Term (PT), subjects are included only once, even if they experienced multiple events in that PT. TEAEs are presented in descending order of frequency in the HTX-011 group.

Source: HTX-011-301 Study Report Body, p. 94 (PDF), Applicant's submission, NDA 211988.

Of these TEAEs, those that appeared to occur with a higher incidence in the HTX-011 treatment group compared to the saline placebo or bupivacaine HCl treatment groups included incision site odema (sic), headache, incision site erythema, impaired healing, and muscle twitching.

Of these TEAEs, those that appeared to occur with a lower incidence in the HTX-011 treatment group compared to the saline placebo or bupivacaine HCl treatment groups included nausea, vomiting, constipation, sinus arrhythmia, dysgeusia, pruritis generalized, and tinnitus.

The majority of TEAEs for all treatment groups were mild or moderate in severity and the incidence of severe TEAEs was similar across groups. Of the SAEs reported, none were thought to be related to study drug administration. Refer to the following table for additional information.

Table 38: Summary of Treatment-Emergent Adverse Events by Severity, Study 301 (Safety Population)

	HTX-011 60 mg/1.8 mg (2.1 mL) (N=157)	Saline Placebo (2.1 mL) (N=101)	Bupivacaine HCl 50 mg (10 mL) (N=154)
Total Number of TEAEs	512	313	553
Number (%) of Subjects Reporting at Least One:			
TEAE	131 (83.4%)	79 (78.2%)	131 (85.1%)
TEAE Possibly Related to Study Drug	29 (18.5%)	21 (20.8%)	35 (22.7%)
Opioid-Related TEAE ^[1]	69 (43.9%)	54 (53.5%)	78 (50.6%)
TEAE Leading to Premature Withdrawal from the Study	1 (0.6%)	0	0
TEAE by Severity ^[2]			
Mild	73 (46.5%)	45 (44.6%)	71 (46.1%)
Moderate	53 (33.8%)	31 (30.7%)	53 (34.4%)
Severe	5 (3.2%)	3 (3.0%)	7 (4.5%)
Total Number of TESAEs	4	1	4
Number (%) of Subjects Reporting at Least One:			
TESAE	3 (1.9%)	1 (1.0%)	3 (1.9%)
TESAE Possibly Related to Study Drug	0	0	0
TESAE Leading to Premature Withdrawal from the Study	1 (0.6%)	0	0
TESAE by Severity ^[2]			
Mild	1 (0.6%)	0	0
Moderate	1 (0.6%)	1 (1.0%)	0
Severe	1 (0.6%)	0	3 (1.9%)
Fatal TESAE	0	0	1 (0.6%)

Abbreviations: TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

[1] Opioid-related adverse events include those with sponsor pre-specified preferred terms of nausea, vomiting, constipation, pruritus, pruritus generalised, somnolence, respiratory depression, and urinary retention.

[2] Subjects reporting more than one event are counted only once using the highest severity.

Source: HTX-011-301 Study Report Body, p. 300 (PDF), Applicant's submission, NDA 211988.

Of the severe TEAEs reported, the majority resolved at database lock. Those ongoing were associated with SAEs in the same patient and included the patient in the HTX-011 treatment group with a common bile duct stone and associated complications and a patient in the bupivacaine HCl treatment group with DVT and pulmonary embolism, both previously described.

LAST-related adverse events are summarized in the following table.

Table 39: Incidence of Potential LAST-Related Adverse Events, Study 301 (Safety Population)

	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=101)	Bupivacaine HCl 50 mg (N=154)
Any Potential LAST-Related TEAE	55 (35.0%)	34 (33.7%)	64 (41.6%)
Dizziness	34 (21.7%)	18 (17.8%)	36 (23.4%)
Bradycardia	12 (7.6%)	6 (5.9%)	12 (7.8%)
Muscle twitching	9 (5.7%)	5 (5.0%)	8 (5.2%)
Hypotension	7 (4.5%)	2 (2.0%)	7 (4.5%)
Sinus arrhythmia	6 (3.8%)	6 (5.9%)	10 (6.5%)
Dysgeusia	4 (2.5%)	6 (5.9%)	6 (3.9%)
Paraesthesia	3 (1.9%)	2 (2.0%)	0
Tinnitus	2 (1.3%)	2 (2.0%)	8 (5.2%)
Paraesthesia oral	2 (1.3%)	0	0
Tremor	0	2 (2.0%)	2 (1.3%)
Arrhythmia supraventricular	0	0	1 (0.6%)
Sinus bradycardia	0	0	3 (1.9%)
Vision blurred	0	0	1 (0.6%)
Visual impairment	0	0	1 (0.6%)

Abbreviations: LAST, Local Anesthetic Systemic Toxicity, TEAE, treatment-emergent adverse event.

Notes: Symptoms possibly attributed to LAST were reviewed by searching the clinical database using a custom list of Preferred Terms (PTs) created by the Sponsor. TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.1. For each PT, subjects are included only once, even if they experienced multiple events in that PT. TEAEs are presented in descending order of frequency in the HTX-011 group.

Source: HTX-011-301 Study Report Body, p. 98 (PDF), Applicant's submission, NDA 211988.

Review of this data indicates that several TEAEs possibly related to LAST were reported with a lower incidence in the HTX-011 treatment group compared to saline placebo and bupivacaine HCl treatment groups. The single TEAE reported with increased frequency in the HTX-011 group was muscle twitching.

Because HTX-011 is described as an extended-release product, it is important to consider the time-frame for reported LAST-related adverse events. The following table summarizes the incidence of adverse events with rapid onset and those with delayed onset.

Table 40: Incidence of Rapid and Delayed Onset of Potential LAST-Related Adverse Events, Study 301 (Safety Population)

	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=101)	Bupivacaine HCl 50 mg (N=154)
Any Potential LAST-Related TEAE	55 (35.0%)	34 (33.7%)	64 (41.6%)
Rapid Onset: ≤1 hour after start of study drug administration	13 (8.3%)	9 (8.9%)	17 (11.0%)
Delayed Onset: >1 hour and ≤72 hours after start of study drug administration	46 (29.3%)	28 (27.7%)	52 (33.8%)

Abbreviations: LAST, Local Anesthetic Systemic Toxicity; TEAE, treatment-emergent adverse event.

Note: For each category, subjects reporting more than 1 potential LAST-related TEAE are counted only once.

Source: HTX-011-301 Study Report Body, p. 99 (PDF), Applicant's submission, NDA 211988.

Interestingly, this table suggests that there was an increased incidence in delayed onset LAST-related adverse events when compared to rapid onset for all treatment groups and there did not appear to be a larger percentage of patients with delayed onset adverse events in the HTX-011 treatment group when compared to bupivacaine HCl treatment group. The distinction between rapid and delayed onset, however, may not truly differentiate LAST-related TEAEs due to bupivacaine HCl wound infiltration or HTX-011 treatment. Specifically, toxicity associated with bupivacaine HCl wound infiltration may not be restricted to ≤ 1 hour, such that patients in both treatment groups could have experienced toxicity that was characterized as delayed onset, thereby minimizing the true difference, and potential risk, between the two groups.

PK data was captured during this study and indicated that the highest reported plasma bupivacaine concentration in the HTX-011 treatment group was 190 ng/mL. Of patients in the HTX-011 treatment group who reported LAST-related adverse events, the highest plasma bupivacaine concentration was reported to be 154 ng/mL and the highest concentration at the time of the adverse event was 127 ng/mL. Two patients treated with HTX-011 experienced severe potential LAST-related adverse events. The highest reported plasma concentration at the time of the adverse event was 27.9 ng/mL. One patient treated with HTX-011 experienced the adverse event of "tremors, local, per LAST", verbatim, on Day 3, approximately 58 hours post-dose. The patient's *estimated* plasma bupivacaine concentration at that time was reportedly 20.8 ng/mL.

A comprehensive discussion involving wound-related adverse events and opioid-related adverse events is included in Section 8.5.

Study 302

A total of 418 patients received a single dose of study drug, placebo, or bupivacaine HCl and are included in the safety population for this study. A brief summary of TEAEs is include in the following table.

Table 41: Overall Summary of Treatment-Emergent Adverse Events, Study 302 (Safety Population)

TEAE Categories	HTX-011 300 mg/9 mg (N=163)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=173)
Any TEAEs	119 (73.0%)	61 (74.4%)	127 (73.4%)
TEAEs Possibly Related to Study Drug	41 (25.2%)	15 (18.3%)	31 (17.9%)
Severe TEAEs	3 (1.8%)	2 (2.4%)	2 (1.2%)
ORAEs	53 (32.5%)	36 (43.9%)	73 (42.2%)
Local Inflammatory TEAEs	6 (3.7%)	2 (2.4%)	10 (5.8%)
Potential LAST-Related TEAEs	54 (33.1%)	28 (34.1%)	71 (41.0%)
TEAEs Leading to Study Withdrawal	0	0	0
SAEs	2 (1.2%)	1 (1.2%)	1 (0.6%)
SAEs Possibly Related to Study Drug	0	0	0
Fatal TEAE	0	0	0

Abbreviations: LAST, local anesthetic systemic toxicity; ORAE, opioid-related adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Source: HTX-011-302 Study Report Body, p. 94 (PDF), Applicant's submission, NDA 211988.

In general, the proportion of patients who experienced a TEAE was similar across all treatment groups. There was, however, a higher incidence of TEAEs possibly related to study drug and a lower incidence of opioid-related TEAEs in the HTX-011 treatment group compared to the saline placebo and bupivacaine HCl treatment groups. There was a similar percentage of SAEs across all treatment groups. There did not appear to be an increased incidence of local inflammatory TEAEs reported in the HTX-011 treatment group.

TEAEs were most commonly reported in the Nervous System Disorders and Gastrointestinal Disorders SOC. The incidence of TEAEs in these SOC was similar across all treatment groups. There was a higher incidence of TEAEs reported in the HTX-011 treatment group compared to either the saline placebo or bupivacaine HCl treatment group for the following SOC: Cardiac Disorders, Investigations, Skin and Subcutaneous Tissue Disorders, and Injury, Poisoning, and Procedural Complications. With the exception of bradycardia, the incidence of adverse events in the Cardiac Disorders SOC was low across all treatment groups and did not appear clinically significant. The bupivacaine HCl and HTX-011 treatment groups had the highest reported incidence of bradycardia, 9%, compared to the saline placebo group, 7%. The adverse events reported in the Investigations SOC, summarized in the table below, did include clinically significant ECG changes, however, the numbers of patients were low and therefore, not believed to impact the overall safety profile of HTX-011.

Table 42: Incidence of Treatment-Emergent Adverse Events for the Investigations System Order Class by Preferred Term, Study 302 (Safety Population)

System Organ Class / Preferred Term ^[1]	HTX-011 300 mg/9 mg (10.3 mL) (N=163)	Saline Placebo (10.3 mL) (N=82)	Bupivacaine HCl 75 mg (30 mL) (N=173)
Investigations	17 (10.4%)	12 (14.6%)	10 (5.8%)
Respiratory rate decreased	3 (1.8%)	0	2 (1.2%)
Blood glucose increased	2 (1.2%)	1 (1.2%)	0
Blood potassium increased	2 (1.2%)	0	0
Gamma-glutamyltransferase increased	2 (1.2%)	6 (7.3%)	5 (2.9%)
Hepatic enzyme increased	2 (1.2%)	1 (1.2%)	0
Liver function test increased	2 (1.2%)	2 (2.4%)	1 (0.6%)
Alanine aminotransferase increased	1 (0.6%)	4 (4.9%)	2 (1.2%)
Aspartate aminotransferase increased	1 (0.6%)	2 (2.4%)	1 (0.6%)
Body temperature increased	1 (0.6%)	0	0
Electrocardiogram QRS complex prolonged	1 (0.6%)	0	0
Electrocardiogram T wave abnormal	1 (0.6%)	0	0
Heart rate decreased	1 (0.6%)	0	0
Platelet count increased	1 (0.6%)	0	0
Blood alkaline phosphatase increased	0	1 (1.2%)	0
Blood lactate dehydrogenase increased	0	2 (2.4%)	0
Blood pressure increased	0	1 (1.2%)	1 (0.6%)
Blood uric acid increased	0	1 (1.2%)	0
Body temperature decreased	0	1 (1.2%)	0

Source: HT-011-302 Study Report Body, p. 284 (PDF), Applicant's submission, NDA 211988.

In the Skin and Subcutaneous Tissue Disorders SOC, there was an increased incidence of skin odour (sic) abnormal in patients treated with HTX-011 compared to those treated with saline placebo or bupivacaine HCl. The increased incidence was limited to a single investigative site, Site 024, and the abnormal odor reportedly resembled garlic. The Applicant determined that the odor was likely due to the dimethyl sulfoxide (DMSO) solvent in the HTX-011. However, given that it was only reported at one investigative site, there was concern that this abnormal odor may have been related to a compositional change in the HTX-011, which may have resulted in other safety findings or had an adverse impact on the observed efficacy for that site. This concern was conveyed to the Applicant in the Filing Communication – Filing Review Issues Identified Letter, dated December 28, 2018. The Applicant responded, in a Clinical Information Amendment dated January 18, 2019, with the following additional information:

- 13 patients in the HTX-011 treatment group experienced this TEAE
- Study 202, a Phase 2a study in herniorrhaphy did not report this TEAE
- All investigative sites for Study 302 received study drug from the same drug lot
- No patient with this TEAE developed an SAE or a local inflammatory TEAE
- There was no evidence of reduced efficacy in the 13 patients with this TEAE

Based on this additional information, it seems unlikely that the garlic odor was based on an inherent change in the HTX-011 drug product and there did not appear to be differences in other safety or efficacy endpoints relative to the overall HTX-011 study group population.

The following table summarizes the differences between treatment groups in the Injury, Poisoning, and Procedural Complications SOC.

Table 43: Incidence of Treatment-Emergent Adverse Events for the Injury, Poisoning, and Procedural Complications System Organ Class by Preferred Term, Study 302 (Safety Population)

System Organ Class / Preferred Term ^[1]	HTX-011 300 mg/9 mg (10.3 mL) (N=163)	Saline Placebo (10.3 mL) (N=82)	Bupivacaine HCl 75 mg (30 mL) (N=173)
Injury, poisoning and procedural complications	17 (10.4%)	4 (4.9%)	16 (9.2%)
Scrotal haematoma	5 (3.1%)	1 (1.2%)	2 (1.2%)
Incision site swelling	3 (1.8%)	0	0
Procedural pain	2 (1.2%)	0	1 (0.6%)
Head injury	1 (0.6%)	0	0
Incision site haematoma	1 (0.6%)	0	0
Incision site haemorrhage	1 (0.6%)	0	0
Incision site hypoaesthesia	1 (0.6%)	0	1 (0.6%)
Post procedural haemorrhage	1 (0.6%)	0	0
Post procedural swelling	1 (0.6%)	0	0
Procedural site reaction	1 (0.6%)	0	0
Wound dehiscence	1 (0.6%)	0	0
Wound secretion	1 (0.6%)	0	1 (0.6%)
Fall	0	1 (1.2%)	0
Incision site complication	0	0	1 (0.6%)
Incision site erythema	0	0	4 (2.3%)
Incision site pain	0	1 (1.2%)	3 (1.7%)
Incision site rash	0	0	1 (0.6%)
Incision site vesicles	0	0	1 (0.6%)
Ligament sprain	0	0	1 (0.6%)
Post procedural complication	0	1 (1.2%)	0
Postoperative wound complication	0	0	1 (0.6%)
Seroma	0	1 (1.2%)	0
Suture related complication	0	0	1 (0.6%)

Source: HTX-011-302 Study Report Body, p. 285 (PDF, Applicant's submission, NDA 211988).

In general, there was a slightly higher percentage of patients treated with HTX-011 who experienced an adverse event in this SOC, however, the overall numbers for each preferred term were low. Additionally, the more clinically significant adverse events, such as wound dehiscence and secretion, did not appear to occur with a meaningful difference between groups.

The most common TEAEs are summarized in the following table. There did appear to be a lower incidence of nausea, constipation, dizziness, tremor, vomiting, tinnitus, and GGT elevation when compared to saline placebo and bupivacaine HCl treatment groups.

Table 44: Incidence of Most Common Treatment-Emergent Adverse Events by Preferred Term, Study 302 (Safety Population)

	HTX-011 300 mg/9 mg (N=163)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=173)
Any TEAE	119 (73.0%)	61 (74.4%)	127 (73.4%)
Nausea	30 (18.4%)	28 (34.1%)	37 (21.4%)
Constipation	28 (17.2%)	15 (18.3%)	41 (23.7%)
Dizziness	24 (14.7%)	13 (15.9%)	42 (24.3%)
Headache	21 (12.9%)	10 (12.2%)	24 (13.9%)
Bradycardia	15 (9.2%)	6 (7.3%)	16 (9.2%)
Dysgeusia	15 (9.2%)	3 (3.7%)	21 (12.1%)
Skin odour abnormal	13 (8.0%)	1 (1.2%)	1 (0.6%)
Tremor	7 (4.3%)	8 (9.8%)	12 (6.9%)
Vomiting	7 (4.3%)	4 (4.9%)	12 (6.9%)
Tinnitus	3 (1.8%)	5 (6.1%)	6 (3.5%)
Gamma-glutamyltransferase increased	2 (1.2%)	6 (7.3%)	5 (2.9%)

Abbreviation: TEAE, treatment-emergent adverse event.

Notes: Most common was defined as $\geq 5\%$ of subjects in any treatment group. TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.1. For each Preferred Term (PT), subjects are included only once, even if they experienced multiple events in that PT. TEAEs are presented in descending order of frequency in the HTX-011 group.

Source: HTX-011-302 Study Report Body, p. 95 (PDF), Applicant's submission, NDA 211988.

The majority of TEAEs for all treatment groups were mild to moderate in severity and the incidence of severe TEAEs was similar across groups. Refer to the following table for additional information.

Table 45: Summary of Treatment-Emergent Adverse Events by Severity, Study 302 (Safety Population)

	HTX-011 300 mg/9 mg (10.3 mL) (N=163)	Saline Placebo (10.3 mL) (N=82)	Bupivacaine HCl 75 mg (30 mL) (N=173)
Total Number of TEAEs	318	172	387
Number (%) of Subjects Reporting at Least One:			
TEAE	119 (73.0%)	61 (74.4%)	127 (73.4%)
TEAE Possibly Related to Study Drug	41 (25.2%)	15 (18.3%)	31 (17.9%)
Opioid-Related TEAE ^[1]	53 (32.5%)	36 (43.9%)	73 (42.2%)
TEAE Leading to Premature Withdrawal from the Study	0	0	0
TEAE by Severity ^[2]			
Mild	92 (56.4%)	44 (53.7%)	96 (55.5%)
Moderate	24 (14.7%)	15 (18.3%)	29 (16.8%)
Severe	3 (1.8%)	2 (2.4%)	2 (1.2%)
Total Number of TESAEs	2	3	1
Number (%) of Subjects Reporting at Least One:			
TESAE	2 (1.2%)	1 (1.2%)	1 (0.6%)
TESAE Possibly Related to Study Drug	0	0	0
TESAE Leading to Premature Withdrawal from the Study	0	0	0
TESAE by Severity ^[2]			
Mild	0	0	0
Moderate	1 (0.6%)	1 (1.2%)	1 (0.6%)
Severe	1 (0.6%)	0	0
Fatal TESAE	0	0	0

Abbreviations: TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

[1] Opioid-related adverse events include those with sponsor pre-specified preferred terms of nausea, vomiting, constipation, pruritus, pruritus generalised, somnolence, respiratory depression, and urinary retention.

[2] Subjects reporting more than one event are counted only once using the highest severity.

Source: HTX-011-302 Study Report Body, p. 278 (PDF), Applicant's submission, NDA 211988.

There were no patient deaths and no adverse event discontinuations. Of the SAEs reported, all but one had resolved at database lock. The patient who experienced COPD exacerbation in the HTX-011 treatment group had ongoing cough at the end of the study.

The incidence of TEAEs related to study drug was higher in the HTX-011 treatment group compared to the saline placebo or bupivacaine HCl treatment groups, as indicated in the above table. As previously discussed, skin odour (sic) abnormal was higher in the HTX-011 treatment group compared to the saline placebo or bupivacaine HCl groups and was considered related to study drug treatment.

LAST-related adverse events are summarized in the following table.

Table 46: Incidence of Potential LAST-Related Treatment-Emergent Adverse Events, Study 302 (Safety Population)

	HTX-011 300 mg/9 mg (N=163)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=173)
Any Potential LAST-Related TEAE	54 (33.1%)	28 (34.1%)	71 (41.0%)
Dizziness	24 (14.7%)	13 (15.9%)	42 (24.3%)
Bradycardia	15 (9.2%)	6 (7.3%)	16 (9.2%)
Dysgeusia	15 (9.2%)	3 (3.7%)	21 (12.1%)
Hypotension	7 (4.3%)	3 (3.7%)	7 (4.0%)
Tremor	7 (4.3%)	8 (9.8%)	12 (6.9%)
Muscle twitching	6 (3.7%)	4 (4.9%)	6 (3.5%)
Paraesthesia oral	4 (2.5%)	0	3 (1.7%)
Visual impairment	3 (1.8%)	2 (2.4%)	5 (2.9%)
Sinus arrhythmia	3 (1.8%)	0	3 (1.7%)
Tinnitus	3 (1.8%)	5 (6.1%)	6 (3.5%)
Paraesthesia	1 (0.6%)	0	1 (0.6%)
Sinus bradycardia	1 (0.6%)	0	0
Vision blurred	1 (0.6%)	0	1 (0.6%)

Abbreviations: LAST, Local Anesthetic Systemic Toxicity, TEAE, treatment-emergent adverse event.

Notes: Symptoms possibly attributed to LAST were reviewed by searching the clinical database using a custom list of Preferred Terms (PTs) created by the Sponsor. TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.1. For each PT, subjects are included only once, even if they experienced multiple events in that PT. TEAEs are presented in descending order of frequency in the HTX-011 group.

Source: HTX-011-302 Study Report Body, p. 98 – 99 (PDF), Applicant's submission, NDA 211988.

The most common LAST-related TEAEs in the HTX-011 treatment group were dizziness, bradycardia, and dysgeusia. In general, the incidence of adverse events possibly related to LAST was similar between the HTX-011 treatment group compared to the saline placebo or bupivacaine HCl treatment groups. There was a single patient in the HTX-011 treatment group who experienced the severe LAST-related TEAE of dizziness.

Because HTX-011 is described as an extended-release product, it is important to consider the time-frame for reported LAST-related adverse events. The following table summarizes the incidence of adverse events with rapid onset and those with delayed onset.

Table 47: Incidence of Rapid and Delayed Onset of Potential LAST-Related Adverse Events, Study 302 (Safety Population)

	HTX-011 300 mg/9 mg (N=163)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=173)
Any Potential LAST-Related TEAE	54 (33.1%)	28 (34.1%)	71 (41.0%)
Rapid Onset: ≤1 hour after start of study drug administration	26 (16.0%)	12 (14.6%)	29 (16.8%)
Delayed Onset: >1 hour and ≤72 hours after start of study drug administration	39 (23.9%)	17 (20.7%)	56 (32.4%)

Abbreviations: LAST, Local Anesthetic Systemic Toxicity; TEAE, treatment-emergent adverse event.

Note: For each category, subjects reporting more than 1 potential LAST-related TEAE are counted only once.

Source: HTX-011-302 Study Report Body, p. 99 (PDF), Applicant's submission

Similar to the observations for Study 301, there was a higher percentage of patients in all treatment groups who experienced delayed onset LAST-related TEAEs when compared to rapid onset. Furthermore, the bupivacaine HCl treatment group appeared to have the highest incidence of delayed onset TEAEs compared to the saline placebo or HTX-011 treatment groups. As discussed for Study 301, however, the time cut-off for rapid and delayed onset is likely to have resulted in overlap in reported toxicity for the treatment groups.

PK data was captured during this study and indicated that the highest measured plasma bupivacaine concentration in the HTX-011 treatment group was 1290 ng/mL at 24 hours post-dose and was estimated to be 1310 ng/mL at 33 hours and 1150 ng/mL at 48 hours post-dose. This patient reportedly did not experience vital sign or ECG changes consistent with LAST, however, he did experience headache and a syncopal episode. Of the patients with potential LAST-related TEAEs, the highest measured bupivacaine plasma concentration was 717 ng/mL. For the two patients with a moderate and severe potential LAST-related TEAE, the plasma bupivacaine concentrations were 258 and 93 ng/mL, respectively.

A comprehensive discussion involving wound-related adverse events and opioid-related adverse events is included in Section 8.5.

8.4.6. Laboratory Findings

The clinical laboratory (lab) evaluations conducted during the Phase 3 studies included the following:

- Pregnancy testing and drug screening performed at screening
- Hematology assessments conducted at screening and 24 and 72 hours post-operatively and on Day 10 and included:
 - hematocrit (hct), hemoglobin (hgb), platelet count, red blood cell (RBC) count, and white blood cell (WBC) count with differential
- Serum chemistry evaluated at screening and at 72 hours and on Day 10 post-operatively

and included:

- alanine aminotransferase (ALT), albumin, alkaline phosphatase, aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, direct bilirubin, gamma-glutamyltransferase (GGT), glucose, lactate dehydrogenase (LDH), magnesium, phosphorous, potassium, sodium, total bilirubin, total protein, and uric acid

Any clinically significant findings pre-operatively were assessed by the investigators for clinical significance. Positive pregnancy screening or drug screening were exclusion criteria. Abnormal results after study drug administration were recorded as adverse events.

For both Phase 3 studies, in general, it did not appear that there were any clinically meaningful differences between treatment groups in mean or mean change from baseline for measured hematology parameters and observed changes were consistent with post-operative expectations. Review of the WBC count with differential data was reviewed for evidence of an inflammatory response after HTX-011 administration. Emphasis was placed on Study 301 due to the observed increase in wound-related adverse events. Screening and baseline values were consistent across all treatment groups in the Phase 3 studies. In Study 301, the mean change from baseline at 24 and 72 hours and Day 10 was slightly larger in the HTX-011 treatment group compared to the saline placebo and bupivacaine HCl treatment groups. In Study 302, the mean change from baseline at 72 hours and Day 10 was slightly larger in the HTX-011 treatment group compared with saline placebo and bupivacaine HCl treatment groups. The WBC count results for both Phase 3 studies are presented in the table below.

Table 48: Mean Change from Baseline in WBC Count*, Study 301 and Study 302 (Safety Population)

Study 301			
Timepoint	HTX-011 60 mg/1.8 mg (2.1 mL), N=157	Saline Placebo (2.1 mL), N=101	Bupivacaine HCl 50 mg (10 mL), N=154
24 hours	2.2	1.8	2.1
72 hours	1.0	0.4	0.6
Day 10	0	-0.2	-0.4
Study 302			
Timepoint	HTX-011 300 mg/9 mg (10.3 mL), N=163	Saline Placebo (10.3 mL), N=82	Bupivacaine HCl 75 mg (30 mL), N=173
24 hours	2.4	2.7	2.9
72 hours	1.3	1.0	0.9
Day 10	0.9	0.5	0.2

WBC: white blood cell count ($10^9/L$); L: liter

These changes in WBC count do support an inflammatory reaction in response to treatment with HTX-011, which is consistent with the local tissue findings, however, all mean values were within normal laboratory limits. Additionally, the mean change from baseline to maximum post-dose value was lowest in the HTX-011 treatment group in Study 302 and only slightly

higher in the HTX-011 group in Study 301 (results not shown).

Review of the neutrophil differential data from both Phase 3 studies did suggest a higher percentage of neutrophils in the differential post-dose for the HTX-011 groups compared to the saline placebo and bupivacaine HCl groups. It is worth noting, however, that all treatment groups had an increase in neutrophil percentage post-operatively and a slight elevation above normal, defined as $> 70\%$, at the 24-hour timepoint, which returned to normal by the next measurement, 72 hours. No other inflammatory markers were assessed during the Phase 3 studies.

For both the Phase 2b (209 and 211) and Phase 3 studies, there was a total of 24 patients who had a reported adverse event of leukocytosis, white blood cell count increased, neutrophilia, or eosinophilia. The highest reported incidence of these adverse events was in Study 209, with six patients in the HTX-011 400 mg/12 mg + ropivacaine treatment group and four patients in the HTX-011 400 mg/12 mg treatment group and in Study 301 with four patients in the bupivacaine HCl 50 mg wound infiltration treatment group. Because there was an overall low number of patients affected in the safety population, it does not appear these adverse events are clinically significant or indicate a concerning trend toward inflammation after treatment with HTX-011.

For both Phase 3 studies, in general, it did not appear that there were any clinically meaningful differences between treatment groups in mean or mean change from baseline for measured serum chemistry parameters. There were patients with elevated serum glucose levels, however, the assessments were not in the fasting state and there did not appear to be clinically significant differences between treatment groups. Because liver toxicity has been reported in patients treated with NSIADs, the Applicant evaluated liver function and categorized abnormal values using the following parameters.

Table 49: Criteria for Abnormal Liver Function, Study 301 and Study 302

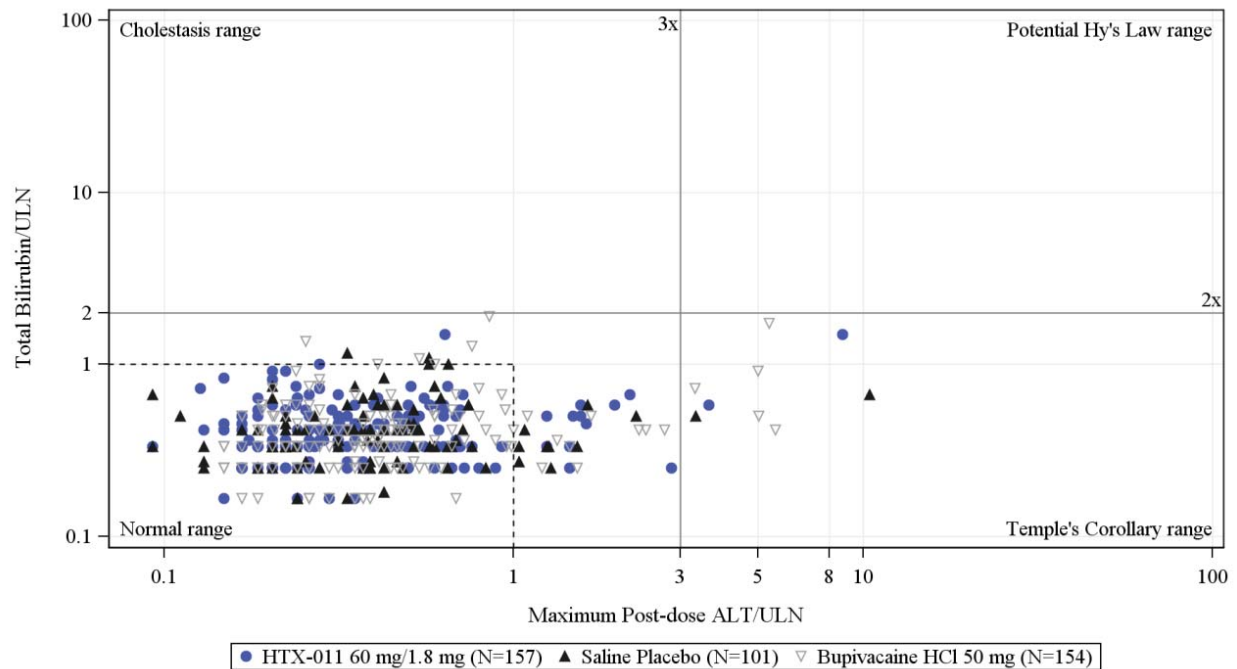
Test	Criteria for Abnormality
ALT or AST	$>1 \times \text{ULN}$ $\geq 2 \times \text{ULN}$ $\geq 3 \times \text{ULN}$ $\geq 4 \times \text{ULN}$ $\geq 5 \times \text{ULN}$
Total bilirubin	$\geq 2 \times \text{ULN}$
ALP	$\geq 1.5 \times \text{ULN}$ $\geq 2 \times \text{ULN}$
ALT and AST	$\geq 3 \times \text{ULN}$
ALT and total bilirubin	$\text{ALT} \geq 3 \times \text{ULN}$ and $\text{total bilirubin} \geq 2 \times \text{ULN}$
AST and total bilirubin	$\text{AST} \geq 3 \times \text{ULN}$ and $\text{total bilirubin} \geq 2 \times \text{ULN}$
Potential Hy's Law	$\text{ALT or AST} \geq 3 \times \text{ULN}$ and $\text{ALP} < 2 \times \text{ULN}$ and $\text{total bilirubin} \geq 2 \times \text{ULN}$

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

Source: HTX-011-301 and HTX-011-302 Study Report Bodies, Applicant's submission, NDA 211988.

The results indicate that in general, the proportion of patients treated with HTX-011 who had elevated liver enzymes was either lower or similar to the proportion of patients treated with saline placebo or bupivacaine. All abnormalities returned to normal by the last post-dose value. No patient in any treatment group met the Hy's Law criteria. The eDISH Plots of ALT versus Total Bilirubin for both Phase 3 studies are pictured below.

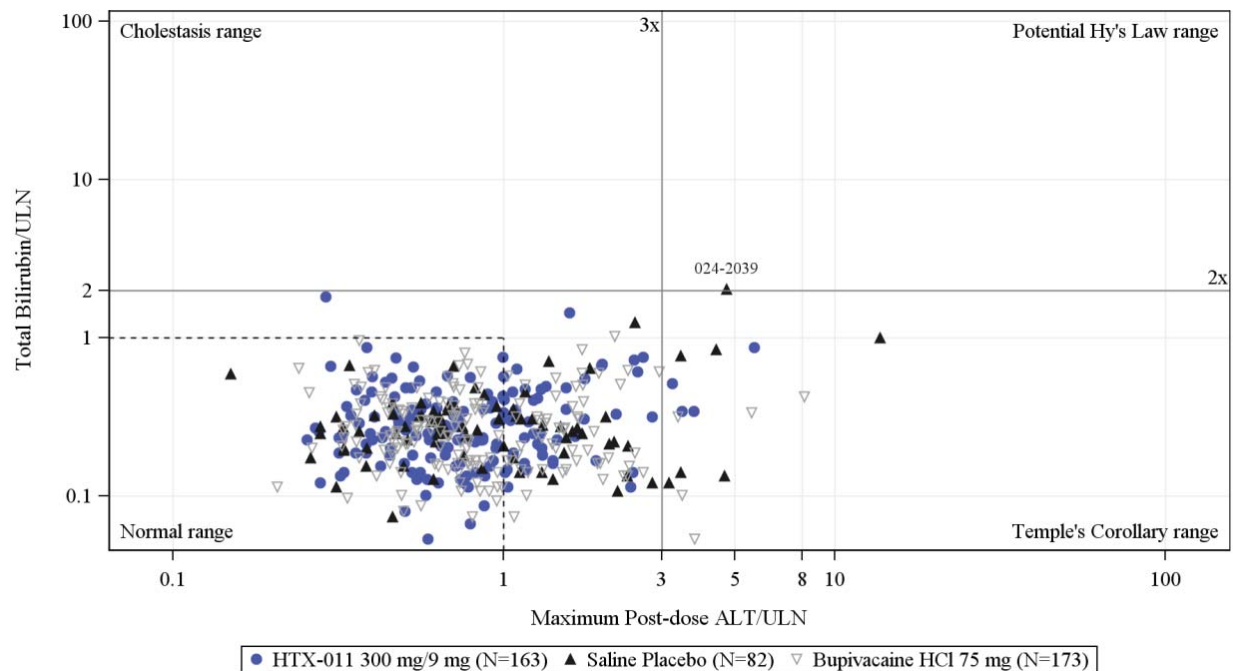
Figure 20: eDISH Plot: Maximum Postdose ALT versus Total Bilirubin, Study 301 (Safety Population)



Source: HTX-011-301 Study Report Body, p. 104 (PDF), Applicant's submission, NDA 211988.

There was a single patient in Study 301 treated with HTX-011 who had normal liver enzymes during screening and had elevated measurements on Day 1. This patient developed a common bile duct stone, had complicated hospital course, and was withdrawn from the study (refer to Section 8.4.3. Dropouts and/or Discontinuations Due to Adverse Events for additional information).

Figure 21: eDISH Plot: Maximum Postdose ALT versus Total Bilirubin, Study 302 (Safety Population)



Source: HTS-011-302 Study Report Body, p. 104 (PDF), Applicant's submission, NDA 211988.

There was a single patient in Study 302 treated with saline placebo who met laboratory criteria for Hy's Law. This patient had elevated bilirubin levels at screening and met Hy's Law criteria 72 hours post-dose. These lab changes were reported as adverse events possibly related to study drug (saline placebo). On Day 9, the transaminase and bilirubin levels had returned to normal.

Across the drug development program, there did not appear to be clinically significant differences in elevated liver function tests between treatment groups, with the exception of elevated alkaline phosphatase. There was a higher incidence in elevated alkaline phosphatase in the HTX-011 200 mg/6 mg and HTX-011 400 mg/12 mg treatment groups, as indicated in the following table.

Table 50: Incidence of Clinically Relevant Abnormalities in Liver Function Tests (Safety Population)

Parameter Criteria	Saline Placebo (N = 247)	Bupivacaine HCl			HTX-011			
		50 mg (N = 154)	75 mg (N = 173)	125 mg (N = 65)	60 mg/1.8 mg (N = 157)	200 mg/6 mg (N = 20)	300 mg/9 mg (N = 163)	400 mg/12 mg (N = 164)
Highest Post-baseline Value	n = 247	n = 154	n = 172	n = 65	n = 157	n = 20	n = 162	n = 164
ALT								
≥3 × ULN	9 (3.6%)	5 (3.2%)	5 (2.9%)	0	2 (1.3%)	0	4 (2.5%)	3 (1.8%)
≥4 × ULN	5 (2.0%)	4 (2.6%)	2 (1.2%)	0	1 (0.6%)	0	1 (0.6%)	1 (0.6%)
≥5 × ULN	2 (0.8%)	4 (2.6%)	2 (1.2%)	0	1 (0.6%)	0	1 (0.6%)	1 (0.6%)
AST								
≥3 × ULN	3 (1.2%)	4 (2.6%)	2 (1.2%)	0	2 (1.3%)	0	1 (0.6%)	1 (0.6%)
≥4 × ULN	3 (1.2%)	0	2 (1.2%)	0	1 (0.6%)	0	1 (0.6%)	1 (0.6%)
≥5 × ULN	3 (1.2%)	0	1 (0.6%)	0	1 (0.6%)	0	1 (0.6%)	0
Total Bilirubin ≥2 × ULN	1 (0.4%)	0	0	1 (1.5%)	0	0	0	2 (1.2%)
ALP								
≥1.5 × ULN	13 (5.3%)	9 (5.8%)	0	5 (7.7%)	4 (2.5%)	2 (10.0%)	1 (0.6%)	21 (12.8%)
≥2 × ULN	6 (2.4%)	4 (2.6%)	0	1 (1.5%)	1 (0.6%)	1 (5.0%)	0	11 (6.7%)
ALT ≥3 × ULN and AST ≥3 × ULN	3 (1.2%)	3 (1.9%)	2 (1.2%)	0	2 (1.3%)	0	1 (0.6%)	1 (0.6%)
ALT ≥3 × ULN and Total Bilirubin ≥2 × ULN	1 (0.4%)	0	0	0	0	0	0	0
AST ≥3 × ULN and Total Bilirubin ≥2 × ULN	0	0	0	0	0	0	0	0
Potential Hy's Law	1 (0.4%)	0	0	0	0	0	0	0

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

Source: Adapted from Summary of Clinical Safety, p. 152 (PDF), Applicant's submission, NDA 211988.

The clinical significance of isolated elevations in alkaline phosphatase is not clear and may be related to manipulation of bone, as in the case of TKA and bunionectomy. This does not, explain, however, the increased incidence in patients treated with HTX-011 compared to saline placebo or bupivacaine HCl. Because there did not appear to be a corresponding increase in gamma-glutamyl transferase, however, it is somewhat reassuring that the increase in alkaline phosphatase is likely not indicative of hepatic or bile duct dysfunction.

8.4.7. Vital Signs

In general, in Study 301, there were no clinically meaningful differences between treatment groups in the mean or the mean change from baseline for diastolic blood pressure (DBP), heart rate (HR), or respiratory rate (RR). There was a higher percentage of patients in the HTX-011 treatment group with clinically relevant changes in systolic blood pressure (SBP), as indicated in the table below.

Table 51: Summary of Clinically Relevant Abnormalities in Vital Signs, Study 301 (Safety Population)

	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=101)	Bupivacaine HCl 50 mg (N=154)
Any Postbaseline Vital Sign			
Subjects with baseline and at least one postbaseline vital signs value	33 (21.0%)	22 (21.8%)	31 (20.1%)
Heart Rate (beats/min)			
≤50 and ≥15 beats/min decrease from baseline	3 (1.9%)	7 (6.9%)	6 (3.9%)
≥120 and ≥15 beats/min increase from baseline	0	0	0
Systolic Blood Pressure (mmHg)			
≤90 and ≥20 mmHg decrease from baseline	11 (7.0%)	3 (3.0%)	6 (3.9%)
≥160 and ≥20 mmHg increase from baseline	14 (8.9%)	6 (5.9%)	7 (4.5%)
Any Postbaseline Vital Sign	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=101)	Bupivacaine HCl 50 mg (N=154)
Diastolic Blood Pressure (mmHg)			
≤50 and ≥15 mmHg decrease from baseline	8 (5.1%)	9 (8.9%)	16 (10.4%)
≥100 and ≥15mmHg increase from baseline	2 (1.3%)	2 (2.0%)	1 (0.6%)

Notes: Baseline was defined as the last available measurement taken prior to study drug administration. Denominators for percentages were based on the number of subjects with a non-missing baseline value and at least 1 non-missing postbaseline value of the vital sign of interest.

Source: HTX-011-301 Study Report Body, p. 106 (PDF), Applicant's submission, NDA 211988.

In Study 302, there were some treatment group differences in mean vital sign changes including a higher percentage of patients in the HTX-011 treatment group who experienced a decrease in SBP, DBP, and HR compared to patients in the saline placebo and bupivacaine HCl treatment groups. Refer to the following table for additional vital sign information from Study 302.

Table 52: Summary of Clinically Relevant Abnormalities in Vital Signs, Study 302 (Safety Population)

Any Postbaseline Vital Sign	HTX-011 300 mg/9 mg (N=163)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=173)
Subjects with baseline and at least one postbaseline vital signs value	n=162	n=82	n=173
Any postbaseline clinically relevant abnormality	44 (27.2%)	20 (24.4%)	43 (24.9%)
Heart Rate (beats/min)			
≤50 and ≥15 beats/min decrease from baseline	15 (9.3%)	5 (6.1%)	10 (5.8%)
≥120 and ≥15 beats/min increase from baseline	0	1 (1.2%)	0
Systolic Blood Pressure (mmHg)			
≤90 and ≥20 mmHg decrease from baseline	10 (6.2%)	1 (1.2%)	7 (4.0%)
≥160 and ≥20 mmHg increase from baseline	6 (3.7%)	6 (7.3%)	17 (9.8%)
Diastolic Blood Pressure (mmHg)			
≤50 and ≥15 mmHg decrease from baseline	20 (12.3%)	6 (7.3%)	14 (8.1%)
≥100 and ≥15mmHg increase from baseline	4 (2.5%)	2 (2.4%)	7 (4.0%)

Notes: Baseline was defined as the last available measurement taken prior to study drug administration. Denominators for percentages were based on the number of subjects with a non-missing baseline value and at least 1 non-missing postbaseline value of the vital sign of interest.

Source: HTX-011-302 Study Report Body, p. 106 (PDF), Applicant's submission, NDA 211988.

Vital sign abnormalities that were considered by investigators to be clinically significant were recorded as adverse events. In general, there were no differences in the incidence of reported vital sign adverse events across treatment groups.

8.4.8. Electrocardiograms (ECGs)

The integrated ECG report provided by the Applicant included analyses of holter data from Study 209 and 211 and serial ECG data from Studies 301 and 302. The focus of the report was data analysis and comparison for the HTX-011 and saline placebo treatment groups across the four studies. In general, the report concluded the following (the impact of HTX-011 administration on QTcF is discussed in Section 8.4.9 QT):

- there was no large or consistent effect of HTX-011 on heart rate
- there were small positive changes in the PR interval, but the outlier analysis was unremarkable
- there was minimal change in the QRS duration, with evenly distributed outliers.

In the Phase 3 studies, ECGs were performed at Screening and at 4, 18, 24, 48, and 72 hours after study drug administration and were analyzed for changes from baseline in heart rate, and PR, RR, QRS, and QT intervals. Additional analyses were conducted to evaluate the potential impact of HTX-011 on the QT interval or other ECG parameters compared to saline placebo or bupivacaine HCl treatment groups. For both studies, in general, there were no clinically

meaningful differences between treatment groups in mean or mean change from baseline for heart rate, or PR, RR or QRS interval. As described in detail below, Section 8.4.10. QT, there were no clinically significant changes in the QT interval, using the QT interval corrected via Fridericia's formula, QTcF, between treatment groups.

In the Phase 2b studies, 209 and 211, patients had continuous holter monitoring from at least 24 hours pre-operatively to 72 hours post-study drug administration. Evaluations included analysis of ECG intervals and the presence of arrhythmias. In Study 209, Cohort 1, there was an increase of approximately five to seven beats per minute in the placebo-corrected heart rate for the HTX-011 200 mg/6 mg treatment group. In Cohort 2, however, patients were treated with a higher dose of HTX-011 (400 mg/12 mg) and there were no observed increases in placebo-corrected heart rate. For both Cohorts, the central tendency analysis for QTcF, which compared baseline to each post-baseline timepoint, did not identify a clinically significant effect on cardiac repolarization, including for patients treated with HTX-011 400 mg/12 mg plus ropivacaine. Overall, in Study 209, there did not appear to be any clinically significant changes in measured ECG parameters for the HTX-011 200 mg/6 mg, HTX-011 400 mg/12 mg with and without ropivacaine, or for bupivacaine HCl treatment groups.

In Study 211, the holter monitoring did not identify clinically relevant signals for any changes in heart rate or PR, RR, or QRS intervals. The central tendency analyses did not identify clinically significant changes in cardiac repolarization, but did suggest a decrease in the QTcF duration in patients treated with HTX-011 when compared to patients treated with saline placebo or bupivacaine HCl.

8.4.9. QT

The Interdisciplinary Review Team for QT Studies (IRT-QT) was consulted to assist with the assessment of the potential for HTX-011 to impact ECG intervals, particularly the QT interval. The discussion here will focus primarily on the IRT-QT review, findings, and recommendations.

The Applicant did not conduct a thorough QT study, TQT, based on the ICH guidelines regarding reformulated approved products without a demonstrated significant increase in systemic exposure. Previous studies have demonstrated no prolongation of the QTc interval after administration of liposomal bupivacaine in doses of up to 750 mg. The Applicant evaluated the potential impact of HTX-011 on the QT interval in Study HTX-011-09 [sic]. At the highest proposed marketing dose of HTX-011, 400 mg/12 mg, evaluated in augmentation mammoplasty, the highest mean C_{max} for bupivacaine was 710 ng/mL. In general, the systemic exposure and subsequent toxicity of bupivacaine are dependent on the total dose and concentration administered, the route of administration, and the vascularity of the injection site.

The IRT-QT has determined that there is no significant QTc prolongation effect of HTX-011 as demonstrated in the QT assessment of Study HTX-011-09 [sic]. This study evaluated the highest

proposed marketing dose of HTX-011 and included robust, high quality ECG recordings and analysis. The data from this study were analyzed using central tendency analysis, which indicated there is a slight shortening of the QTcF interval in patients treated with HTX-011 compared to those treated with placebo control, as shown in the table below.

Table 53: The Largest Mean $\Delta\Delta$ QTcF and the 90% CIs by Time Post Dosing (FDA Analysis)

ECG parameter	Treatment	Time	$\Delta\Delta$ (ms)	90% CI (ms)
QTc	HTX-011 (400 mg bupivacaine and 12 mg meloxicam)	4 h	-0.7	-6.4, 5.0

Source: IRT-QT Consultation Review for NDA 211988, p.1 (PDF).

These findings are consistent with the results from a published TQT study for another reformulated bupivacaine product. The IRT-QT did comment that although this study did not include a positive control for assay sensitivity, the QT/QTc measurements were found to be unbiased.

Patients with hepatic impairment and the elderly female population are thought to have the greatest risk of developing bupivacaine and meloxicam toxicity, respectively. This worst-case clinical scenario was considered during the review by the IRT-QT. They concluded that there is no increased risk of meloxicam toxicity after treatment with HTX-011 when compared to oral Mobic® in elderly female patients due to the lower peak systemic concentrations. The Applicant's data indicates that the peak bupivacaine concentrations after treatment with HTX-011 would be 1.125 times higher in patients with hepatic impairment (Child-Pugh Scores ranging from 5 to 15), likely not clinically relevant.

In conclusion, the Applicant has conducted an adequate assessment of the potential for HTX-011 to prolong the QT interval. My review, in combination with the consultation review by the IRT-QT, indicates there is no increased risk of bupivacaine-induced cardiotoxicity, as demonstrated by QT prolongation, with administration of HTX-011. The IRT-QT has recommended the following edits to Section 12.2. Pharmacodynamics, of the label:

12.2 Pharmacodynamics

Effect on Cardiac Repolarization

The effect of ZYNRELEF on cardiac repolarization as assessed by the QTc interval was evaluated following single application in patients undergoing surgical procedures. ZYNRELEF, at single doses up to the maximum recommended dose, did not demonstrate an effect on the QTc interval.

We propose to use labeling language for this product consistent with the “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format” guidance.

Source: IRT-QT Consultation Review, p.3 (PDF), NDA 211988.

8.4.10. Immunogenicity

It does not appear that administration of HTX-011 in the evaluated surgical populations generates a measurable immunological response.

8.5. Analysis of Drug-Specific Safety Issues

8.5.1. Local Anesthetic Systemic Toxicity (LAST)

Three surgical procedures evaluated the safety and efficacy of HTX-011 400 mg/12 mg, the highest proposed dose, including mini- or complete abdominoplasty, bilateral augmentation mammoplasty, and total knee arthroplasty. As previously discussed, each procedure had a different PK profile. The highest mean bupivacaine C_{max} value (710 ng/mL) was reported in Study 211, in patients undergoing bilateral augmentation mammoplasty, and the highest individual bupivacaine C_{max} values were reported in Study 209, in patients undergoing TKA. Refer to Section 4.5.2. Pharmacokinetics (PK), for additional information.

There does appear to be a larger proportion of patients treated with HTX-011 400 mg/12 mg via instillation in Study 211 with an increased incidence of specific LAST-related adverse events when compared to saline placebo or bupivacaine HCl. Specifically, hypotension, dysgeusia, and bradycardia were reported in a higher percentage of patients, albeit overall low number, treated with HTX-011 400 mg/12 mg compared to patients treated with saline placebo or bupivacaine HCl. Interestingly, the highest percentage of patients with LAST-related adverse events were treated with a lower HTX-011 dose, 240 mg/7.2 mg, via nerve block. The following table summarizes the incidence of LAST-related adverse events for all treatment groups.

Table 54: Incidence of Potential LAST-Related Treatment-Emergent Adverse Events, Study 211 (Safety Population)

Preferred Term ^a n (%)	Saline Placebo via NB (N=41)	Bupivacaine HCl 50 mg via NB (N=41)	HTX-011 via NB				HTX-011 400 mg/12 mg via Instillation (N=50)
			60 mg/ 1.8 mg (N=12)	120 mg/ 3.6 mg (N=27)	240 mg/ 7.2 mg (N=25)	400 mg/ 12 mg (N=47)	
Any Potential LAST-Related TEAE	9 (22.0%)	10 (24.4%)	3 (25.0%)	6 (22.2%)	13 (52.0%)	13 (27.7%)	13 (26.0%)
Dizziness	4 (9.8%)	8 (19.5%)	1 (8.3%)	6 (22.2%)	10 (40.0%)	4 (8.5%)	6 (12.0%)
Hypotension	1 (2.4%)	1 (2.4%)	1 (8.3%)	0	0	6 (12.8%)	6 (12.0%)
Dysgeusia	2 (4.9%)	1 (2.4%)	0	0	5 (20.0%)	5 (10.6%)	2 (4.0%)
Muscle twitching	0	2 (4.9%)	0	0	4 (16.0%)	2 (4.3%)	0
Bradycardia	1 (2.4%)	1 (2.4%)	1 (8.3%)	0	0	2 (4.3%)	2 (4.0%)
Tremor	2 (4.9%)	1 (2.4%)	0	0	2 (8.0%)	1 (2.1%)	1 (2.0%)
Vision blurred	1 (2.4%)	0	0	1 (3.7%)	1 (4.0%)	0	0
Visual impairment	1 (2.4%)	0	0	0	0	1 (2.1%)	1 (2.0%)
Tinnitus	1 (2.4%)	0	0	0	1 (4.0%)	0	1 (2.0%)
Paraesthesia oral	2 (4.9%)	0	0	0	2 (8.0%)	0	0
Paraesthesia	1 (2.4%)	0	0	0	1 (4.0%)	0	0

Abbreviations: LAST, Local Anesthetic System Toxicity; TEAE, treatment-emergent adverse event.

Notes: at each level of summarization (any event, system organ class, and preferred term), subjects reporting more than one LAST TEAE are counted only once. Symptoms attributed to LAST were reviewed by searching the safety database using a custom list of Preferred Terms created by Heron.

^a Adverse events are coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.1.

Source: HTX-011-211 Study Report Body, p. 102 (PDF), Applicant's submission, NDA 211988.

The above table represents LAST-related adverse events occurring at any time during the study. Because of the slow release profile of HTX-011, it is important to consider the timing of observed adverse events. Specifically, delayed LAST is more of a concern with local anesthetic products characterized by a slow release profile, particularly in the setting of outpatient surgery and early discharge. The following table summarizes LAST-related adverse events as those occurring within one hour, rapid onset, and those occurring between one and 72 hours, delayed onset.

Table 55: Proportion of Patients With Rapid and Delayed Onset of Potential LAST-Related TEAEs, Study 211 (Safety Population)

Onset Time n (%)	Saline Placebo via NB (N=41)	Bupivacaine HCl 50 mg via NB (N=41)	HTX-011 via NB				HTX-011 400 mg/12 mg via Instillation (N=50)
			60 mg/ 1.8 mg (N=12)	120 mg/ 3.6 mg (N=27)	240 mg/ 7.2 mg (N=25)	400 mg/ 12 mg (N=47)	
Rapid Onset: ≤1 Hour from Dosing Start	2 (4.9%)	1 (2.4%)	1 (8.3%)	0	0	1 (2.1%)	3 (6.0%)
Delayed Onset: >1 Hour and ≤72 Hours from Dosing Start	7 (17.1%)	8 (19.5%)	2 (16.7%)	6 (22.2%)	13 (52.0%)	11 (23.4%)	13 (26.0%)

Abbreviations: LAST, Local Anesthetic System Toxicity; TEAE, treatment-emergent adverse event.

Notes: at each level of summarization (any event, system organ class, and preferred term), subjects reporting more than one LAST TEAE are counted only once. Symptoms attributed to LAST were reviewed by searching the safety database using a custom list of Preferred Terms created by Heron.

Source: HTX-011-211 Study Report Body, p. 103 (PDF), Applicant's submission, NDA 211988.

This table indicates that while the incidence of delayed onset LAST-related adverse events is higher in the HTX-011 400 mg/12 mg instillation treatment group compared to saline placebo or bupivacaine HCl treatment groups, the incidence of delayed onset LAST-related adverse events is higher than the incidence of rapid onset LAST-related adverse events in *all* treatment groups. This suggests that the one-hour cut-off between rapid and delayed onset does not differentiate LAST-related adverse events due to immediate-release or extended-release bupivacaine products. A later timepoint, e.g., four hours, may have differentiated the LAST-related adverse event profile for the evaluated bupivacaine products better.

There were five patients in this study with C_{max} values greater than 1000 ng/mL with the latest reported T_{max} 5.98 hours. There did not appear to be an increased incidence of LAST-related adverse events reported for these patients. There was one patient, however, with a C_{max} value of 1360 ng/mL at 1.75 hours who reportedly who experienced dizziness, hypotension, and tremor. The dizziness and tremor may have been related to the bupivacaine concentration, but the hypotension was reported the next day, unlikely to be caused by HTX-011.

In Study 209, Cohort 2, patients undergoing TKA, the highest individual C_{max} values were reported. The following table summarizes the incidence of LAST-related adverse events in this study across treatment groups.

Table 56: Incidence of Potential LAST-Related Treatment-Emergent Adverse Events, Study 209, Cohort 2 (Safety Population)

	Saline Placebo (N=53)	Bupivacaine HCl 125 mg (N=55)	HTX-011 400 mg/12 mg (N=58)	HTX-011 400 mg/12 mg + low-dose ropivacaine (N=56)
Any potential LAST-related TEAE	14 (26.4%)	11 (20.0%)	15 (25.9%)	10 (17.9%)
Dizziness	9 (17.0%)	8 (14.5%)	9 (15.5%)	8 (14.3%)
Hypotension	2 (3.8%)	1 (1.8%)	3 (5.2%)	2 (3.6%)
Bradycardia	0	1 (1.8%)	1 (1.7%)	0
Muscle twitching	0	0	0	1 (1.8%)
Tinnitus	0	1 (1.8%)	1 (1.7%)	0
Tremor	1 (1.9%)	1 (1.8%)	1 (1.7%)	0
Dysgeusia	1 (1.9%)	0	0	0
Paraesthesia	1 (1.9%)	0	0	0

Abbreviations: LAST, local anesthetic systemic toxicity; TEAE, treatment-emergent adverse event.

Notes: Symptoms possibly attributed to LAST were reviewed by searching the clinical database using a custom list of Preferred Terms (PTs) created by the Sponsor. TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.1. For each PT, subjects are included only once, even if they experienced multiple events in that PT.

Source: HTX-011-209 Study Report Body, p. 151 (PDF), Applicant's submission, NDA 211988.

There were 10 patients in this study with C_{max} values greater than 1000 ng/mL. Of these 10 patients, six had T_{max} later than 24 hours, the latest being 59.27 hours. There were four patients who experienced tachycardia, four patients who experienced muscle spasms, two who experienced dizziness, and one who experienced hypotension. In general, there did not appear to be an increased incidence in LAST-related adverse events in these 10 patients compared to others treated with HTX-011 400 mg/12 mg with C_{max} values less than 1000 ng/mL.

In Study 203, there were no patients treated with HTX-011 400 mg/12 mg via instillation who had a C_{max} greater than 1000 ng/mL.

In the Phase 3 studies, there did not appear to be an increased incidence of LAST-related adverse events in patients treated with HTX-011. The PK data from Study 302 indicated the mean C_{max} for bupivacaine after HTX-011 300 mg/9 mg administration was 271 ng/mL and the mean T_{max} was 18 hours. There was one patient with a reported C_{max} greater than 1000 ng/mL; measured 1290 ng/mL at 24 hours and estimated to be 1310 ng/mL at T_{max} 33 hours. The Applicant stated that this patient did not experience any LAST-related adverse events, or vital sign or ECG changes, however, review of the safety data for this patient indicated a syncopal episode of moderate intensity approximately five hours after study drug administration. The investigator reported it was unlikely related to study drug administration.

8.5.2. Meloxicam-Related Cardiovascular (CV) and Gastrointestinal (GI) Adverse Events

The pathophysiology of Mobic®-related cardiovascular thrombotic adverse events is thought to be associated with the inhibition of COX-2-dependent prostacyclin (PGI₂) production in the setting of insufficient COX-1-dependent platelet inhibition activity, suggesting NSAIDs of greatest concern are those with extensive inhibition of COX-2 and less inhibition of COX-1. Administration of oral meloxicam exhibits a dose-dependent inhibition in monocyte COX-2 activity, with 70% reduction observed after administration of meloxicam 15 mg. The risk of an acute myocardial infarction is related to the degree of COX-2 inhibition, such that the greatest risk is observed with NSAIDs leading to > 90% inhibition of COX-2. In addition to the degree of COX-2 inhibition, the duration of the inhibition also appears to increase the risk. Specifically, administration of NSAIDs for 31 to 365 days appears to be the inflection point for increased risk, however, there are individual products associated with increased risk after a shorter duration of treatment. While the systemic exposure to meloxicam after administration of HTX-011 is much lower in both magnitude and duration than that observed after administration of oral meloxicam 7.5 mg and the apparent risk of cardiovascular thrombotic adverse events appears low, the boxed warning currently applies to all NSAID-containing products, including topically administered medications used in the treatment of arthritic pain.

There were no reported cardiovascular thrombotic adverse events, such as myocardial infarction, reported during Studies 209, Cohort 2, 301, or 302. The single patient death, which may have been caused by an acute myocardial infarction, occurred in the bupivacaine HCl infiltration group in Study 301, as previously described. There was a single patient in Study 209, Cohort 2, who experienced an elevated troponin-I, felt to be secondary to ventricular strain as a result of bilateral pulmonary emboli. In the absence of additional patients with signs or symptoms of myocardial ischemia or infarction, coupled with the reported low systemic meloxicam exposure compared to oral administration, the apparent risk of cardiovascular thrombotic events associated the use of HTX-011 is low.

Administration of NSAIDs is known to increase the risk of GI bleeding due to inhibition of COX-1 mediated thromboxane (Tx). Specifically, ≥ 95% inhibition of serum TxB₂ results in a decrease in thromboxane-dependent platelet activation. Administration of oral meloxicam 7.5 mg results in approximately 25% to 37% inhibition of TxB₂, much less than necessary to inhibit platelet activation. Given the low systemic meloxicam exposure after administration of HTX-011, the risk for GI bleeding in treated patients appears quite low, and similar to CV risks, potentially theoretical. It also seems unlikely that a single administration of HTX-011 would result in gastric mucosal injury or ulceration typically caused by inhibition of COX-1-mediated prostaglandins, given supportive data that suggest repeat oral meloxicam administration did not acutely damage the gastric mucosa compared to placebo treatment.

Review of the clinical safety data did not identify any cases of GI bleeding, ulceration, or perforation after treatment with HTX-011. In the studies which evaluated the highest proposed

marketing dose, HTX-011 400 mg/12mg, there were no related adverse events reported for the Gastrointestinal Disorders SOC. Additionally, review of the reported cases of anemia or low hemoglobin/hematocrit none were due to an episode of GI bleeding.

In conclusion, it appears that based on the low systemic meloxicam exposure with HTX-011 administration, the risk of CV or GI-related adverse events is low; however, the boxed warnings present in the Mobic® label are likely necessary for this NSAID-containing product. The final determination, however, had not been made at the time of completion of this clinical review.

8.5.3. Wound-Related Adverse Events

Throughout this clinical review, wound-related adverse events and local inflammatory treatment-emergent adverse events, as referred to by the Applicant, will be used interchangeably. Initial concerns surrounding the potential for HTX-011 treatment to adversely impact the wound and delay or impair healing involved bunionectomy procedures, initially observed in Study 208 and Study 301. Because of the required boney manipulation and the potential for long-term, irreversible bone changes, these studies, in combination with Study 209, Cohort 2, were extensively reviewed.

The Applicant conducted a search of the clinical study databases for local inflammatory TEAEs using a prespecified list of preferred terms. The following table includes the results for Study 209, Cohort 2.

Table 57: Local Inflammatory TEAEs, Study 209, Cohort 2 (Safety Population)

	Saline Placebo (N=53)	Bupivacaine HCl 125 mg (N=55)	HTX-011 400 mg/12 mg (N=58)	HTX-011 400 mg/12 mg + low-dose ropivacaine (N=56)
Any Local Inflammatory TEAE	3 (5.7%)	0	5 (8.6%)	5 (8.9%)
Erythema	1 (1.9%)	0	2 (3.4%)	1 (1.8%)
Incision site erythema	2 (3.8%)	0	2 (3.4%)	1 (1.8%)
Incision site cellulitis	0	0	0	1 (1.8%)
Incision site rash	0	0	1 (1.7%)	0
Incision site swelling	0	0	1 (1.7%)	0
Incision site vesicles	0	0	0	1 (1.8%)
Post procedural cellulitis	0	0	0	1 (1.8%)
Wound complication	0	0	1 (1.7%)	0

Abbreviations: TEAE, treatment-emergent adverse event.

Notes: Local inflammatory TEAEs were reviewed by searching the safety database using a custom list of Preferred Terms (PTs) created by the Sponsor. TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.1. For each PT, subjects are included only once, even if they experienced multiple events in that PT.

Source: HTX-011-209 Study Report Body, p. 150 (PDF), Applicant's submission, NDA 211988.

There is an increase in the incidence of the local inflammatory TEAEs in the HTX-011 treatment groups when compared to saline placebo and bupivacaine. It does appear, however, that for more clinically serious wound-related adverse events such as cellulitis, the incidence does not appear to be increased in the HTX-011-only treatment group. The single adverse event of cellulitis in the HTX-011 400 mg/12 mg + ropivacaine was reported as an SAE, as previously discussed. The Applicant further states that the surgical wound assessments, via the Southampton Wound Scoring System conducted at 72 hours and on Days 10 and 28 for all patients and at 96 and 120 hours for patients still hospitalized, indicated that more patients treated with HTX-011 400 mg/12 mg with and without ropivacaine had a Grade 0 (normal healing) finding as the worst post-baseline assessment compared to patients treated with saline placebo or bupivacaine HCl. The percentage of patients with normal healing documented on Day 28 was similar across all treatment groups.

Bone healing assessments were not conducted during this study, but there were no reported adverse events of fractures, osteomyelitis, or failure of the prosthetic implant. Additionally, the Applicant evaluated the potential interaction of HTX-011 with polymethyl methacrylate (PMMA) bone cement and concluded the following:

“...the mechanical properties, including compressive strength and surface hardness, of PMMA bone cement are not affected by HTX-011. Additionally, the molecular weight of cured bone cement was unchanged, and visual inspection revealed no erosion or degradation. The only leachables observed were components from the bone cement known to leach into interstitial fluid in vivo” (HTX-011-209 Study Report Body, p. 27 [PDF], Applicant’s submission, NDA 211988).

A possible interaction between titanium and cobalt-chromium, used in some joint implants, with HTX-011 was also evaluated. The Applicant provided the following information:

“Within the limit of quantitation for each element, there was no detectable difference in the metal concentrations in phosphate-buffered saline (PBS) solution whether there was drug product alone or drug product exposed to alloys, and there was no substantial loss of either bupivacaine or meloxicam after exposure of HTX-011 to either type of metal alloy” (HTX-011-209 Study Report Body, p. 27 [PDF], Applicant’s submission, NDA 211988).

For Study 301, the database search for local inflammatory TEAEs yielded the following.

Table 58: Incidence of Local Inflammatory TEAEs for Study 301 (Safety Population)

	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=101)	Bupivacaine HCl 50 mg (N=154)
Any Local Inflammatory TEAE	45 (28.7%)	20 (19.8%)	34 (22.1%)
Incision site oedema	27 (17.2%)	13 (12.9%)	22 (14.3%)
Incision site erythema	20 (12.7%)	8 (7.9%)	18 (11.7%)
Impaired healing	10 (6.4%)	1 (1.0%)	6 (3.9%)
Incision site cellulitis	7 (4.5%)	1 (1.0%)	2 (1.3%)
Wound dehiscence	7 (4.5%)	2 (2.0%)	1 (0.6%)
Incision site infection	4 (2.5%)	0	1 (0.6%)
Erythema	3 (1.9%)	1 (1.0%)	0
Incision site rash	2 (1.3%)	0	0
Post procedural cellulitis	2 (1.3%)	2 (2.0%)	0
Wound secretion	2 (1.3%)	0	0
Cellulitis	1 (0.6%)	0	1 (0.6%)
Postoperative wound infection	1 (0.6%)	1 (1.0%)	0
Incision site haemorrhage	1 (0.6%)	1 (1.0%)	2 (1.3%)
Blister	0	2 (2.0%)	1 (0.6%)

Abbreviation: TEAE, treatment-emergent adverse event.

Notes: Local inflammatory TEAEs were reviewed by searching the clinical database using a custom list of Preferred Terms (PTs) created by the Sponsor. TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.1. For each PT, subjects are included only once, even if they experienced multiple events in that PT. TEAEs are presented in descending order of frequency in the HTX-011 group.

Source: HTX-011-301 Study Report Body, p. 97 (PDF), Applicant's submission, NDA 211988.

As indicated in the above table, there is an increase in the incidence of the local inflammatory TEAEs in the HTX-011 treatment group when compared to saline placebo or bupivacaine HCl. Unlike the reported results for Study 209, Cohort 2, discussed above, it appears that there was an increased incidence in the HTX-011 treatment group for the majority of TEAEs, including those considered more clinically significant such as wound dehiscence and incision site cellulitis. These results are similar to those reported for Study 208, which evaluated different HTX-011 formulations and doses in patients also undergoing bunionectomy. That study demonstrated what appeared to be a dose-dependent increase in wound-related adverse events, such that the highest incidence was observed in the HTX-011 200 mg/6 mg treatment group. The wound data from this study, in part, informed the final dose of HTX-011 60 mg/1.8 mg to be used in the confirmatory Phase 3 study, Study 301.

The Applicant stated that one possible explanation for the measurable increase in wound-related adverse events in Study 301 may be due to the volume of HTX-011 instilled in the small bunionectomy surgical wound. Specifically, several investigators noted that the required volume of HTX-011, 2.1 mL, resulted in excess drug being expressed from the surgical site during suturing in some patients. This drug leakage may have contributed to poor approximation of the wound resulting in a local inflammatory response and delayed wound healing, which was then documented as an adverse event. This may also explain the dose-

response for wound-related adverse events observed in Study 208, such that the largest volume of administered HTX-011 (200 mg/6 mg, 6.8 mL) resulted in the highest incidence of wound-related adverse events.

My concerns regarding the apparent increased incidence of wound-related adverse events observed in Study 301 were conveyed to the Applicant in the Filing Communication – Filing Review Issues Identified, dated December 28, 2018. The Applicant submitted a Clinical Information Amendment, dated January 18, 2019, which included five additional arguments to support the safe use of HTX-011 during bunionectomy surgery. First, the Applicant clarified that “impaired healing” referred to verbatim terms for delayed healing of the surgical wound, and was not intended to imply improper wound healing or wound healing complications. Additionally, of the TEAEs associated with impaired healing, the majority were mild in severity for all treatment groups. No severe TEAEs of impaired healing were reported in any treatment group. A single patient treated with HTX-011 had a mild TEAE of impaired healing on study Day 25, which was ongoing on the last study day assessment, Day 53.

Second, the Applicant stated that surgical wound healing was assessed throughout the study at various time points, including 72 hours, and Days 10, 28, and 42, using a list of terms prespecified by FDA. The proportion of patients reported to have any of these TEAEs (bruising, erythema, edema, heat, drainage, cellulitis, dehiscence, delayed healing) was similar for all treatment groups (81% for HTX-011, 81% for saline placebo, and 84% for bupivacaine HCl). The most common wound healing findings across all treatment groups at any time were bruising, erythema, and edema.

Third, the Applicant stated that individual investigators may have used different criteria for defining the term “delayed healing”, such that normal healing may have been erroneously categorized as delayed. Therefore, the condition of the wound at Day 42 would more accurately reflect clinically meaningful differences in the wound across treatment groups. The data in the table below represent healing at Day 42 in Study 301.

Table 59: Summary of Wound Healing Assessment Results at Day 42, Study 301 (Safety Population)

	Saline Placebo (N=101)	Bupivacaine HCl 50 mg (N=154)	HTX-011 60 mg/1.8 mg (N=157)
Any Wound Healing Sign or Symptom at Day 42	37/100 (37.0%)	50/151 (33.1%)	48/154 (31.2%)
Edema	33 (33.0%)	39 (25.8%)	42 (27.3%)
Erythema	10 (10.0%)	16 (10.6%)	11 (7.1%)
Bruising	2 (2.0%)	5 (3.3%)	3 (1.9%)
Delayed healing	2 (2.0%)	3 (2.0%)	7 (4.5%)
Heat	0	1 (0.7%)	3 (1.9%)
Cellulitis	1 (1.0%)	0	1 (0.6%)
Drainage	0	1 (0.7%)	1 (0.6%)
Dehiscence	1 (1.0%)	0	0

Source: Clinical Information Amendment, p. 7 (PDF), January 18, 2019, Applicant's submission, NDA 211988.

The data indicate that there were no clinically meaningful differences between groups for more serious TEAEs such as cellulitis, dehiscence, or drainage at Day 42.

Fourth, the Applicant requested an external independent review of the wound healing data from Study 301 as well as the entire development program by (b) (4)

His review concluded the following:

"It should be noted that in all the other surgical trials performed using HTX-011 there was no suggestion of abnormal or delayed healing. Thus, I conclude that the data in the 301 trial was spurious and not indicative of any real impact on wound healing. The combination of the thin skin flaps exposing the vasodilatory impact of HTX-011 combined with the use of a non-validated wound assessment tool resulted in an artifactual result that had nothing to do with the normal wound healing that was occurring in all three of the treatment groups."

And lastly, bone healing assessments, via a single x-ray between four to six weeks post-operatively in Study 208 or via repeat post-operative x-rays on Days 28 and 42 in Study 301, did not identify clinically meaningful changes in bone healing across treatment groups. The results by study are presented below.

Table 60: Summary of Bone Healing Results by Treatment Group for Study 208 (Safety Population)

Interpretation	Saline Placebo (N=104)	Bupivacaine HCl (N=25)	HTX-011-56 (N=174)	HTX-002 (N=64)	HTX-009 (N=30)	HTX-011-49 (N=33)
Normal	98 (94.2%)	24 (96.0%)	167 (96.0%)	64 (100%)	30 (100%)	31 (93.9%)
Improper healing	0	0	1 (0.6%)	0	0	0
Not Assessed	6 (5.8%)	1 (4.0%)	6 (3.4%)	0	0	2 (6.1%)
Not required (Protocol Version 1.1)	0	0	2 (1.1%)	0	0	1 (3.0%)
Terminated early	3 (2.9%)	0	3 (1.7%)	0	0	1 (3.0%)
Not done	3 (2.9%)	1 (4.0%)	1 (0.6%)	0	0	0

Source: HTX-011-208 Study Report Body, p. 120 (PDF), Applicant's submission, NDA 211988.

The case of improper healing in the HTX-011(-56) treatment group was further described as mal-union and was felt to be due to poor compliance with post-operative care (premature weight-bearing and rapid return to work).

Table 61: Summary of X-ray for Bone Healing Assessment Results for Study 301 (Safety Population)

Timepoint Grade	HTX-011 60 mg/1.8 mg (2.1 mL) (N=157)	Saline Placebo (2.1 mL) (N=101)	Bupivacaine HCl 50 mg (10 mL) (N=154)
Day 28	n=144	n=99	n=148
Normal healing	141 (97.9%)	99 (100%)	147 (99.3%)
Delayed healing	1 (0.7%)	0	1 (0.7%)
Mal-union	2 (1.4%)	0	0
Safety Follow-up on Day 42	n=153	n=100	n=149
Normal healing	149 (97.4%)	99 (99.0%)	148 (99.3%)
Delayed healing	1 (0.7%)	1 (1.0%)	1 (0.7%)
Mal-union	3 (2.0%)	0	0
Last X-ray result for bone healing assessment	n=155	n=100	n=152
Normal healing	152 (98.1%)	100 (100%)	151 (99.3%)
Delayed healing	0	0	1 (0.7%)
Mal-union	3 (1.9%)	0	0

Source: HTX-011-301 Study Report Body, p. 568 (PDF), Applicant's submission, NDA 211988.

Of the three patients with mal-union identified in the last study x-ray, two were felt to be due to poor compliance with post-operative care instructions and one was due to trauma (stubbed toe).

An additional review issue for Study 301 involved a report from pre-marketing IND safety reporting, which indicated a higher incidence of wound-related adverse events reported at one investigative site, when compared to others. My review did identify Site 020 as having a higher

incidence of wound-related adverse events, however, the increased incidence was reported for all treatment groups, including saline placebo and bupivacaine HCl. This suggests that surgical technique may have had more influence versus the drug product. Additionally, the majority of events were mild and included incision site erythema, oedema [sic], and post-procedural contusion.

While emphasis has been placed on studies which evaluated the safety and efficacy of HTX-011 in boney surgical models, a comprehensive review of soft tissue surgical procedures, evaluated in Studies 203, 211, and 302, was also completed. Study 203, which evaluated the safety and efficacy of HTX-011 in mini- and complete abdominoplasty, was the single soft tissue study that also demonstrated a potentially clinically significant increase in wound-related adverse events. Specifically, patients undergoing complete abdominoplasty treated with either HTX-011 300 mg/9 mg or 400 mg/12 mg via combination route of administration reportedly had a higher incidence of several local inflammatory TEAEs, wound dehiscence being the most concerning. There were 20% of patients treated with HTX-011 300 mg/9 mg, administered via injection and instillation, who experienced wound dehiscence. Refer to the following table for information regarding the incidence of local inflammatory TEAEs across all treatment groups.

Table 62: Overall Incidence of Local Inflammatory Treatment-Emergent Adverse Events for HTX-011-56, Bupivacaine HCl, and Saline Placebo – Complete Abdominoplasty, Study 203 (Safety Population)

Preferred Term n (%)	Saline Placebo (N = 32)	Bupivacaine HCl 100 mg (N = 17)	HTX-011-56		
			300 mg/ 9 mg	400 mg/ 12 mg	400 mg/ 12 mg
			Combination ^a (N=35)	Combination ^a (N=25)	Instillation (N=17)
Any TEAE	6 (18.8%)	4 (23.5%)	11 (31.4%)	6 (24.0%)	3 (17.6%)
Impaired healing	0	0	0	0	1 (5.9%)
Incision site infection	1 (3.1%)	0	1 (2.9%)	0	0
Postoperative wound infection	1 (3.1%)	0	0	0	0
Incision site complication	0	0	1 (2.9%)	1 (4.0%)	0
Incision site erythema	0	0	1 (2.9%)	0	0
Incision site vesicles	0	0	0	1 (4.0%)	0
Postoperative wound complication	0	1 (5.9%)	0	1 (4.0%)	1 (5.9%)
Wound complication	2 (6.3%)	0	0	1 (4.0%)	0
Wound dehiscence	4 (12.5%)	2 (11.8%)	7 (20.0%)	2 (8.0%)	1 (5.9%)
Wound secretion	1 (3.1%)	0	3 (8.6%)	1 (4.0%)	0
Erythema	0	2 (11.8%)	1 (2.9%)	0	0

Abbreviations: TEAE, treatment-emergent adverse event.

Notes: TEAEs are events that started during or after study drug administration or those that started before study drug administration but worsened during or after study drug administration. Adverse events are coded to Preferred Terms using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.1. TEAE information for Subject (b) (6) who received HTX-002 for complete abdominoplasty surgery is presented in Listing 16.2.7.1 and is not summarized in study tables.

^a Combination dosing is defined as 2/3 dosing via injection and 1/3 dosing via instillation.

Source: HTX-011-203 Study Report Body, p. 122 (PDF), Applicant's submission, NDA 211988.

Of additional concern is the duration of these wound-related adverse events. The following table highlights the wound changes observed through Day 28. These findings suggest that additional safety information is needed prior to recommended use of HTX-011 in this surgical population.

Table 63: Summary of Abnormal Wound Healing Findings Post-Treatment by Treatment Group – Complete Abdominoplasty, Study 203 (Safety Population)

Domain	Saline Placebo (N = 32)	Bupivacaine HCl 100 mg	HTX-011-56		
		Injection (N=17)	300 mg/ 9 mg	400 mg/ 12 mg	400 mg/ 12 mg
			Combination ^a (N=35)	Combination ^a (N=25)	Instillation (N=17)
Subjects evaluated at any timepoint, n	32	17	35	25	17
Wet	2 (6.3%)	4 (23.5%)	6 (17.1%)	1 (4.0%)	1 (5.9%)
Dehiscence	3 (9.4%)	1 (5.9%)	8 (22.9%)	2 (8.0%)	3 (17.6%)
Erythema	2 (6.3%)	3 (17.6%)	6 (17.1%)	3 (12.0%)	0
Drainage	3 (9.4%)	4 (23.5%)	6 (17.1%)	2 (8.0%)	2 (11.8%)
Bruising	2 (6.3%)	0	1 (2.9%)	0	0
Swelling	1 (3.1%)	1 (5.9%)	2 (5.7%)	0	0
Subjects evaluated on Day 28, n	31	17	35	25	16
Wet	2 (6.5%)	1 (5.9%)	5 (14.3%)	1 (4.0%)	1 (6.3%)
Dehiscence	3 (9.7%)	1 (5.9%)	7 (20.0%)	2 (8.0%)	3 (18.8%)
Erythema	2 (6.5%)	1 (5.9%)	4 (11.4%)	1 (4.0%)	0
Drainage	1 (3.2%)	1 (5.9%)	5 (14.3%)	2 (8.0%)	1 (6.3%)
Bruising	1 (3.2%)	0	1 (2.9%)	0	0
Swelling	1 (3.2%)	0	2 (5.7%)	0	0

Note: Wound healing information for Subject (b) (6) who received HTX-002 for complete abdominoplasty surgery is presented in Listing 16.2.9.7 and is not summarized in study tables. Additionally, inconsistent data entries were recorded for wound healing data, where the wound site was recorded as normal but there was at least 1 abnormal wound description reported; therefore, wound site is excluded from this table.

^a Combination dosing is defined as 2/3 dosing via injection and 1/3 dosing via instillation.

Source: HTX-011-203 Study Report Body, p. 136 (PDF), Applicant's submission, NDA 211988.

Regarding patients undergoing mini-abdominoplasty in the same study, 203, (results not shown) those treated with HTX-011 400 mg/12 mg via injection or a combination of injection and instillation had a higher incidence of wound dehiscence than the other treatment groups, including different doses of HTX-011 as well as saline placebo. While the numbers of patients in each treatment group were low, less than 20, with the exception of the saline placebo group which had 63 treated patients, the incidence of wound dehiscence is concerning. For both surgical procedures evaluated in Study 203, mini- and complete abdominoplasty, the increased incidence of wound-related adverse events did not appear to be dose-dependent.

Study 211, evaluated the safety and efficacy of various doses of HTX-011 administered via nerve block or via instillation in patients undergoing bilateral augmentation mammoplasty. For instillation, the doses were divided and administered in each surgically-created pocket prior to placement of the breast implant. Because the administered doses were divided in amount and

separated in time, the interpretation of the PK and systemic exposure data as well as the local toxicity is challenging. Therefore, the absence of clinically significant local inflammatory TEAEs in the HTX-011 treatment groups is reassuring, however, this data cannot be extrapolated to a single HTX-011 400 mg/12 mg administration in a breast implant pocket.

Study 302 evaluated the safety and efficacy of HTX-011 in patients undergoing open inguinal hernia repair with mesh. The incidence of local inflammatory TEAEs across all treatment groups is outlined in the following table.

Table 64: Incidence of Local Inflammatory Treatment-Emergent Adverse Events, Study 302 (Safety Population)

	HTX-011 300 mg/9 mg (N=163)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=173)
Any Local Inflammatory TEAE	6 (3.7%)	2 (2.4%)	10 (5.8%)
Incision site swelling	3 (1.8%)	0	0
Incision site infection	1 (0.6%)	1 (1.2%)	1 (0.6%)
Incision site haemorrhage	1 (0.6%)	0	0
Wound dehiscence	1 (0.6%)	0	0
Wound secretion	1 (0.6%)	0	1 (0.6%)
Incision site cellulitis	0	0	1 (0.6%)
Postoperative wound infection	0	1 (1.2%)	0
Incision site complication	0	0	1 (0.6%)
Incision site erythema	0	0	4 (2.3%)
Incision site rash	0	0	1 (0.6%)
Incision site vesicles	0	0	1 (0.6%)
Postoperative wound complication	0	0	1 (0.6%)

Source: HTX-011-302 Study Report Body, p. 97 (PDF), Applicant's submission, NDA 211988.

These results suggest that while there is variability in the incidence of these TEAEs, it does not appear that administration of HTX-011 increased the risk of developing any of these prespecified TEAEs. Additionally, of the TEAEs reported in the HTX-011 treatment group, they were all mild or moderate in severity. A single patient in the saline placebo treatment group experienced an SAE of post-operative wound infection.

8.5.4. Opioid-Related Adverse Events

Opioid-related adverse events were evaluated by the Applicant

(b) (4)

Those adverse events will not be discussed in exhaustive detail, beyond agreeing that there did appear to be a trend toward a decreased incidence in patients treated with HTX-011 when compared to the saline placebo or bupivacaine HCl wound infiltration in the Phase 3 studies. However, the differences were generally small and unlikely to result in

substantial improvements in patient satisfaction or clinically significant decreases in administration of medications for treatment of these adverse events; i.e., antiemetics.

In Study 301, approximately 21% of patients treated with HTX-011 and 30% of patients treated with bupivacaine HCl were administered an antiemetic medication, a difference that is arguably clinically relevant. Review of specific medication administration, however, suggests the differences were less impressive. Specifically, there was no difference between the two treatment groups in administration of metoclopramide, which is commonly used for post-operative nausea and vomiting although categorized in these studies as a treatment for 'functional gastrointestinal disorders'. It was administered to 1% of the patients in both treatment groups. Similar results are reported in Study 302. Specifically, approximately 12% of patients treated with HTX-011 and 16% of patients treated with bupivacaine HCl received an antiemetic medication. Metoclopramide was administered in approximately 2% of patients treated with HTX-011 and 1% of patients treated with bupivacaine HCl. In Study 209, Cohort 2, the differences in antiemetic administration were negligible and a large percentage of patients in all treatment groups (between 43% and 49% of patients) required an antiemetic medication post-operatively.

In summary, the incidence of opioid-related adverse events appeared to trend lower for patients treated with HTX-011, however, the clinical significance is not well-defined and there are three confounding influences. First, because all patients received concomitant sedation (Study 301) or general (Studies 209 and 302) or spinal (Study 209) anesthesia during the evaluated procedures, interpretation of the data is challenging. Second, it does not appear the study protocols stratified patients with a history of post-operative nausea and vomiting. And lastly, patient factors, such as gender and smoking history, impact the incidence of post-operative nausea and vomiting.

8.6. **Safety Analyses by Demographic Subgroups**

Safety results, including adverse events, clinical laboratory data, vital signs, and wound healing assessments, were analyzed by the following demographic subgroups:

- Age (<65 or ≥65 years)
- Sex (male or female)
- Race (White or Other Race, which included American Indian or Alaska Native, Asian, Black or African Descent, Native Hawaiian or other Pacific Islander)

Refer to the following table for a summary of the incidence of adverse events for all evaluated demographic subgroups in the Phase 2b and Phase 3 studies.

Table 65: Summary of Treatment-Emergent Adverse Events in Phase 2b and Phase 3 Studies by Subgroup (Safety Population)

Category	Subgroup	Saline Placebo		Total Bupivacaine HCl		Total HTX-011	
		N	n (%)	N	n (%)	N	n (%)
Any TEAE	Age <65 years	211	168 (79.6%)	342	278 (81.3%)	408	335 (82.1%)
	Age ≥65 years	36	33 (91.7%)	50	41 (82.0%)	96	89 (92.7%)
	Female	122	104 (85.2%)	179	152 (84.9%)	266	237 (89.1%)
	Male	125	97 (77.6%)	213	167 (78.4%)	238	187 (78.6%)
	White	219	180 (82.2%)	334	272 (81.4%)	414	357 (86.2%)
	Other Races	28	21 (75.0%)	58	47 (81.0%)	90	67 (74.4%)
Any SAE	Age <65 years	211	3 (1.4%)	342	6 (1.8%)	408	6 (1.5%)
	Age ≥65 years	36	2 (5.6%)	50	1 (2.0%)	96	5 (5.2%)
	Female	122	1 (0.8%)	179	2 (1.1%)	266	5 (1.9%)
	Male	125	4 (3.2%)	213	5 (2.3%)	238	6 (2.5%)
	White	219	4 (1.8%)	334	4 (1.2%)	414	10 (2.4%)
	Other Races	28	1 (3.6%)	58	3 (5.2%)	90	1 (1.1%)
Any ORAE ^a	Age <65 years	211	114 (54.0%)	342	172 (50.3%)	408	211 (51.7%)
	Age ≥65 years	36	23 (63.9%)	50	26 (52.0%)	96	55 (57.3%)
	Female	122	80 (65.6%)	179	103 (57.5%)	266	164 (61.7%)
	Male	125	57 (45.6%)	213	95 (44.6%)	238	102 (42.9%)
	White	219	125 (57.1%)	334	169 (50.6%)	414	220 (53.1%)
	Other Races	28	12 (42.9%)	58	29 (50.0%)	90	46 (51.1%)
Any Local Inflammatory TEAE	Age <65 years	211	23 (10.9%)	342	41 (12.0%)	408	47 (11.5%)
	Age ≥65 years	36	4 (11.1%)	50	3 (6.0%)	96	15 (15.6%)
	Female	122	23 (18.9%)	179	26 (14.5%)	266	45 (16.9%)
	Male	125	4 (3.2%)	213	18 (8.5%)	238	17 (7.1%)
	White	219	24 (11.0%)	334	41 (12.3%)	414	56 (13.5%)
	Other Races	28	3 (10.7%)	58	3 (5.2%)	90	6 (6.7%)
Any Potential LAST-related TEAE	Age <65 years	211	65 (30.8%)	342	132 (38.6%)	408	127 (31.1%)
	Age ≥65 years	36	15 (41.7%)	50	18 (36.0%)	96	25 (26.0%)
	Female	122	40 (32.8%)	179	62 (34.6%)	266	89 (33.5%)
	Male	125	40 (32.0%)	213	88 (41.3%)	238	63 (26.5%)
	White	219	75 (34.2%)	334	139 (41.6%)	414	130 (31.4%)
	Other Races	28	5 (17.9%)	58	11 (19.0%)	90	22 (24.4%)

Abbreviations: LAST, local anesthetic systemic toxicity; ORAE, opioid-related adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

^a Opioid-related adverse events include those with sponsor prespecified preferred terms of nausea, vomiting, constipation, pruritus, pruritus generalized, somnolence, respiratory depression, and urinary retention.

Source: Summary of Clinical Safety, p. 169 (PDF), Applicant's submission, NDA 211988.

In general, there was a low number of patients treated who were older than 65 years of age (36 total in the Phase 2b and Phase 3 studies) and race other than White (28 total in the Phase 2b and Phase 3 studies).

- Age: There did not appear to be an apparent treatment effect by age for the treatment-

emergent adverse events reported for the HTX-011 treatment groups, with the exception of constipation and urinary retention. Regarding local-inflammatory AEs reported in Study 301, the incidence of abnormal wound healing was reportedly higher in the ≥ 65 -year-old group compared to the < 65 -year-old group for both the HTX-011 and saline placebo treatment groups. Regarding potential LAST-related AEs in the Phase 3 studies, the incidence for the HTX-011 treatment groups was lower for ≥ 65 -year-olds compared to < 65 -year-olds.

- Sex: There did appear to be an increased incidence in treatment-emergent adverse events reported for female patients in all treatment groups, however, the incidence of SAEs was higher among male patients. There was also an increased incidence of opioid-related and local inflammatory AEs reported for female patients across all treatment groups. The difference in opioid-related AEs is likely to be clinically significant, such that female patients may be at higher risk for requiring additional medication(s) to treat the opioid-related adverse events, such as anti-emetics. This observation, however, is likely not limited to the evaluated surgical procedures and is in general consistent with findings comparing male and female surgical outcomes.

Interestingly, the incidence of local inflammatory AEs was higher in females across all HTX-011 treatment groups, however, for HTX-011 60 mg/1.8 mg group, the incidence was higher in males (42% versus 27%, results not shown). A post-hoc analysis of local inflammatory AEs for Study 301 did suggest a possible sex effect, with males having higher incidence of incision site infection (21% vs. 0%), wound dehiscence (16% vs. 3%), and impaired healing (11% versus 6%). There were, however, only 19 total male patients treated in Study 301, thereby limiting the interpretation of these results.

The incidence of potential LAST-related AEs was higher for female patients compared to males treated with HTX-011 400 mg/12 mg. There was a low number of female patients treated with HTX-011 300 mg/9 mg and 200 mg/6 mg, therefore meaningful comparisons were not feasible. In studies 301 and 302, the incidence of any potential LAST-related AE was higher in males than females at the four-hour timepoint for HTX-011 treatment and higher in females at 18 and 24 hours. The incidence was comparable at 72 hours for both sexes.

- Race: In general, there did not appear to be any clinically meaningful differences in the incidence of AEs across all treatment groups for White and Other Race subgroups. However, the low number of patients in the Other Races subgroup limits the interpretation of the results.

8.7. Recently Completed Clinical Trials

The Applicant conducted two additional Phase 2 open-label clinical studies, Study 215 and Study 218, evaluating the safety and efficacy of HTX-011 as part of a multimodal analgesic regimen designed to reduce post-operative opioid use. A total of 93 patients were treated with

HTX-011 in the two studies. Preliminary safety information was submitted to the Agency on February 21, 2019, as part of the required four-month safety update (4MSU). Refer to the following table for summary information for each study.

Table 66: Overview of Studies Contributing to the 4-Month Safety Update

Study (Region)	Study Design	Surgery	Treatment Group (Number of Subjects)	Study Status
215 (US)	Phase 2, open-label efficacy and safety study	Unilateral open inguinal herniorrhaphy	Cohort 1 (33 subjects): HTX-011 300 mg/9 mg by instillation into the surgical site with scheduled postoperative analgesic regimen as follows: oral ibuprofen 600 mg once subjects are able to tolerate oral intake in the postoperative care unit followed by oral acetaminophen 1 g after 3 hours, then alternate these 2 medications so a dose is administered every 3 hours until the completion of the 72-hour postoperative period Cohort 2 (30 subjects): the same treatment as in Cohort 1 with the addition of a single intraoperative IV dose of ketorolac 15 or 30 mg prior to wound closure ^a	Concluded
218 (US)	Phase 2, open-label efficacy, safety, and PK study	Unilateral simple bunionectomy	Cohort 1 (30): HTX-011 up to 60 mg/1.8 mg (ie, up to 2.1 mL) by instillation into the surgical site	Ongoing

Abbreviations: IV, intravenous; PK, pharmacokinetics; US, United States.

Note: the number of subjects in each treatment group is based on the Safety Population.

^a Subjects ≥65 years of age, with serum creatinine >1.5 upper limit of normal, and/or weight <50 kg received 15 mg of ketorolac.

Subjects <65 years of age and/or with weight ≥50 kg received 30 mg of ketorolac.

Source: Four-Month Safety Update, p. 11 (PDF), Applicant's submission, NDA 211988.

Briefly, Study 215 was conducted in patients undergoing open inguinal hernia repair. The analgesic regimen included pre-operative acetaminophen, intraoperative HTX-011 300 mg/9 mg, and post-operative ibuprofen and acetaminophen for Cohorts 1 and 2. Cohort 2 also included intra-operative IV ketorolac. Study 218 was conducted in patients undergoing bunionectomy and included multiple cohorts evaluating HTX-011 administered by individualized dosing. Specifically, patients were administered a sufficient amount of HTX-011 up to 60 mg/1.8 mg (2.1 mL) to coat the tissues without leakage of excess drug product from the surgical site during closure. Only the results for Cohort 1 are included in the 4MSU because Cohort 2 was still enrolling at the time of the cutoff date and the enrollment for Cohort 3 had not started. The review of the safety database for SAEs for the 4MSU included all cohorts.

The safety results of most clinical relevance are potential cases of LAST and wound-related AEs. Preliminary safety results are as follows:

- LAST: There were no reported adverse events related to LAST in either study. Furthermore, there were no clinically relevant changes in vital signs or ECG across treatment groups.

- Wound-related adverse events:

In Study 215, there was a single local inflammatory treatment-emergent adverse event reported for one patient.

In Study 218, Cohort 1, there were no reported local inflammatory treatment-emergent adverse events; specifically, no reported cases of wound cellulitis or dehiscence. Additionally, there was a lower incidence of wound healing findings in this study compared to Study 301, 70% versus 81%. The Applicant suggests that the reported lower incidence of these adverse events is likely due to the administration instructions, describing use of HTX-011 in a volume necessary to cover the tissues. The mean volume of HTX-011 administered was 1.7 mL. While the results for Cohort 2 were not included in the 4MSU, the Applicant included information for one patient with a past medical history of diabetes mellitus who experienced the SAE of cellulitis and abscess.

These clinical studies also evaluated the safe use of concomitant administration of other NSAIDs and acetaminophen with HTX-011. Preliminary results suggest there was not an increased incidence of adverse events associated with concomitant use of these non-opioid analgesics with HTX-011 in patients undergoing open inguinal hernia repair and bunionectomy.

The preliminary safety results from studies 215 and 218 submitted in the 4MSU appear to support the safe use of HTX-011 during open inguinal hernia repair and bunionectomy surgery. Further review of the final safety data will determine the acceptability of concomitant use of non-opioid analgesics, particularly NSAIDs, with HTX-011 during these surgical procedures.

8.8. Additional Safety Explorations

8.8.1. Pregnancy and Lactation

The Applicant did not conduct clinical studies in pregnant or lactating women and is relying on the prescribing information for Marcaine™ (without epinephrine) for the bupivacaine component and Mobic® for the meloxicam component of HTX-011.

Bupivacaine does rapidly cross the placenta and can cause fetal toxicity depending on the dose and route of administration. Reported adverse reactions primarily involve the cardiovascular and central nervous systems. Bupivacaine and the primary metabolite, pipercoloxylidine, are present in human breast milk. There is no information on the effects of the drug on the breastfed infant or its impact on milk production.

Use of NSAIDs, including meloxicam, during the third trimester of pregnancy increases the risk of premature closure of the ductus arteriosus in the fetus, which can ultimately lead to progressive right heart failure with tricuspid regurgitation, congestive heart failure, fetal hydrops, and intrauterine death. Meloxicam is not recommended for use in pregnant woman

beyond 30 weeks gestation.

There are no data on whether meloxicam is present in human milk, or on the effects of meloxicam on breastfed infants or milk production. In nonclinical studies, meloxicam was detected in the milk of lactating rats at concentrations higher than those observed in plasma.

8.8.2. Pediatrics and Assessment of Effects on Growth

The safety and efficacy of HTX-011 has not been evaluated in pediatric patients. The Applicant submitted an initial pediatric study plan (iPSP) on August 13, 2017, and it was agreed upon on September 27, 2018. Refer to Section 11. Postmarketing Requirements and Commitments for additional information on the planned pediatric studies.

8.8.3. Overdose

The risk of meloxicam overdose after a low-dose single injection during a surgical procedure appears low, and of theoretical concern only, and will not be included in this discussion.

Local anesthetics such as bupivacaine HCl have a well-characterized toxicity profile, commonly referred to as LAST, which generally relates to high systemic concentrations. The relative risk of experiencing LAST is dependent on many factors, including systemic absorption from different sites of administration. Specifically, inadvertent intravascular administration is associated with the highest plasma concentration and results in the fastest onset and typically most severe signs and symptoms, followed by intercostal nerve block, caudal/epidural block, brachial plexus block, and lastly subcutaneous administration (Open Anesthesia, 2018).

The toxicities associated with local anesthetic administration initially manifest as central nervous system (CNS) symptoms followed by cardiovascular system symptoms (CVS). Historically, it has been reported in the published literature that plasma concentrations of bupivacaine ≥ 2000 ng/mL may result in CNS toxicity and concentrations ≥ 4000 ng/mL may result in CVS toxicity; however, there have been reports of LAST symptoms occurring at concentrations much lower than those commonly referenced. Because the prolonged release bupivacaine products, such as HTX-011, have a different, and potentially more variable, pharmacokinetic profile than that observed with the immediate release products, the Agency agrees with the findings by Scott et al (1989), suggesting that bupivacaine toxicity may be observed at systemic concentrations >1000 ng/mL. The following table summarizes the CNS and CVS symptoms commonly associated with bupivacaine toxicity.

Table 67: CNS and CVS Symptoms of Bupivacaine and Other Local Anesthetic Toxicity

Symptom
<u>CNS</u>
– Tinnitus, blurred vision, tongue paresthesias, circumoral numbness, lightheadedness
– Nervousness, agitation, restlessness, disorientation, tremor
– Tonic-clonic seizures
– CNS depression, respiratory failure
– Coma
<u>CVS</u>
– Decreased electrical excitability, conduction disturbances including heart block, myocardial contraction, PR interval, QRS, and QT prolongation
– Bradycardia
– Arteriolar dilation, hypotension
– Ventricular fibrillation, CV collapse
– Death

Source: Adapted from Gadsden, 2017.

There are weight-based dosing guidelines aimed at reducing the risk of LAST. Specifically, the maximum recommended dose of bupivacaine with or without epinephrine should not exceed 2 to 3 mg/kg, with an approximate duration of action of 1.5 to 8 hours.

Treatment of LAST

As described in the review article by Christie *et al* (2015), the management of LAST begins with immediate recognition of the associated signs and symptoms and resuscitation measures focused on maintaining airway, breathing, and circulation, as per Advanced Cardiac Life Support (ACLS) guidelines. Cardiopulmonary resuscitation (CPR) may be necessary in cases of cardiac arrest. Seizures should be treated with benzodiazepines, thiopental, or possibly propofol depending the hemodynamic status of the patient. Cardiac arrhythmias, conduction blocks, and hypotension can be managed according to ACLS protocols, however lidocaine should not be administered in this situation.

The development of Intralipid®, a lipid emulsion comprised of soya oil, glycerol, and egg phospholipids, has positively impacted the resuscitation outcomes after documented cases of LAST and the American Society of Regional Anesthesia (ASRA) includes lipid emulsion therapy, such as Intralipid®, in the practice advisory on local anesthetic systemic toxicity (Neal *et al*, 2010). Cardiopulmonary bypass, while not used often, is still a viable treatment option in the setting of refractory toxicity in the critically ill patient.

While the likelihood of developing local anesthetic systemic toxicity with HTX-011 may be low, the following recommendations should be followed:

- HTX-011 should only be administered to patients undergoing indicated procedures
- the total dose of bupivacaine should not exceed the recommended 2 to 3 mg/kg

- additional local anesthetic medications should not be administered in combination with HTX-011 or within at least 72 hours of administration
- resuscitation medications, including a lipid emulsion such as Intralipid®, and equipment should be immediately available in the clinical settings where HTX-011 will be administered.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

HTX-011 has not been marketed anywhere in the world at the time of this NDA review, therefore, no post-marketing information is available. The clinical concerns surrounding bupivacaine are well-documented and relate primarily to the development of LAST. The clinical concerns surrounding meloxicam include risks of CV or GI adverse events, associated with all orally and intravenously administered NSAIDs. The clinical concerns surrounding administration of HTX-011 included delayed wound healing in limited surgical models.

8.9.2. Expectations on Safety in the Postmarket Setting

There may be an increased incidence in wound-related adverse events when administered in small or tight surgical spaces or those in which a viscous liquid may disrupt the surgical repair.

8.9.3. Additional Safety Issues From Other Disciplines

The Agency's current thinking regarding the approval of extended-release local anesthetic products is that because the PK profile generally differs at various sites of administration and may depend on the total dose, method of administration, and the vascularity of the anatomical site, it should be characterized for all sites and methods of administration (b) (4)

8.10. Integrated Assessment of Safety

8.10.1. Integrated Assessment of Safety of HTX-011 400 mg/12 mg

I do not recommend approval of the highest proposed dose of HTX-011 400 mg/12 mg for three reasons. First, the evaluation of safety (and efficacy) of the proposed maximum dose administered via the proposed route was in a low number of patients in adequate and well-controlled studies. Specifically, there were only 58 patients in the adequate and well-controlled arm of Study 209 (Cohort 2), who received HTX-011 400 mg/12 mg via the proposed route of

administration, instillation. An additional 56 patients received that same dose in combination with a posterior capsule injection of ropivacaine. Because the treatments differed, HTX-011 ± ropivacaine, the results cannot be pooled to support a safety conclusion for HTX-011 administered alone. Furthermore, as discussed in Section 7. Integrated Review of Effectiveness, the addition of the ropivacaine posterior capsule injection improved postsurgical analgesia and reduced opioid consumption beyond that observed for HTX-011 treatment alone. The pooling of safety data from different treatment groups does not support the safety profile of HTX-011 administered alone and is, therefore, not acceptable.

With respect to Study 203, an evaluation in patients undergoing complete abdominoplasty, only 17 patients were treated with HTX-011 400 mg/12 mg via instillation. As previously discussed in Section 8.4.5. Treatment-Emergent Adverse Events, Wound-Related Adverse Events, the additional 25 patients treated with HTX-011 400 mg/12 mg administered via injection and instillation appeared to have a higher incidence of specific local inflammatory TEAEs.

With respect to Study 211, an evaluation in patients undergoing bilateral augmentation mammoplasty, only 50 patients received the maximum proposed dose via the indicated route of administration. In addition to this being a low number of evaluated patients, the dose was divided such that approximately HTX-011 200 mg/6 mg was administered per surgical site (right and left breast implant pockets) separated in time. The following excerpt was taken from the HTX-011-211 Study Report Body, p. 27 (PDF), Applicant's submission, NDA 211988:

"After creation of the potential space where the implant would be placed, but prior to actual placement of the implant, HTX-011 was applied to the tissues that bordered this space, ensuring equal distribution of study drug throughout the pocket. Half of the study drug was used for each side (i.e., 200 mg/6 mg instilled per side). After the breast implant was placed on the first side, the procedure was repeated on the second side."

It is unacceptable to consider divided dosing, separated in time equivalent to a single administration when evaluating the safety of a locally-acting drug product with systemic toxicity.

Second, as discussed in Section 4.5.2. Pharmacokinetics, and referred to in Figures 1 and 2 and Tables 4 and 5, the bupivacaine and meloxicam PK data from three surgical procedures evaluating the maximum proposed HTX-011 dose, 400 mg/12 mg, was variable making extrapolation to other surgical models challenging and unsafe. Dr. Suresh Naraharisetti, the clinical pharmacology reviewer, has made the following summary statements regarding the PK data from the surgical models in which HTX-011 400 mg/12 mg was administered:

- Comparison of C_{max} and AUC_t between soft tissue procedures (i.e., abdominoplasty vs. mammoplasty):
 - For bupivacaine: ~49% and 34% lower for abdominoplasty compared to

- mammoplasty
 - For meloxicam: ~73 and 67%, lower for abdominoplasty compared to mammoplasty
- Comparison of C_{max} and AUC_t between soft tissue vs. boney procedures (i.e., TKA vs. abdominoplasty or mammoplasty):
 - For bupivacaine –
 - o ~90% and 100% higher, respectively for TKA compared to abdominoplasty
 - o ~equal and 31% higher, respectively for TKA compared to mammoplasty
 - For meloxicam –
 - o ~94% and 95% higher, respectively for TKA compared to abdominoplasty
 - o ~48% and 36% lower, respectively for TKA compared to mammoplasty

Because the PK data of a single dose, HTX-011 400 mg/12 mg, are variable and cannot be extrapolated to different surgical models, it appears that each indication (surgical site) will need data to support the safety profile of HTX-011, which will likely require additional clinical studies.

And third, while I agree that the cumulative systemic exposure to bupivacaine is greater after administration of HTX-011 due to a slower release when compared to immediate release bupivacaine HCl, the AUC_{0-inf} data for this dose has not been supported by either clinical or nonclinical information in the NDA submission. As discussed in Section 4.5.2. Pharmacokinetics, the Applicant attempted to address this issue using extrapolated AUC information based on bupivacaine HCl dose-matching. However, the mathematical calculations and extrapolation of PK data for purposes of supporting the systemic safety of HTX-011 may not be acceptable, primarily because the PK dose-proportionality for different doses of bupivacaine HCl for different surgical procedures is lacking.

8.10.2. Integrated Assessment of Safety of Other HTX-011 Doses

For the doses of HTX-011 evaluated in the Phase 3 studies, HTX-011 60 mg/1.8 mg and 300 mg/9 mg, and those likely to be approved, the safety issues of greatest concern include the potential adverse impact on surgical wound healing and the risk of development of LAST. The need for Mobic® boxed warning in the HTX-011 label will be discussed briefly. Because the IRT-QT concluded that HTX-011 does not prolong the QT interval, that potential safety issue will not be included in this discussion.

Based on the totality of the wound healing data and information presented in this NDA submission, I conclude that there does appear to be an increased incidence of wound-related adverse events associated with administration of HTX-011 60 mg/1.8 mg in a bunionectomy wound. Based on nonclinical data, the increased incidence appears to be most closely related to excipients in the Biochronomer® formulation (b) (4). While it is possible that meloxicam may contribute to the observed wound-related adverse events, it seems unlikely given the anti-inflammatory properties of meloxicam and the proposed

mechanism of action when administered locally in HTX-011. Specifically, the Applicant theorizes that meloxicam prolongs the efficacy of bupivacaine by raising the tissue pH, resulting in more bupivacaine in the nonionized state, the therapeutically active state. More simply stated, meloxicam is thought to allow bupivacaine to overcome the ion trapping that occurs when local anesthetics are exposed to an acidic environment. Nonclinical data suggest, however, that any observed changes in tissue pH do not correlate with meloxicam release from HTX-011, therefore, the mechanism of action may be something other than altered tissue pH. This alternate mechanism of action may also contribute to the observed changes in postsurgical wounds reported in both the clinical and nonclinical studies. For additional nonclinical information, refer to the pharmacology-toxicology review by Dr. Jaime D'Agostino.

An additional explanation for the increase in wound-related adverse events in patients treated with HTX-011 after particular surgical procedures involves the viscous nature of the drug product. The Applicant has described HTX-011 has a *“viscous liquid that does not readily disperse into the tissues”* (Summary of Clinical Safety, p. 129 [PDF], Applicant's submission, NDA 211988). Because of this, HTX-011 may distort or even disrupt the anatomy of otherwise tight, adherent spaces or cavities. For example, the plication of the posterior rectus sheath that occurs during complete abdominoplasty is generally a tight repair, such that patients must maintain a semi-recumbent position post-operatively to minimize stress on the surgical repair and facilitate healing. Administration of a viscous liquid, either via injection or instillation, may expand this repair and thus adversely impact healing. Similarly, the surgical space for bunionectomy is considered small and tight and may also be disrupted with administration of a viscous liquid, resulting in delayed or even impaired healing.

Despite the documented increases in wound-related adverse events observed after bunionectomy surgery, I recommend approval of HTX-011 60 mg/1.8 mg for use in bunionectomy surgery for four reasons. First, the Applicant's discussion regarding the leakage of excess HTX-011 from the wound potentially contributing to the development of local inflammatory changes in the short-term (less than 42 days) is a reasonable explanation for the observed increases in wound-related adverse events, and this may be mitigated by language in the DOSAGE AND ADMINISTRATION section of the package insert. Specifically, language describing the potential for excess HTX-011 resulting in leakage, poor wound approximation, and delayed healing may mitigate this risk.

Second, while an increase in adverse events at any time during the post-operative recovery period is concerning, it is reassuring that these changes do not appear to have resulted in more serious, longer-lasting adverse events. Third, there were no reported cases in Study 301, or Study 208, of adverse bone changes such as fracture, loosening or loss of hardware, or osteomyelitis. Follow-up post-operative x-rays from both clinical studies did not indicate an adverse effect of HTX-011 on bone healing, suggesting that the observed wound-related changes observed on physical exam were likely superficial and did not result in long-term disability.

And fourth, as is often the case in clinical studies, the captured data may not accurately reflect real-world adverse events or their incidence. It may be the case in this clinical development program that several observers “over-graded” the surgical wounds and documented adverse events that would not have been in a standard clinical setting. This rationale is supported by review of the wound-healing data (b) (4). As previously mentioned, he concluded that the results from Study 301 were spurious and not reflective of the overall safety of HTX-011 demonstrated across the entire drug development program.

Regarding soft tissue surgical procedures, in Study 302, patients treated with HTX-011 300 mg/9 mg during IHR surgery did not appear to have an increased incidence of wound-related adverse events compared to patients treated with saline placebo or bupivacaine HCl. There was a higher percentage of patients with documented incision site swelling but that is not entirely unexpected given the viscous nature of HTX-011 and is likely not clinically significant. In Study 203, however, in patients undergoing complete abdominoplasty, the HTX-011 300 mg/9 mg treatment group, administered via combination of injection and instillation, had a clinically significantly higher incidence of wound dehiscence when compared to the other treatment groups. The combination route of administration is described as follows:

“Approximately 1/3 of the total volume of study drug was administered to the plication area of the posterior rectus sheath via approximately 5 (for mini-abdominoplasty) or 8 (for complete abdominoplasty) injections. Another 1/3 of study drug volume was administered just above and below the external fascial layers of the rectus and external oblique muscles via approximately 10 (for mini-abdominoplasty) or 12 (for complete abdominoplasty) injections at a 45° angle in 2 tracks parallel on each side of the central midline of the abdomen (ie, the semilunaris).” (HTX-011-203 Study Report Body, p. 34 [PDF], Applicant’s submission, NDA 211988)

It is possible that multiple (eight) injections of HTX-011, described as viscous liquid, into the posterior rectus sheath resulted in disruption of the plication leading to wound complications. This does not explain, however, why the complication of dehiscence was observed most in the HTX-011 300 mg/9 mg treatment group. Another possibility is whether the increased incidence was observed more in patients also undergoing umbilicus repositioning. The overall number of patients per treatment group in Study 203 is low, making definitive conclusions about the safety profile in this surgical model difficult, however, the reported incidence of local inflammatory TEAEs warrants further investigation before widespread use in this population is recommended.

The second main safety concern with HTX-011 administration is the risk of LAST. The challenge with extended or delayed release bupivacaine products is that the local efficacy is unrelated to the systemic concentration, such that the recommend time for safety monitoring can be difficult to predict. The systemic bupivacaine concentration at which LAST can develop is debatable and appears to depend on many factors, including the dose, route, and site of administration and the underlying medical condition of the treated patient. Historically, ≥ 2000

ng/mL was the systemic level concerning for the development of neurotoxicity and ≥ 4000 ng/mL for the development of cardiotoxicity. As described in the article by Scott *et al* (1989), however, bupivacaine toxicity can develop at systemic concentrations > 1000 ng/mL and it is well-known that due to the high degree of protein binding and strong affinity for cardiac Na^+ channels, the management of bupivacaine toxicity can be challenging and prolonged.

The risks of developing LAST after administration of HTX-011 are related to the following:

- The variable PK profile for HTX-011, as demonstrated after administration of HTX-011 400 mg/12 mg in three different surgical models. The C_{max} , AUC, and T_{max} demonstrated wide variability across the three models evaluated. This variability makes post-operative safety monitoring recommendations challenging.
- The pharmacodynamic response does not correlate with the systemic bupivacaine concentrations, also making safety monitoring recommendations challenging.
- Bunionectomy and IHR with mesh are generally performed on an outpatient basis, such that most patients will be in an unmonitored setting during the time of peak systemic exposure and potential toxicity. This further complicates postoperative safety assessments.
- The maximum recommended dose of bupivacaine delivered via HTX-011 is greater than that recommended in the Marcaine™ product label.

Despite the concerns surrounding the development of LAST with administration of HTX-011 in doses greater than those recommended in the Marcaine™ product label, I recommend approval up to 300 mg/9 mg for five reasons. First, there did not appear to be an increased incidence in potential LAST-related adverse events in patients treated with HTX-011 300 mg/9 mg compared to patients treated with saline placebo or bupivacaine HCl in Study 302. Specifically, the potential LAST-related adverse events reported with a higher incidence in the HTX-011 treatment group compared to the bupivacaine HCl treatment group were hypotension, paresthesia oral, sinus arrhythmia, and sinus bradycardia. The differences in incidence were small and did not appear to be clinically significant. A potential confounder for interpretation of these adverse events is the administration of general anesthesia, which can make detection of LAST postoperatively challenging.

Second, there was only a single patient treated with HTX-011 300 mg/9 mg with a C_{max} value greater than 1000 ng/mL at T_{max} 33 hours. That patient had one potential LAST-related adverse event, syncope, five hours after study drug administration, which appears unrelated to the bupivacaine plasma concentration. Third, the safety evaluation of HTX-011 400 mg/12 mg, the highest proposed dose although unlikely to be approved, did not demonstrate an increased incidence of LAST-related adverse events after administration when compared to the bupivacaine HCl treatment group. Furthermore, of the patients with reported C_{max} values greater than 1000 ng/mL, none appeared to have an increased incidence of potential LAST-related adverse events compared to those with C_{max} values less than 1000 ng/mL.

Fourth, review of the continuous holter data from Study 209 and Study 211 and the serial ECG data from Study 301 and Study 302 did not reveal any clinically meaningful differences in measured parameters across treatment groups. Specifically, there was no large or consistent effect of HTX-011 treatment on heart rate and the small changes observed in PR interval were not significant as determined by outlier analysis. The change in QTcF was noted to be a decrease, likely clinically insignificant.

And fifth, administration of HTX-011 may offer a degree of safety over other delayed-release bupivacaine formulations based on the proposed route of administration, instillation. Because HTX-011 is applied to the tissues with a needleless syringe, the risk of intravascular administration is low. Admittedly, systemic exposure may still be high in the setting of extensive application to large areas of exposed blood vessels or denuded tissue, however, these clinical situations can be adequately addressed in the product label.

One outstanding clinical concern regarding the development of LAST is the risk of delayed onset, such that patients become symptomatic after discharge, in an unmonitored setting. The Applicant did evaluate the occurrence of potential LAST-related adverse events with rapid or delayed onset and found no differences between treatment groups in the studies evaluated. However, the defining time course for rapid versus delayed is not likely to distinguish delayed LAST symptoms associated with HTX-011 versus those associated with bupivacaine HCl. Specifically, delayed onset LAST was defined as symptoms occurring after one hour to less than or equal to 72 hours of study drug administration. It seems unlikely that such a large observation window would distinguish symptoms between groups. Toxicity associated with bupivacaine administration is likely to occur around T_{max} , generally within three hours of administration for bupivacaine HCl wound infiltration and from four to 60 hours after administration of HTX-011, suggesting that the delayed onset window would capture LAST-related adverse events potentially associated with both treatments. This ultimately resulted in a similar delayed onset adverse event incidence for both groups, making the risk assessment for HTX-011 based on this data challenging. Furthermore, it seems unlikely that the time course for toxicity associated with bupivacaine HCl wound infiltration and HTX-011 administration is similar. If that were the case, the Applicant's claim of slow or delayed release would be questionable.

Despite the potential risk of delayed onset LAST in patients in an unmonitored setting, I still recommend approval of HTX-011 up to doses of 300 mg/9 mg. There was only a single patient in Study 302 who had bupivacaine levels greater than 1000 ng/mL, and while that patient did have an episode of syncope, which could be considered a LAST-related adverse event, it was documented approximately 28 hours before T_{max} . I believe the risk of delayed onset LAST can be mitigated by adequate safety monitoring and limited use of HTX-011 in the surgical populations most extensively evaluated, bunionectomy and open inguinal hernia repair with mesh. The safety monitoring must include standard ASA monitoring post-operatively until such time as facility-issued discharge criteria have been met and discharge instructions and education provided. The discharge instructions should be detailed and comprehensive such

that patients and caregivers are confident they are able to recognize the early signs and symptoms of bupivacaine-induced neurotoxicity.

The final safety issue for consideration during review of this NDA is the need to include the Mobic® boxed warning in the HTX-011 label. The following two arguments can be made that they are not necessary. First, HTX-011 is administered as a single instillation and repeated exposure during the same surgical procedure is not indicated, therefore, the risk of developing a cardiovascular thrombotic or gastrointestinal adverse event appears low. Second, because the systemic exposure to meloxicam after a single dose of HTX-011 is much lower in both magnitude and duration than that reported in the Mobic® label after a 7.5 mg oral dose, the likelihood these adverse events will occur is quite low. However, because all NSAID-containing products must contain the boxed warnings, including topically administered NSAIDs, it is likely that they cannot be omitted from the final Zynrelef® product label.

I conclude that HTX-011 is a safe treatment option for surgical patients undergoing bunionectomy and open inguinal hernia repair with mesh in the doses evaluated during the Phase 3 clinical studies, HTX-011 60 mg/1.8 mg and HTX-011 300 mg/9 mg, respectively. Additional indications and HTX-011 doses will need to be supported by clinical data, which will likely include additional clinical studies.

9. Labeling Recommendations

9.1. Prescription Drug Labeling

The original proposed label indication included the following language:

[REDACTED] (b) (4)

In the Clinical Information Amendment – Response to Potential Filing Review Issues, dated January 18, 2019, the Applicant proposed the following two revised indications. Option 1 was included in the updated USPI.

Option 1 –

[REDACTED] (b) (4)

OR

Option 2 –

(b) (4)

Because this application is receiving a Complete Response, the final label edits were not completed at the time of this clinical review.

10. Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not indicated at this time. If the Agency becomes aware of future safety concerns, one may become necessary.

11. Postmarketing Requirements and Commitments

The Pediatric Research Equity Act (PREA) applies to this NDA. Under PREA, the Applicant is required to conduct studies to assess safety, efficacy, and appropriate dosing. The Applicant submitted an initial pediatric study plan (iPSP) on August 13, 2017, and it was agreed upon on September 27, 2018. The proposed pediatric studies evaluating HTX-011 and the proposed deferral requests are as follows:

- (b) (4)

 - The Applicant requested a deferral for study completion because HTX-011 was ready for approval for use in adults before pediatric studies were complete in accordance with section 505B(a)(3)(A)(i). Additional time for study completion was requested based on receiving Agency agreement on the revised draft protocol in late December 2018, and the ongoing drug shortage for the active comparator, bupivacaine HCl. The deferral request appears to alter the timeline by approximately 6 months.
 - Study 1 will be initiated with adolescents $\geq$

(b) (4)

 to < 17 years of age.

(b) (4)
 - Study initiation is projected for May 2019 and final report submission projected for May 2022.
- (b) (4)

- The Applicant requested a deferral for study initiation and completion in accordance with section 505B(a)(3)(A)(ii), and until additional safety data has been collected from Study 1 and the after completion of the juvenile animal studies. The timeline for protocol submission and study initiation and completion have not changed from the Agreed iPSP.
- Study initiation is projected for July 2020 and final report submission projected for June 2023.

12. Appendices

12.1. References

Christie LE, Picard J, Weinberg GL. Local anaesthetic systemic toxicity. *BJA Education*. 2015;15(3):136-142.

Gadsden, J. Local anesthetics: clinical pharmacology and rationale selection. The New York School of Regional Anesthesia (2017). <https://www.nysora.com/local-anesthetics-clinical-pharmacology-and-rational-selection>.

Morgan, GE, Mikhail, MS, Murray, MJ. *Clinical Anesthesiology*. (2002) New York, NY: McGraw-Hill.

Neal JM, Bernardis CM, Butterworth JF, Di Gregorio G, Drasner K, Hejtmanek MR, Mulroy MF, Rosenquist RW, Weinberg GL. ASRA practice advisory on local anesthetic systemic toxicity. *Regional Anes and Pain Med*. 2010;35(2):152-161.

Scott DB, Lee A, Fagan D, Bowler GM, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. *Anesth & Analg*. 1989;69(5):563-9.

Vasques, F., A. U. Behr, G. Weinberg, C. Ori and G. Di Gregorio (2015). *A Review of Local Anesthetic Systemic Toxicity Cases Since Publication of the American Society of Regional Anesthesia Recommendations: To Whom It May Concern*. *Regional Anesthesia and Pain Medicine* 40(6): 698-705.

Wildsmith, JAW, Tucker, GT, Cooper, S, Scott, DB, Covino. Plasma concentrations of local anaesthetics after interscalene brachial plexus block. *Br. J. Anaesth*. 49;461-466, 1977.

12.2. Financial Disclosure

The Applicant disclosed that one investigator, (b) (6) participated in financial

arrangements requiring disclosure per 21 CFR part 54. Per form FDA 3455, the Applicant provided information to address the concern for bias, including confirmation that (b) (6) was blinded for the (b) (6) studies for which was a clinical investigator.

Covered Clinical Studies: Study HTX-011-301 and Study HTX-011-302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>22</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>1</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

NDA 211988

Bupivacaine and Meloxicam Extended-Release Solution

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RENEE L PETIT-SCOTT
04/29/2019 12:00:50 PM

MARTHA A VAN CLIEF
04/30/2019 09:42:12 AM