CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Supplement #:	211-988
Drug Name:	HTX-011 (Bupivacaine and Meloxicam) extended-release solution
Indication(s):	(b) (4)
Applicant:	Heron Therapeutics, Inc.
Date(s):	Letter date: October 30, 2018 Review due date: April 2, 2019 PDUFA date: April 30, 2019
Review Priority:	Priority
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Keywords:	NDA review, clinical studies

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1 EXECUTIVE SUMMARY

Heron Therapeutics, Inc. has developed HTX-011, a fixed-dose combination solution of bupivacaine and low-dose meloxicam, and is seeking an indication (b) (4) To support efficacy, two Phase 3 studies were reviewed, Study HTX-011-301 in subjects with bunionectomy surgery and Study HTX-011-302 in subjects with herniorrhaphy surgery. These were randomized (R), multicenter (MC), double-blind (DB), placebo and active-controlled studies. Subjects with inadequately controlled pain symptoms could request rescue analgesia (oral immediate-release (IR) oxycodone, IV morphine and/or oral acetaminophen). The applicant also conducted a Phase 2b study (Study HTX-011-209) in subjects undergoing primary unilateral total knee arthroplasty (TKA) and included the results in Section 14 of the product label. However, this study failed to demonstrate that HTX-011 was better than bupivacaine and was deemed not adequate to support an indication for post-operative pain due to TKA (See Section 3.2.3 for a detailed discussion of this study).

In both Phase 3 studies, the applicant's primary efficacy endpoint was the mean area under the curve (AUC) of numeric rating scale with activity (NRS-A) pain intensity (PI) scores through 72 hours (AUC_{0-72}) for HTX-011 compared with saline placebo. The applicant's key secondary efficacy endpoints were: mean AUC_{0-72} of the NRS-A PI scores for HTX-011 compared with bupivacaine HCl; Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with saline placebo; Proportion of subjects who are opioid-free through 72 hours for HTX-011 compared with bupivacaine HCl; Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with bupivacaine HCl. A strict hierarchical testing procedure was applied to control study-wise alpha level at 0.05. The difference between treatment groups for AUC_{0-72} was assessed by an analysis of variance (ANOVA) model with a factor of treatment. In both Phase 3 studies, the results indicated there was a statistically significant reduction in pain intensity with activity compared to both bupivacaine and saline placebo for up to 72 hours. A statistically significant reduction in total opioid consumption over 72 hours was also observed for HTX-011 compared to both bupivacaine and placebo. The proportion of subjects who were opioid-free through 72 hours was statistically significantly higher for HTX-011 compared to bupivacaine.

Since both Phase 3 studies were conducted in an inpatient setting, subject discontinuation was not an issue. However, there was a high percentage of subjects in each study that used rescue medication. The applicant utilized a windowed worst observation carried forward (wWOCF) method to account for this in the analyses of the primary and the 1st key secondary endpoints. With this method, PI scores observed during the analgesic window (duration of effect) of any opioid rescue medication were replaced with the worst observed pre-window PI score unless the observed scores were higher than the worst observed pre-window PI score. Additional sensitivity analyses were conducted also considering non-opioid rescue medication, ignoring the use of rescue medication (using pain scores observed after taking rescue medication), and an integrately assessing pain scores (after using rescue medication) and total use of rescue medication (Silverman et.al., 1993). These sensitivity analyses all supported the primary efficacy analysis, there was a significant treatment effect noted for HTX-011 when compared to placebo and bupivacaine.

Based on the review of the two Phase 3 studies submitted, there is sufficient evidence that the proposed study drug, HTX-011 (60 mg bupivacaine/1.8 mg meloxicam and 300 mg bupivacaine/9 mg meloxicam) administered as a single dose, is efficacious to reduce pain for up to 72 hours after unilateral bunionectomy and unilateral open herniorrhaphy surgery.

2 INTRODUCTION

2.1 Overview

Bupivacine, an amide-type local anesthetic, has been approved for surgical anesthesia and for acute pain management in adults and children. A liposomal injectable suspension of bupivacaine is also available and indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia. Meloxicam, a nonsteroidal anti-inflammatory drug (NSAID), has been approved since 2000 for the relief of the signs and symptoms associated with osteoarthritis, rheumatoid arthritis and juvenile rheumatoid arthritis in patients 2 years or older, and management of osteoarthritis pain. Heron Therapeutics, Inc. has developed HTX-011 which is a fixed-dose combination product that contains bupivacaine and low-dose meloxicam. They are seeking an indication (b) (4) HTX-011 is administered as a single dose that is applied into the surgical site to coat the affected tissues. Unlike other local anesthetics, HTX-011 is not injected by needle. It is applied using a syringe with an applicator attached. The applicant claims that the bupivacaine and meloxicam contained in HTX-011 are released slowly for approximately 3 days after administration.

The clinical development program of HTX-011 has been discussed between the agency and the applicant numerous times under IND 125,927. A fast track designation was granted on October 24, 2017 and a breakthrough therapy designation was granted on June 14, 2018. Based on evidence that bupivacaine is the disease-active ingredient and meloxicam enhances the effectiveness of bupivacaine, in the EOP2 meeting held on June 15, 2007, the agency stated that a factorial design study was not required. However, superiority to bupivacaine was required to satisfy the "combination rule" for fixed-combination products and significant results from both Phase 3 studies would be required. In the EOP2 meeting, the agency made the following comments:

- The proposed testing plan for the primary and secondary endpoints does not meet the clinical requirements (see responses to Questions 8, 9, and 16). Therefore your sample size calculations should be rechecked when the endpoints have been revised.

- It is very important to clearly describe the activity to be performed when assessing the NRS-A pain intensity score with activity. It is essential that this activity be consistent for every patient at every time point across all centers.

- The proposed modified Intent-to-Treat (mITT) population for the analyses includes all randomized subjects with at least on post-treatment NRS-A pain intensity score. The preferred population is the ITT population consisting of all randomized subjects. Patients lacking a post-treatment efficacy assessment should not be excluded.

- The nonresponder imputation (NRI) for missing data on binary endpoints, and the windowed worst observation carried forward (wWOCF) imputation for use of rescue medication are acceptable. The proposed last observation carried forward (LOCF) approach for other missing pain intensity scores is not acceptable, as it may attribute a good outcome to a patient that discontinues due to a bad outcome, such as adverse events. Propose an alternative approach for these cases, including multiple imputation strategies. You should also fully document all reasons for missing data.

- The analysis of variance (ANOVA) model does not specify what terms will be included. This must be prespecified in the protocol. Also provide plots of pain scores over the 0-72 hour timeframe by treatment group.

The current submission contains one Phase 1 study in healthy volunteers, three Phase 2a studies, two Phase 2b studies and two Phase 3 clinical studies. This review focuses on the two Phase 3 studies in subjects with unilateral bunionectomy or herniorrhaphy surgery (reviewed by Dr. Yan Zhou) and one Phase 2b study in subjects with unilateral total knee arthroplasty (reviewed by Dr. Yi Ren) (Table 1).

Table 1: Summary of Trials Reviewed

Trial ID	Design†	Treatment/Sample Size	Primary Efficacy Endpoint‡
HTX-011-301	R, DB, MC, saline placebo and active-controlled	HTX-011 60 mg/1.8 mg: 157 Saline placebo: 101 Bupivacine 0.5% 50 mg: 154	Mean AUC_{0-72} of NRS-A for HTX-011 compared with saline placebo
HTX-011-302	R, DB, MC, saline placebo and active-controlled	HTX-011 300 mg/9 mg: 163 Saline placebo: 82 Bupivacine 0.25% 75 mg: 173	Mean AUC_{0-72} of NRS-A for HTX-011 compared with saline placebo
HTX-011-209*	R, DB, MC, saline placebo and active-controlled	HTX-011 400 mg/12 mg: 58 HTX-011 + ropivacaine 0.5% 50 mg: 56 Saline placebo: 53 Bupivacaine 0.25% 125 mg: 55	Mean AUC_{0-48} of NRS-R for HTX-011+ropivacaine / HTX-011 compared with saline placebo

Source: Reviewer's analyses.
† R: randomized; DB: double-blind; MC: multi-center;
‡ AUC: area under the curve;
NRS-A: Numeric Rating Scale of pain intensity score with activity;
NRS-R: Numeric Rating Scale of pain intensity score at rest;
* The sample size was for Cohort 2 only.

2.2 Data Sources

The clinical study reports are located at the following location in the CDER electronic document room (EDR):
\\CDSESUB1\evsprod\NDA211988\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\postoperative-pain-management\5351-stud-rep-contr.

The datasets, define files and programs are located in EDR at:
\\CDSESUB1\evsprod\NDA211988\0002\m5\datasets. Both SDTM and ADaM Datasets were submitted by the applicant to the CDER EDR in SAS transport format.

Note that at the type C meeting dated April 3, 2018, FDA stated that an integrated summary of efficacy (ISE) was not required if all required ISE information including tables, figures and listings are included in Module 2.7.3 Summary Clinical of Efficacy (SCE). There was no

presumption of pooling of efficacy data across studies. There was no ISE in the submission, and the applicant stated studies were not pooled as they had different surgery types and dosages. They did not provide a comprehensive discussion about the effectiveness of their drug including information from the published literature.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The electronic datasets and define files submitted by the applicant were of acceptable quality, and were sufficient for validating study results.

3.2 Evaluation of Efficacy

3.2.1 Study HTX-011-301

3.2.1.1 Study Design and Endpoints

Study HTX-011-301 was a Phase 3, MC, R, DB, saline placebo- and active-controlled study conducted to evaluate the analgesic efficacy, safety and pharmacokinetics (PK) of HTX-011 administrated via instillation into the surgical site in subjects undergoing unilateral simple bunionectomy. The study was conducted at 13 sites in the United States from October 2017 until March 2018.

Eligible subjects were randomized to one of the following three treatment groups in a 3:3:2 ratio: HTX-011 (60 mg/1.8 mg) via instillation into the surgical site; Bupivacaine HCl without epinephrine (0.5%, 50 mg) via injection into the surgical site; saline placebo via instillation into the surgical site. On Day 1, subjects underwent a bunionectomy with no more than 20 mL of 1% lidocaine without epinephrine administrated as a Mayo block. During the surgery, the use of intravenous (IV) fentanyl up to 4 µg/kg was permitted for intraoperative pain control. Near the completion of surgery and after irrigation and suction was complete, a single dose of study drug (HTX-011, saline placebo, or bupivacaine HCl without epinephrine) was administrated intraoperatively into the surgical site. The start of study drug administration was considered as Time 0. Following surgery and immediate postoperative recovery, subjects were transferred to the post-anesthesia care unit. Subjects remained in the hospital/research facility for a minimum of 72 hours to undergo postoperative assessments. After the 72-hour assessments were completed, subjects could be discharged. At discharge, subjects were to be provided a daily diary to record if they took any opioid medication from 72 hours through Day 28. Subjects returned to the study site on Days 10 and 28 to complete follow-up assessments. In addition, subjects returned for a safety follow-up visit on Day 42 that included an X-ray of the surgical foot.

During the 72-hour postoperative observation period, subjects with inadequately controlled pain could request rescue medication which consisted of oral immediate-release oxycodone (≤10 mg within a 4-hour period), IV morphine (≤10 mg within a 2-hour period), and/or oral acetaminophen (≤1000 mg in a 6-hour period).

PI scores were assessed using an 11-point numeric pain rating scale (NRS) at scheduled times during the 72-hour period after surgery (Hour 1, 2, 4, 8, 12, 24,36, 48, 60, and 72) and Day 10 and 28. NRS scores were recorded first at rest (NRS-R) and then with activity (NRS-A). For NRS-R assessments, subjects were 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. For NRS-A assessments, subjects were seated on the plantar surface of the ball with the surgically attended foot touching the floor (no weight-bearing).

The primary objective of the study was 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. The applicant's primary efficacy endpoint was the mean area under the curve (AUC) of NRS-A PI scores through 72 hours (AUC_{0-72}) for HTX-011 compared with saline placebo. The applicant's key secondary efficacy endpoints were:

1. Mean AUC_{0-72} of the NRS-A PI scores for HTX-011 compared with bupivacaine HCl;
2. Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with saline placebo;
3. Proportion of subjects who are opioid-free through 72 hours for HTX-011 compared with bupivacaine HCl;
4. Mean total postoperative opioid consumption (in morphine equivalents) through 72 hours for HTX-011 compared with bupivacaine HCl.

Other secondary efficacy endpoints the applicant used included proportion of subjects who were opioid-free through 72 hours compared with saline placebo, proportion of subjects who were opioid-free from 72 hours through Day 10 and 28, median time in hours to first opioid rescue medication up to 72 hours, mean AUC_{0-72} of the NRS-R PI scores, integrated rank analysis of Silverman using the NRS-A PI AUC scores and total opioid consumption through 72 hours, proportion of subjects who are pain-free with activity at each assessed timepoint through Day 28, proportion of subjects with a NRS-A PI score ≥4 at any timepoint through 72 hours, proportion of subjects with a NRS-A PI score ≥7 at any timepoint through 72 hours, proportion of subjects who first achieve a MPADSS score ≥9 at 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours, and proportion of subjects achieving a score of "good" or better pain control based on PGA at 24, 48, 72 hours and on Day 28.

3.2.1.2 Statistical Methodologies

The primary efficacy analysis population consisted of all subjects who were randomized and received study drug. For the applicant's primary and 1st key secondary efficacy endpoint, the treatment groups were compared using an analysis of variance (ANOVA) model with treatment as the main effect. For the applicant's 2nd and 4th key secondary endpoints, the total postoperative opioid consumption through 72 hours was analyzed using a Wilcoxon rank sum test because the assumption of normality was not met. For the 3rd key secondary endpoint, the proportion of subjects in the HTX-011 group who were opioid-free through 72 hours was compared with bupivacaine HCl using Fisher's exact test. A strict hierarchical testing procedure was applied to control study-wise alpha level at 0.05. If the primary endpoint was significant, then the key secondary endpoints were tested in the order specified above.

In the applicant's analyses, the last observation carried forward (LOCF) method was used to impute intermittent missing PI scores. If there was no post-dose value available prior to the first missing value, then the median of observed values in the same treatment group at that timepoint was used. For subjects who withdrew from the study prior to 72 hours, missing PI scores through 72 hours were imputed using the worst observation carried forward (WOCF) method. Although these methods are single imputation methods which are not recommended by the National Academy of Science (NAS) report on missing data, this was not a concern as very few patients (1%) didn't complete the 72-hour pain assessment.

To account for the use of opioid rescue medication, the applicant utilized a windowed WOCF (wWOCF) method. With this method, PI scores observed during the analgesic window (duration of effect) of any opioid rescue medication were replaced with the worst observed pre-window PI score unless the observed scores were higher than the worst observed pre-window PI score. However, subjects were also allowed to use non-opioid rescue medication and some subjects only used non-opioid rescue medication in the study. To account for this, a sensitivity analysis was conducted using the wWOCF method that accounted for all rescue medication including non-opioids. The 4-hour and 6-hour analgesic windows were applied for non-opioid rescue medication respectively. Sensitivity analyses were also performed on the primary and the 1st key secondary endpoints where the use of rescue medication is ignored. Using actually observed pain scores after rescue use would inflate the treatment effect of the placebo and bupivacaine arms, and thus, tend to reduce the estimated treatment effects between HTX-011 and each of them. However, if the reduced treatment differences are significant in favor of the combination product, this would provide more evidence that HTX-011 reduces post-operative pain associated with the two surgical models studied.

An integrated assessment combing PI scores and amount of opioid rescue medication used (Silverman method[1]) was conducted. In this analysis, each subject was ranked for both the AUC of the NRS-A PI scores (without adjusting for opioid rescue use) and total opioid rescue medication measured by morphine milligram equivalency (MME), without regard to the treatment he/she was assigned to. For each subject, the percent difference between its rank and the overall mean rank was calculated for AUC of the NRS-A PI scores and total opioid use respectively. Finally, the two rank percent differences were added together and analyzed as the integrated rank of Silverman (IRS). The final IRS for each subject ranges approximately from -200% to 200%, with the highest positive score indicating the most pain despite the greatest use of rescue analgesics, and the lowest score indicating the least pain despite the least use of rescue analgesics. Summary statistics of the IRS using NRS-A PI AUC scores and total opioid consumption through 72 hours (IRS_{0-72}) were presented, and the treatment differences were analyzed using a Wilcoxon rank sum test.

For the time to the first dose of opioid rescue medication up to 72 hours, subjects who withdrew from the study prior to 72 hours or completed the 72-hour assessment without any opioid rescue use were censored at the time of study withdrawal or at 72 hours, which ever was earlier. A Kaplan-Meier (KM) survival curve was graphically displayed for each treatment group and the log-rank test was utilized to compare three survival curves. Treatment group comparisons were also summarized with hazard ratios and their associated 95% confidence interval (CI) from a Cox proportional hazard regression model with treatment as the main effect.

As recommended in ICH E9 (R1) addendum, a primary estimand of interest should be pre-specified for a clinical trial. Since this study was conducted prior to this addendum, the applicant did not specify the estimand of interest. However, based on the test drug, proposed indication, study design and efficacy endpoints, we think the primary estimand of interest was:

> The difference in mean AUC of NRS-A PI scores through 72 hours comparing subjects with post-operative pain associated with bunionectomy surgery assigned to HTX-011 versus those assigned to saline placebo regardless of treatment adherence. If rescue medication was used, a windowed WOCF method was utilized to impute what a subjects pain score would have been had they not used rescue medication.

In the sensitivity analyses, an estimand using a treatment policy strategy was examined. This estimand was defined as:

> The difference in mean AUC of NRS-A PI scores through 72 hours comparing subjects with post-operative pain associated with bunionectomy surgery assigned to HTX-011 versus those assigned to saline placebo regardless of treatment adherence and regardless of rescue medication use.

The analysis for this estimand used PI scores regardless of rescue use.

In addition, as a sensitivity analysis, an estimand using a treatment policy strategy and composite strategy was also examined. This estimand was defined as:

> The difference in the distribution of integrated ranks of AUC of NRS-A PI scores through 72 hours and total amount of rescue medication used through 72 hours comparing subjects with post-operative pain associated with bunionectomy surgery assigned to HTX-011 versus those assigned to saline placebo regardless of treatment adherence and regardless of rescue medication use.

The analysis for this estimand using an integrated assessment of PI scores regardless of rescue use and total amount of rescue medication used (Silverman method[1]). These estimands also apply to study HTX-011-302 which evaluated post-operative pain associated with open inguinal herniorrhaphy.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

The disposition of all randomized subjects is shown in Table 2. The intent-to-treat (ITT) population included a total of 412 subjects and 408 subjects (99%) completed the 72-hour pain assessment. There were two subjects (1%) in the HTX-011 treatment group, one subject (1%) in the bupivacaine group, and one subject (1%) in the placebo group who didn't complete the 72-hour pain assessment.

The demographic and other background characteristics for all subjects in the ITT population are presented in the appendix (Table 30). The majority of subjects (86%) were female, white (82%) and the mean age was 47 years. The overall mean body mass index (BMI) was 27.4 kg/m^2. The

demographic and other background characteristics were comparable between the three treatment groups.

Table 2: Subject Disposition in Study HTX-011-301 – Number (%) of Subjects

	Saline Placebo	Bupivacaine Hcl 50 mg	HTX-011 60mg/1.8 mg
Randomized	109	165	164
ITT population	100	155	157
Completed the 72-hour period	99 (99%)	154 (99%)	155 (99%)
Completed the study	99 (99%)	152 (98%)	154 (99%)
Reasons for study withdrawal			
AE			1 (1%)
Lost to follow-up	1 (1%)	1 (1%)	1 (1%)
Withdrawal by subject		1 (1%)	1 (1%)
Death		1 (1%)	

Source: Reviewer's analyses.

3.2.1.4 Results and Conclusions

There were 157 subjects from the HTX-011 treatment group, 155 subjects from the bupivacaine group and 100 subjects from the placebo group included in the primary efficacy analysis. The applicant's analyses of the primary and the first key secondary endpoint where PI scores observed after each use of opioid rescue medication were handled by the wWOCF method were reproducible. Table 3 lists analgesic windows for all opioid rescue medication. The mean NRS-A PI scores over the 72-hour post-operative period for each treatment group are displayed in Figure 1. At all timepoints through 72 hours, the mean NRS-A PI scores were lower in the HTX-011 group compared with the saline placebo group. The mean NRS-A PI scores were also lower in the HTX-011 group compared with the bupivacaine group over 72 hours, with the exception of the first 2 hours after study drug administration. Results of mean AUC_{0-72} of NRS-A PI scores are shown in Table 4. HTX-011 (60 mg/1.8 mg) statistically significantly reduced the mean AUC_{0-72} of the NRS-A PI scores compared with placebo (p-value < 0.0001) and bupivacaine (p-value = 0.0002).

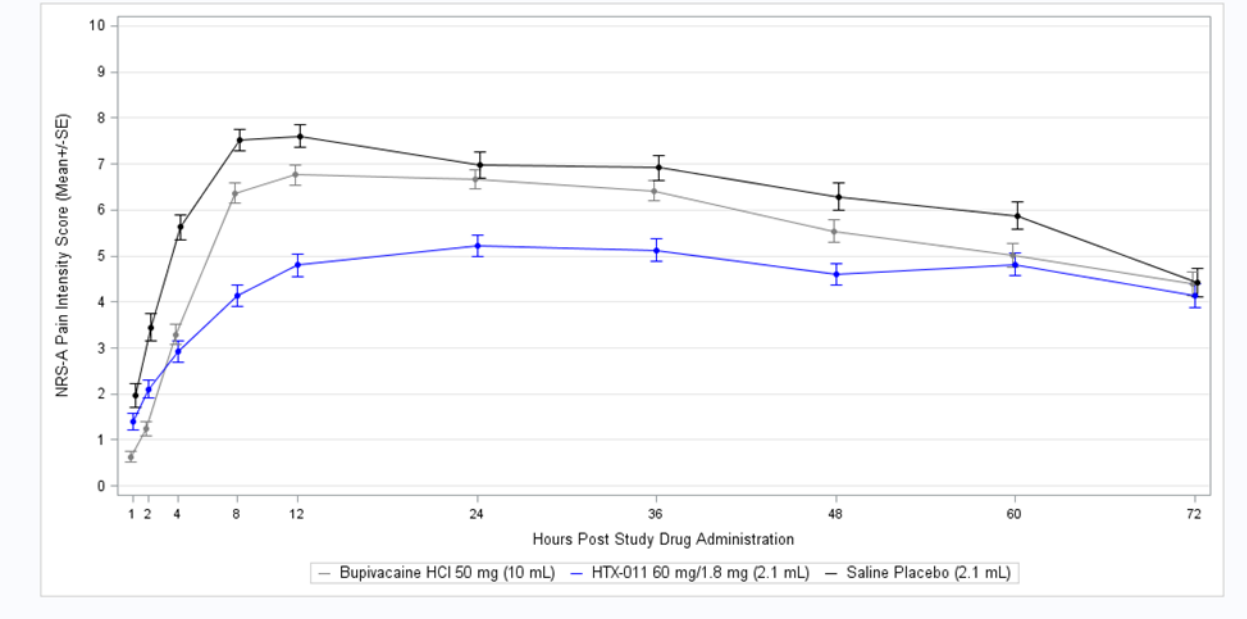
Table 3: Analgesic Windows for Opioid Rescue Medication

Medication	Route	Window (hr)
CODEINE	PO	6
DILAUDID	PO	4
DILAUDID	IV	4
FENTANYL	IV	1
HYDROCODONE	PO	6
MORPHINE	IV	4
MORPHINE	PO	4
MORPHINE	IM	4
MORPHINE	PR	4
OXYCODONE	IV	4
OXYCODONE	IM	4
OXYCODONE	PO	6

SUFENTANIL	PO	2
TRAMADOL	IV	6
TRAMADOL	PO	6

Source: Statistical Analysis Plan (SAP) V1, Table 2.
hr: hours; IM: intramuscular; IV: intravenous; PO: by mouth (orally); PR: per rectum

Figure 1: Mean NRS-A PI Scores over Time (wWOCF for opioid rescue use), Study HTX-011-301



Source: Reviewer's analyses.

Table 4: Analyses of Primary and 1st Key Secondary Endpoint, Study HTX-011-301

AUC_{0-72} of the NRS-A PI Scores (wWOCF for opioid rescue use)	**HTX-011 60 mg/1.8 mg**	**Saline Placebo**	**Bupivacaine Hcl 50 mg**
N	157	100	155
Mean (SD)	323.29 (182.64)	444.70 (155.81)	393.45 (153.76)
LSMD (SE) vs saline placebo	-121.41 (21.22)		
95% CI	(-163.12, -79.70)		
p-value vs saline placebo	< 0.0001		
LSMD (SE) vs bupivacaine Hcl	-70.16 (18.78)		
95% CI	(-107.07, -33.25)		
p-value vs bupivacaine Hcl	0.0002		

Source: Reviewer's analyses. LSMD: least square mean difference; SD: standard deviation; SE: standard error. CI: confidence interval.

Subjects with inadequate pain control following randomization were allowed to use non-opioid rescue analgesia in the study (acetaminophen (≤1000 mg) in a 6-hour period). During the first 72 hours, there were 31 subjects (20%) in the HTX-011 group, 13 subjects (8%) in the bupivacaine group and one subject (1%) in the placebo group that only used non-opioid rescue medication (Table 5). To account for the non-opioid rescue use in the study, sensitivity analyses were conducted where PI scores observed after each use of rescue medication (including both opioid and non-opioid rescue medication) were handled by the wWOCF method. Two analgesic windows were applied respectively for non-opioid rescue medication. Table 6 and Figure 2 list

the results of mean AUC_{0-72} and pain curves of NRS-A PI scores where the 6-hour analgesic window was utilized. Table 7 and Figure 3 list the results of mean AUC_{0-72} and pain curves of NRS-A PI scores where the 4-hour analgesic window was utilized. Both sensitivity analyses confirmed the robustness of the primary analyses results that HTX-011 (60 mg/1.8 mg) statistically significantly reduced PI scores compared to placebo and bupivacaine.

Table 5: Incidence of Rescue Medication Use Through 72 hours, Study HTX-011-301

Subjects who received rescue medication	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=100)	Bupivacaine Hcl 50 mg (N=155)
Any rescue medication	141 (91%)	99 (99%)	151 (97%)
Any opioid rescue medication	112 (71%)	98 (98%)	138 (89%)
Only non-opioid rescue medication	31 (20%)	1 (1%)	13 (8%)

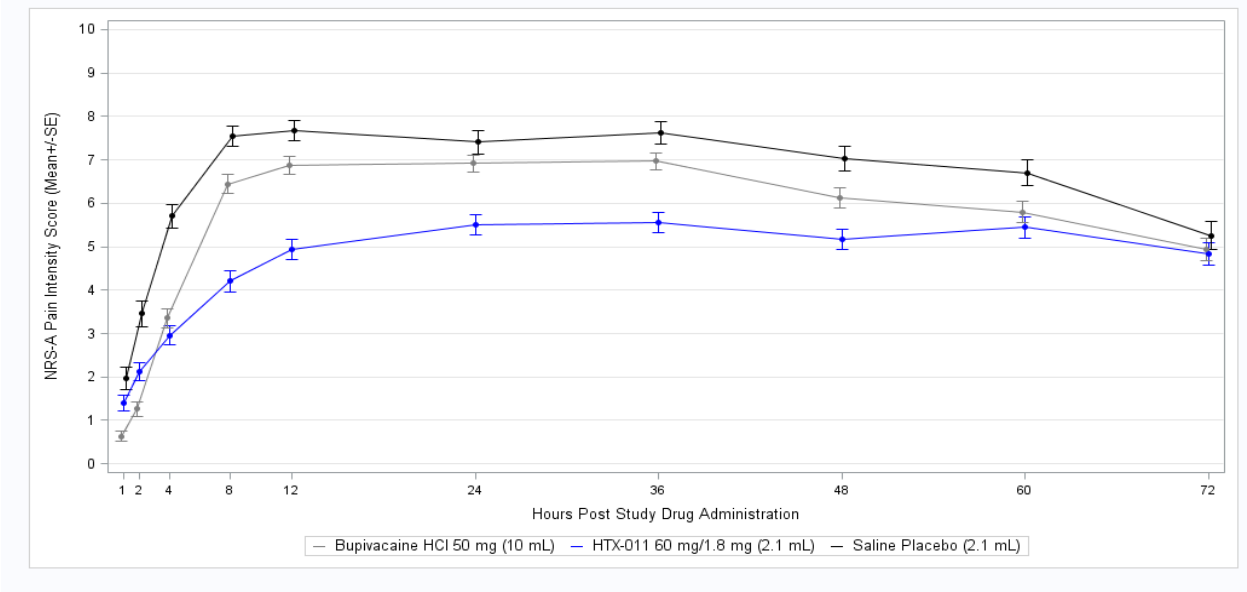
Source: Clinical study report (CSR) Table 19.

Table 6: Sensitivity Analyses of Primary and 1st Key Secondary Endpoint, Study HTX-011-301

AUC_{0-72} of the NRS-A PI scores (wWOCF for opioid and non-opioid (6-hour window) rescue use)	HTX-011 60 mg/1.8 mg	Saline Placebo	Bupivacaine Hcl 50 mg
N	157	100	155
Mean (SD)	351.36 (183.95)	482.48 (158.96)	423.22 (148.89)
LSMD (SE) vs saline placebo	-131.12 (21.17)		
95% CI	(-172.73, -89.51)		
p-value vs saline placebo	< 0.0001		
LSMD (SE) vs bupivacaine Hcl	-71.86 (18.73)		
95% CI	(-108.69, -35.04)		
p-value vs bupivacaine Hcl	0.0001		

Source: Reviewer's analyses. LSMD: least square mean difference; SD: standard deviation; SE: standard error. CI: confidence interval.

Figure 2: Mean NRS-A PI Scores over Time, Study HTX-011-301 (wWOCF for opioid and non-opioid (6-hour window) rescue use, ITT population)



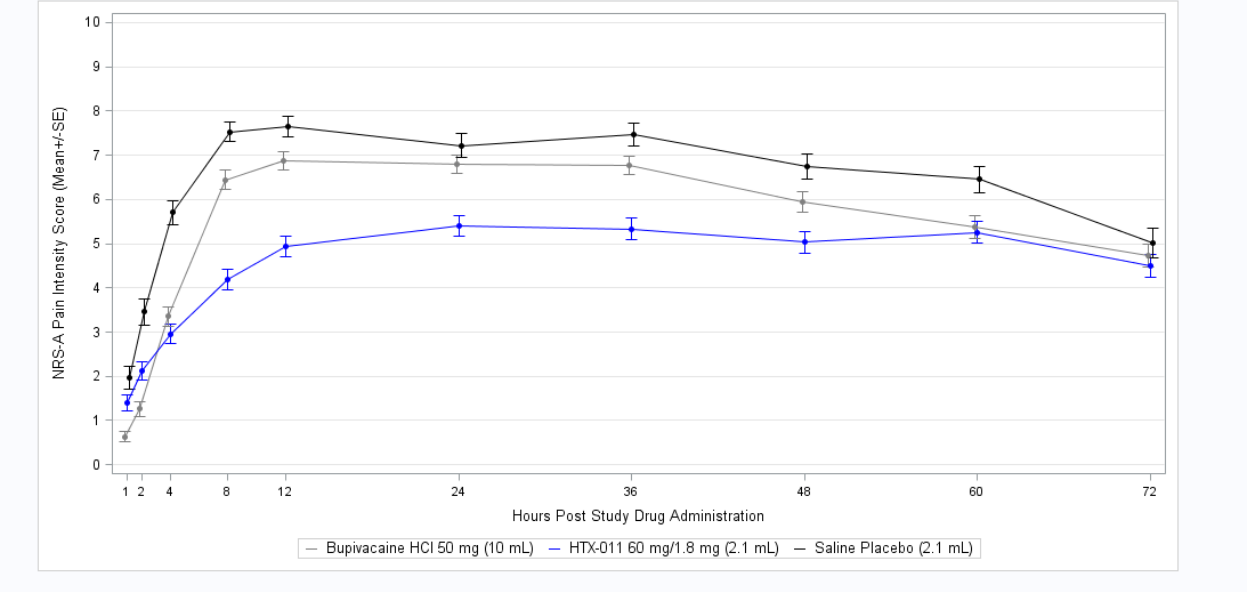
Source: Reviewer's analyses.

Table 7: Sensitivity Analyses of Primary and 1st Key Secondary Endpoint, Study HTX-011-301

AUC_{0-72} of the NRS-A PI scores (wWOCF for opioid and non-opioid (4-hour window) rescue use)	**HTX-011 60 mg/1.8 mg**	**Saline Placebo**	**Bupivacaine Hcl 50 mg**
N	157	100	155
Mean (SD)	341.43 (182.71)	470.31 (157.27)	411.34 (149.32)
LSMD (SE) vs saline placebo	-128.89 (21.07)		
95% CI	(-170.30, -87.47)		
p-value vs saline placebo	< 0.0001		
LSMD (SE) vs bupivacaine Hcl	-69.91 (18.65)		
95% CI	(-106.56, -33.26)		
p-value vs bupivacaine Hcl	0.0002		

Source: Reviewer's analyses. LSMD: least square mean difference; SD: standard deviation; SE: standard error. CI: confidence interval.

Figure 3: Mean NRS-A PI Scores over Time, Study HTX-011-301 (wWOCF for opioid and non-opioid (4-hour window) rescue use, ITT population)



Source: Reviewer's analyses.

Sensitivity analyses were also conducted on the primary and the 1st key secondary endpoints by using observed pain scores after rescue use. Even though this may reduce the treatment effect, HTX-011 was still statistically significantly better than placebo and bupivacaine (Table 8 and Figure 4).

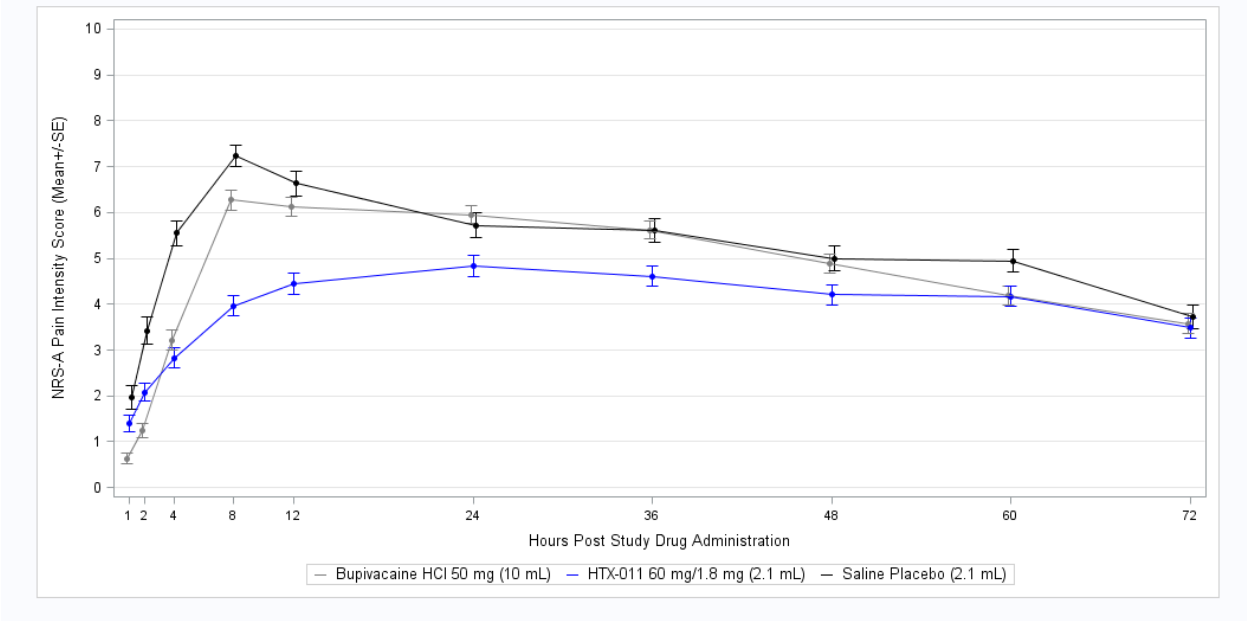
Table 8: Sensitivity Analyses of Primary and 1st Key Secondary Endpoint, Study HTX-011-301

AUC_{0-72} of the NRS-A PI scores (no adjusting for rescue use)	**HTX-011 60 mg/1.8 mg**	**Saline Placebo**	**Bupivacaine Hcl 50 mg**
N	157	100	155
Mean (SD)	291.20 (167.44)	363.36 (143.14)	341.07 (136.76)
LSMD (SE) vs saline placebo	-72.16 (19.27)		
95% CI	(-110.05, -34.27)		

p-value vs saline placebo	0.0002
LSMD (SE) vs bupivacaine Hcl	-49.88 (17.06)
95% CI	(-83.41, -16.35)
p-value vs bupivacaine Hcl	0.0036

Source: Reviewer's analyses. LSMD: least square mean difference; SD: standard deviation; SE: standard error. CI: confidence interval.

Figure 4: Mean NRS-A PI Scores over Time, Study HTX-011-301 (no adjusting for rescue use, ITT population)



Source: Reviewer's analyses.

Opioid use during the 72-hour post-operative period was analyzed and results are listed in Table 9. Total opioid consumption through 72 hours was statistically significantly reduced in the HTX-011 group compared with saline placebo (the 2nd key secondary endpoint) and compared with bupivacaine (the 4th key secondary endpoint). The clinical relevance of this reduction is not clear. The proportion of subjects who did not require any opioid rescue medication during the first 72 hours was statistically significantly higher in the HTX-011 group compared with bupivacaine (the 3rd key secondary endpoint).

Table 9: Analyses of Other Key Secondary Endpoints, Study HTX-011-301

	Saline Placebo (N=100)	**Bupivacaine Hcl 50 mg (N=155)**	**HTX-011 60 mg/1.8 mg (N=157)**
Total Opioid Consumption 0-72 hours (MME)			
Mean (SD)	30.06 (21.02)	25.09 (21.55)	18.80 (19.80)
Median (Min, Max)	25.00 (0.0, 80.0)	17.50 (0.0, 92.5)	12.50 (0.0, 83.0)
2nd Key secondary endpoint:			
p-value vs saline placebo			<0.0001
4th Key secondary endpoint:			
p-value vs bupivacaine Hcl			0.0022

Opioid-free 0-72 hours			
n (%)	2 (2%)	17 (11%)	45 (29%)
p-value vs saline placebo			<0.0001
3rd Key secondary endpoint:			
p-value vs bupivacaine Hcl			0.0001

Source: Reviewer's analyses.

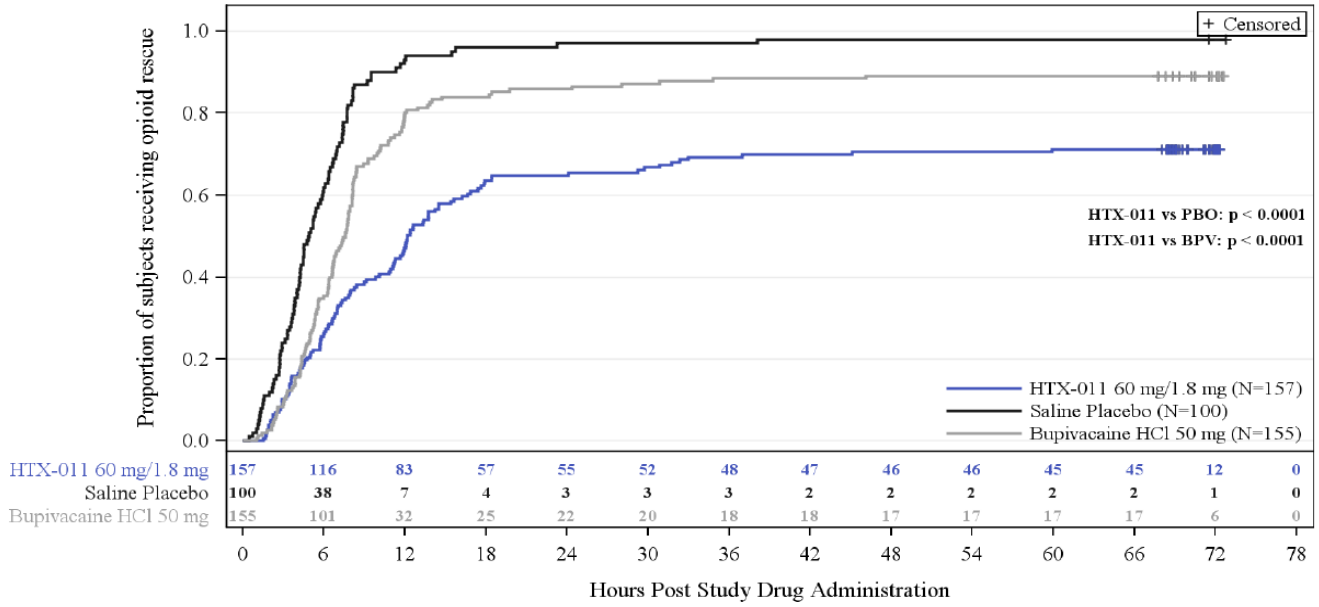
The KM estimates of time to the first opioid rescue medication are displayed in Figure 5. The median time to the first dose of opioid rescue medication during the 72-hour post-operative period was statistically significantly longer in the HTX-011 group compared with the saline placebo and bupivacaine group (Table 10).

Table 10: Time to the First Opioid Rescue Medication, Study HTX-011-301

Time to the first opioid rescue medication through 72 hours	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=100)	Bupivacaine Hcl 50 mg (N=155)
Median	12.18	4.90	7.60
95% CI	(10.95, 14.48)	(4.22, 5.87)	(6.63, 8.07)
Hazard Ratio (95% CI) vs Saline Placebo	0.29 (0.22, 0.39)		
p-value vs Saline Placebo	< 0.0001		
Hazard Ratio (95% CI) vs Bupivacaine Hcl	0.54 (0.42, 0.69)		
p-value vs Bupivacaine Hcl	< 0.0001		

Source: CSR Section 11.4.1.3.3, Table 14.2.4. CI: confidence interval.

Figure 5: Kaplan-Meier Plot of Time to the First Opioid Rescue Medication, Study HTX-011-301



Source: CSR Section 11.4.1.3.3, Figure 14.2.4.

The Silverman integrated assessment of NRS-A PI AUC scores and total opioid consumption was performed, and results are displayed in Table 11. The HTX-011 group had statistically

significantly less pain despite lower use of opioid rescue medication compared with the saline placebo and bupivacaine group through 72 hours.

Table 11: Silverman Integrated Rank Analysis, Study HTX-011-301

	HTX-011 60 mg/1.8 mg (N=157)	Saline Placebo (N=100)	Bupivacaine Hcl 50 mg (N=155)
Mean (SD)	-30.82 (106.59)	34.86 (87.65)	8.73 (97.95)
Median	-44.55	42.74	8.96
Min, Max	(-182.80, 186.40)	(-157.10, 191.30)	(-182.80, 171.40)
p-value vs Saline Placebo	< 0.0001		
p-value vs Bupivacaine Hcl	0.0008		

Source: CSR Section 11.4.1.4.1, Table 14.2.10. CI: confidence interval.

During the review process, we received an email from the applicant stating that study site 001 was closing due to financial instability. To assess the impact of this site on the overall efficacy results, I re-analyzed the primary and key secondary endpoints by excluding this site. As the results were still statistically significant, exclusion of the data from this site would not change the conclusions, there was a significant treatment effect noted for HTX-011.

3.2.2 Study HTX-011-302

3.2.2.1 Study Design and Endpoints

Study HTX-011-302 was a Phase 3, MC, R, DB, saline placebo- and active-controlled study in subjects following unilateral open inguinal herniorrhaphy. The study was conducted at 16 sites in the United States and one site in Belgium from July 2017 until January 2018. Study HTX-011-302 had a similar design to Study HTX-011-301, except that eligible subjects were randomized to one of the following three treatment groups in a 2:2:1 ratio: HTX-011 (300 mg/9 mg) via instillation into the surgical site; Bupivacaine HCl without epinephrine (0.25%, 75 mg) via injection into the surgical site; saline placebo via instillation into the surgical site.

The primary objective of the study was 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. The primary and secondary efficacy endpoints were same as those in Study HTX-011-301.

3.2.2.2 Statistical Methodologies

The statistical methods utilized to analyze the efficacy endpoints in Study HTX-011-301 are same as the methods used in Study HTX-011-302.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

The disposition of all randomized subjects is shown in Table 12. The ITT population included a total of 418 subjects and 413 subjects (99%) completed the 72-hour pain assessment. There were two subjects (1%) in the HTX-011 treatment group, two subjects (1%) in the bupivacaine group, and one subject (1%) in the placebo group who didn't complete the 72-hour pain assessment.

The demographic and other background characteristics for all subjects in the ITT population are presented in the appendix (Table 31). The majority of subjects (95%) were male, white (89%) and the mean age was 49 years. The overall mean BMI was 27.2 kg/m^2. The demographic and other background characteristics were comparable between the three treatment groups.

Table 12: Subject disposition in Study HTX-011-302 – Number (%) of Subjects

	Saline Placebo	Bupivacaine Hcl 75 mg	HTX-011 300mg/9 mg
Randomized	89	179	178
ITT population	82	172	164
Completed the 72-hour period	81 (99%)	170 (99%)	162 (99%)
Completed the study	81 (99%)	170 (99%)	159 (97%)
Reasons for study withdrawal			
Lost to follow-up			1 (1%)
Withdrawal by subject	1 (1%)	2 (1%)	3 (2%)
Protocol deviation			1 (1%)

Source: Reviewer's analyses.

3.2.2.4 Results and Conclusions

There were 164 subjects from the HTX-011 treatment group, 172 subjects from the bupivacaine group and 82 subjects from the placebo group included in the primary efficacy analysis. The applicant's analyses of the primary and the first key secondary endpoint where PI scores observed after each use of opioid rescue medication were handled by the wWOCF method were reproducible. The analgesic windows for all opioid rescue medication were the same as those applied in Study HTX-011-301. The mean NRS-A PI scores over the 72-hour post-operative period for each treatment group are displayed in Figure 6. At all timepoints through 72 hours, the mean NRS-A PI scores were lower in the HTX-011 group compared with the saline placebo group. The mean NRS-A PI scores were also lower in the HTX-011 group compared with the bupivacaine group over 72 hours, with the exception of the first 2 hours after study drug administration. Results of mean AUC_{0-72} of NRS-A PI scores are shown in Table 13. HTX-011 (300 mg/9 mg) statistically significantly reduced the mean AUC_{0-72} of the NRS-A PI scores compared with placebo (p-value = 0.0004) and bupivacaine (p-value < 0.0001).

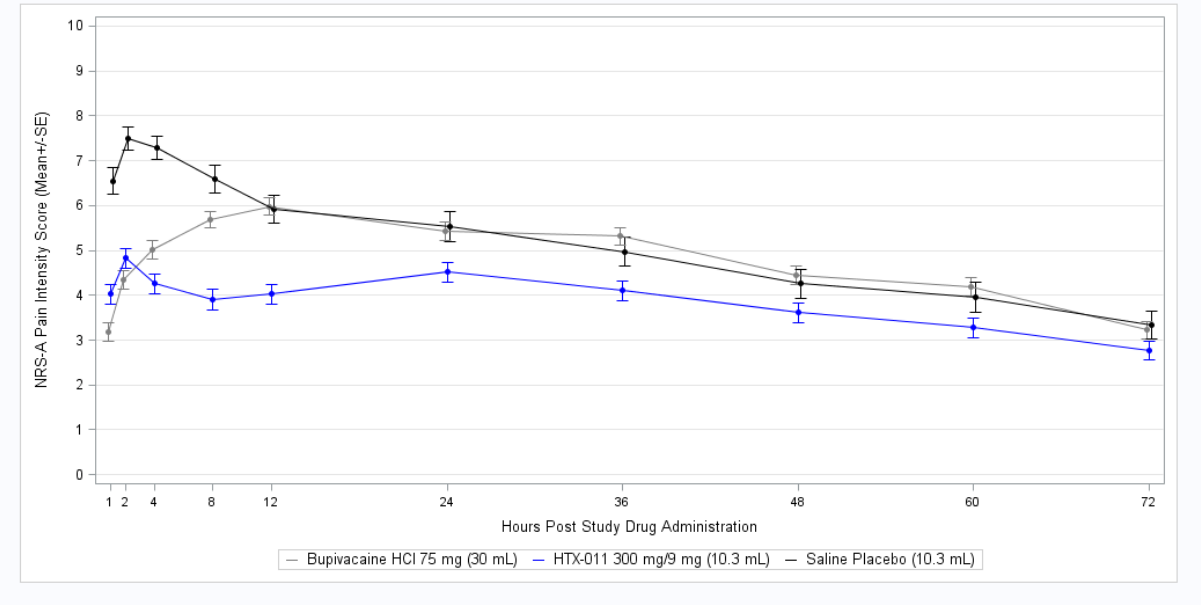
Table 13: Analyses of Primary and 1st Key Secondary Endpoint, Study HTX-011-302

AUC_{0-72} of the NRS-A PI Scores (wWOCF for opioid rescue use)	**HTX-011 300 mg/9 mg**	**Saline Placebo**	**Bupivacaine Hcl 75 mg**
N	164	82	172
Mean (SD)	268.72 (173.13)	349.83 (171.73)	341.14 (158.14)
LSMD (SE) vs saline placebo	-81.11 (22.59)		
95% CI	(-125.51, -36.71)		
p-value vs saline placebo	0.0004		
LSMD (SE) vs bupivacaine HCl	-72.43 (18.24)		

95% CI	(-108.27, -36.58)
p-value vs bupivacaine HCl	< 0.0001

Source: Reviewer's analyses. LSMD: least square mean difference; SD: standard deviation; SE: standard error. CI: confidence interval.

Figure 6: Mean NRS-A PI Scores over Time (wWOCF for opioid rescue use), Study HTX-011-302



Source: Reviewer's analyses.

Similar to Study HTX-011-301, subjects with inadequate pain control following randomization were allowed to use non-opioid rescue analgesia in the study (acetaminophen (≤1000 mg) in a 6-hour period). During the first 72 hours, there were 29 subjects (18%) in the HTX-011 group, 35 subjects (20%) in the bupivacaine group and 10 subjects (12%) in the placebo group that only used non-opioid rescue medication (Table 14). To account for the non-opioid rescue use in the study, sensitivity analyses were conducted where PI scores observed after each use of all rescue medication (including both opioid and non-opioid rescue medication) were handled by the wWOCF method. Two analgesic windows were applied respectively for non-opioid rescue medication. Table 15 and Figure 7 list the results of mean AUC_{0-72} and pain curves of NRS-A PI scores where the 6-hour analgesic window was utilized. Table 16 and Figure 8 list the results of mean AUC_{0-72} and pain curves of NRS-A PI scores where the 4-hour analgesic window was utilized. Both sensitivity analyses confirmed the primary analyses, HTX-011 (300 mg/9 mg) statistically significantly reduced PI scores compared to placebo and bupivacaine.

Table 14: Incidence of Rescue Medication Use Through 72 hours, Study HTX-011-302

Subjects who received rescue medication	HTX-011 300 mg/9 mg (N=164)	Saline Placebo (N=82)	Bupivacaine Hcl 75 mg (N=172)
Any rescue medication	109 (67%)	74 (90%)	138 (80%)
Any opioid rescue medication	80 (49%)	64 (78%)	103 (60%)
Only non-opioid rescue medication	29 (18%)	10 (12%)	35 (20%)

Source: CSR Table 19.

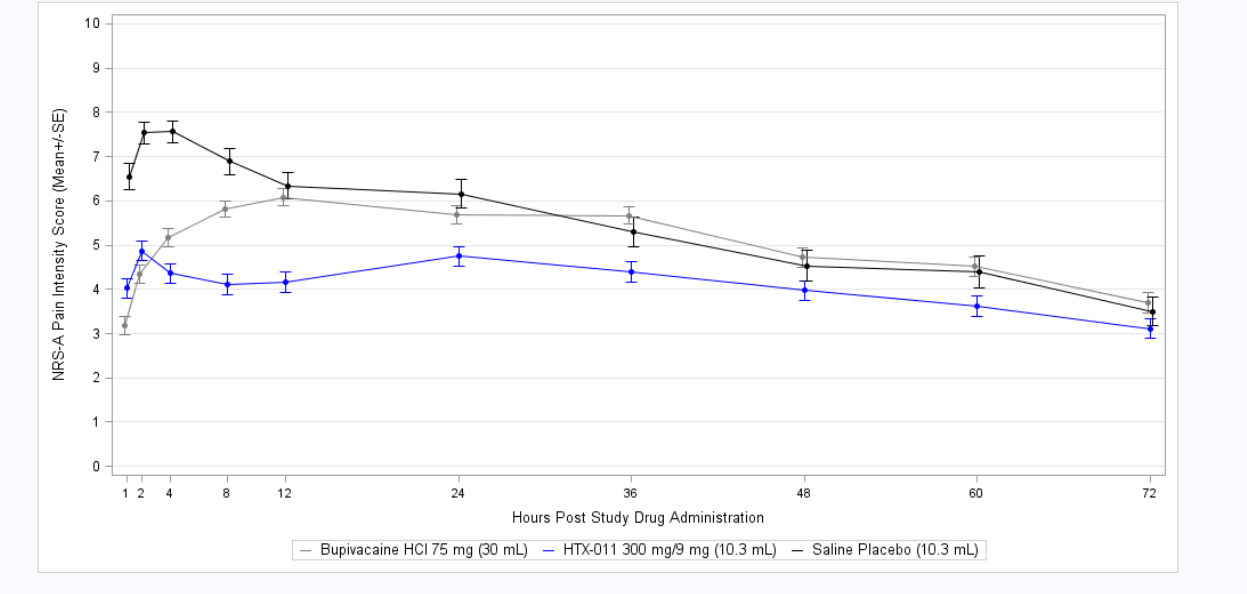
Table 15: Sensitivity Analyses of Primary and 1st Key Secondary Endpoint, Study HTX-011-302

AUC_{0-72} of the NRS-A PI scores (wWOCF for opioid and non-opioid	HTX-011	Bupivacaine Hcl

(6-hour window) rescue use)	300 mg/9 mg	Saline Placebo	75 mg
N	164	82	172
Mean (SD)	287.66 (175.56)	375.86 (170.03)	360.09 (161.95)
LSMD (SE) vs saline placebo	-88.20 (22.88)		
95% CI	(-133.16, -43.23)		
p-value vs saline placebo	0.0001		
LSMD (SE) vs bupivacaine HCl	-72.43 (18.47)		
95% CI	(-108.73, -36.12)		
p-value vs bupivacaine HCl	0.0001		

Source: Reviewer's analyses. LSMD: least square mean difference; SD: standard deviation; SE: standard error. CI: confidence interval.

Figure 7: Mean NRS-A PI Scores over Time, Study HTX-011-302 (wWOCF for opioid and non-opioid (6-hour window) rescue use, ITT population)



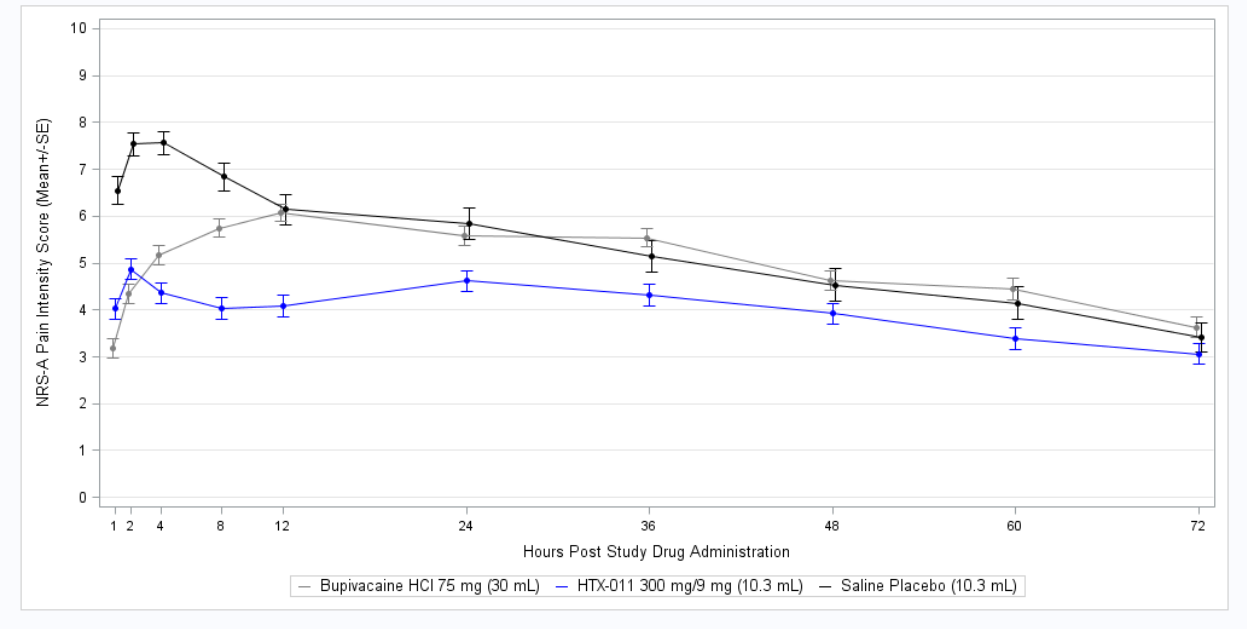
Source: Reviewer's analyses.

Table 16: Sensitivity Analyses of Primary and 1st Key Secondary Endpoint, Study HTX-011-302

AUC_{0-72} of the NRS-A PI scores (wWOCF for opioid and non-opioid (4-hour window) rescue use)	HTX-011 300 mg/9 mg	Saline Placebo	Bupivacaine Hcl 75 mg
N	164	82	172
Mean (SD)	280.50 (173.21)	365.13 (170.03)	354.77 (160.87)
LSMD (SE) vs saline placebo	-84.63 (22.69)		
95% CI	(-129.24, -40.03)		
p-value vs saline placebo	0.0002		
LSMD (SE) vs bupivacaine HCl	-74.28 (18.32)		
95% CI	(-110.29, -38.27)		
p-value vs bupivacaine HCl	< 0.0001		

Source: Reviewer's analyses. LSMD: least square mean difference; SD: standard deviation; SE: standard error. CI: confidence interval.

Figure 8: Mean NRS-A PI Scores over Time, Study HTX-011-302
(wWOCF for opioid and non-opioid (4-hour window) rescue use, ITT population)



Source: Reviewer's analyses.

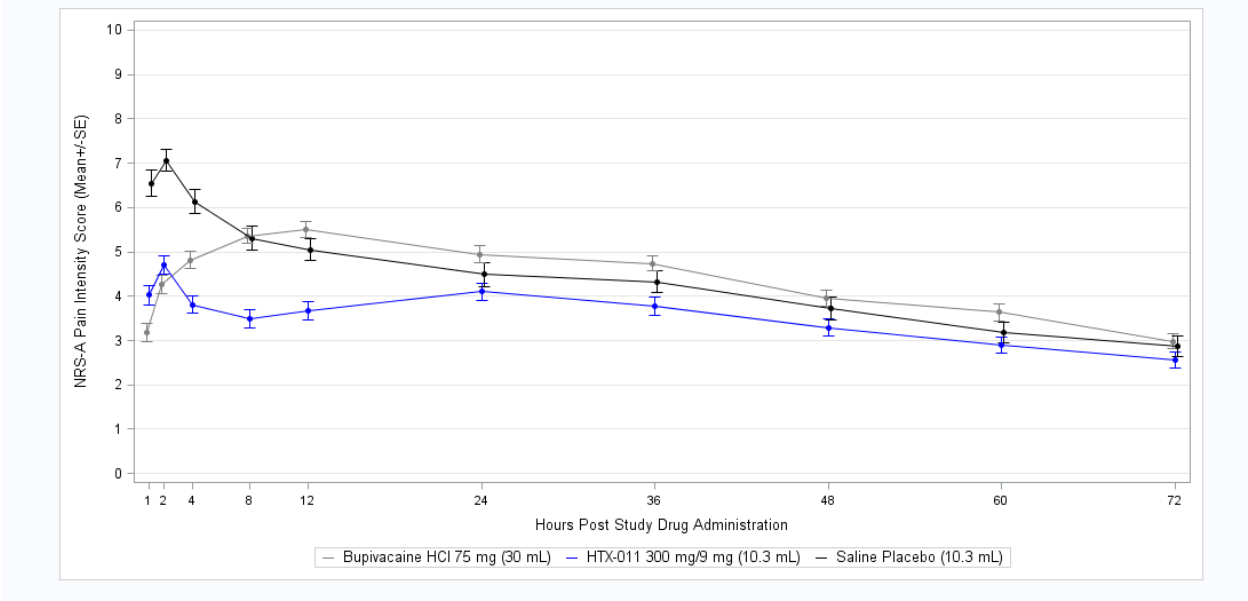
Similar to Study HTX-011-301, sensitivity analyses were also conducted on the primary and the 1st key secondary endpoints by using observed pain scores after rescue use. Even though this may reduce the treatment effect, HTX-011 was still statistically significantly better than placebo and bupivacaine (Table 17 and Figure 9).

Table 17: Sensitivity Analyses of Primary and 1st Key Secondary Endpoint, Study HTX-011-302

AUC_{0-72} of the NRS-A PI scores (no adjusting for rescue use)	**HTX-011 300 mg/9 mg**	**Saline Placebo**	**Bupivacaine Hcl 75 mg**
N	164	82	172
Mean (SD)	236.49 (151.22)	279.60 (137.70)	295.72 (137.98)
LSMD (SE) vs saline placebo	-43.11 (19.40)		
95% CI	(-81.23, -4.98)		
p-value vs saline placebo	0.0268		
LSMD (SE) vs bupivacaine HCl	-59.23 (15.66)		
95% CI	(-90.02, -28.45)		
p-value vs bupivacaine HCl	0.0002		

Source: Reviewer's analyses. LSMD: least square mean difference; SD: standard deviation; SE: standard error. CI: confidence interval.

Figure 9: Mean NRS-A PI Scores over Time, Study HTX-011-302
(no adjusting for rescue use, ITT population)



Source: Reviewer's analyses.

Similar to Study HTX-011-301, opioid use during the 72-hour post-operative period was also analyzed and results are listed in Table 18. Total opioid consumption through 72 hours was statistically significantly reduced in the HTX-011 group compared with saline placebo (the 2nd key secondary endpoint) and compared with bupivacaine (the 4th key secondary endpoint). Again, the clinical relevance of this reduction is not clear. The proportion of subjects who did not require any opioid rescue medication during the first 72 hours was statistically significantly higher in the HTX-011 group compared with bupivacaine (the 3rd key secondary endpoint).

Table 18: Analyses of Other Key Secondary Endpoints, Study HTX-011-302

	Saline Placebo (N=82)	Bupivacaine Hcl 75 mg (N=172)	HTX-011 300 mg/9 mg (N=164)
Total Opioid Consumption 0-72 hours (MME)			
Mean (SD)	17.53 (18.91)	14.51 (18.19)	10.85 (17.06)
Median (Min, Max)	11.25 (0.0, 73.5)	7.25 (0.0, 87.5)	0.0 (0.0, 103.0)
2nd Key secondary endpoint:			
p-value vs saline placebo			0.0001
4th Key secondary endpoint:			
p-value vs bupivacaine Hcl			0.0240
Opioid-free 0-72 hours			
n (%)	18 (22%)	69 (40%)	84 (51%)
p-value vs saline placebo			<0.0001
3rd Key secondary endpoint:			
p-value vs bupivacaine Hcl			0.0486

Source: Reviewer's analyses.

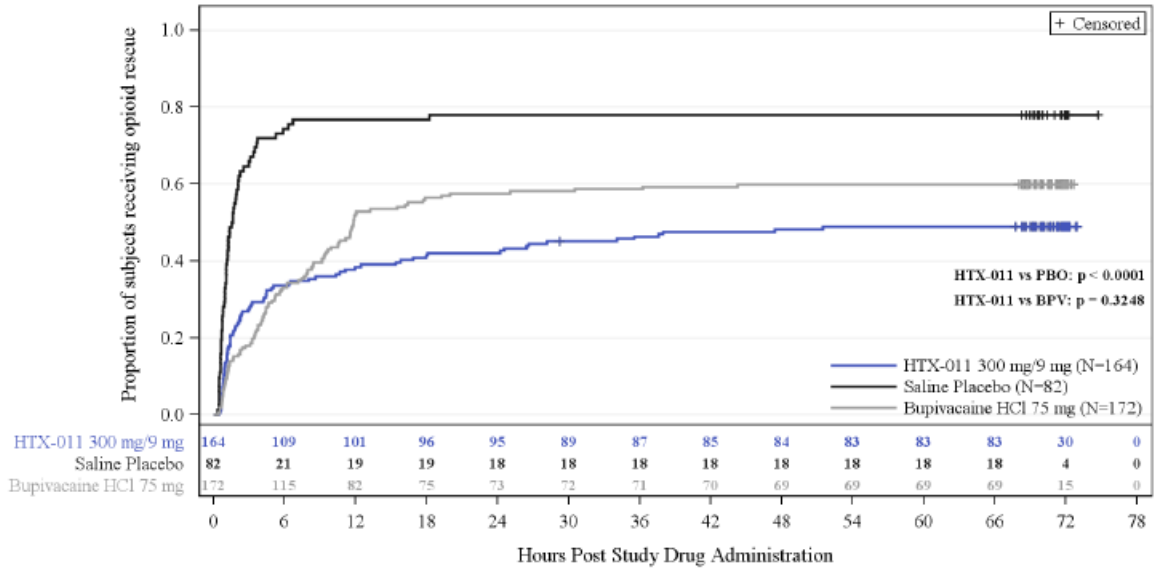
The KM estimates of time to the first opioid rescue medication are displayed in Figure 10. As over 50% of subjects in the HTX-011 group did not use opioid rescue medication during the 72-hour post-operative period, the median time to the first opioid rescue use was not evaluable for the HTX-011 group. The median time to the first opioid rescue medication was 1.57 hours in the saline placebo group and 11.82 hours for the bupivacaine group (Table 19).

Table 19: Time to the First Opioid Rescue Medication, Study HTX-011-302

Time to the first opioid rescue medication through 72 hours	HTX-011 300 mg/9 mg (N=164)	Saline Placebo (N=82)	Bupivacaine Hcl 75 mg (N=172)
Median	NE	1.57	11.82
95% CI	(18.08, NE)	(1.08, 2.10)	(9.48, 19.98)
Hazard Ratio (95% CI) vs. Saline Placebo	0.38 (0.27, 0.53)		
p-value vs Saline Placebo	< 0.0001		
Hazard Ratio (95% CI) vs. Bupivacaine Hcl	0.79 (0.59, 1.06)		
p-value vs Bupivacaine Hcl	0.3248		

Source: CSR Section 11.4.1.3.3, Table 14.2.4. CI: confidence interval. NE: not evaluable.

Figure 10: Kaplan-Meier Plot of Time to the First Opioid Rescue Medication, Study HTX-011-302



Source: CSR Section 11.4.1.3.3, Figure 14.2.4.

As done with Study HTX-011-301, the Silverman integrated assessment of NRS-A PI AUC scores and total opioid consumption was performed. Results are displayed in Table 20. The HTX-011 group had statistically significantly less pain despite lower use of opioid rescue medication compared with the saline placebo and bupivacaine group through 72 hours.

Table 20: Silverman Integrated Rank Analysis, Study HTX-011-302

	HTX-011 300 mg/9 mg (N=164)	Saline Placebo (N=82)	Bupivacaine Hcl 75 mg (N=172)
Mean (SD)	-26.12 (103.91)	22.72 (94.94)	14.08 (98.57)
Median	-52.74	17.90	7.88
Min, Max	(-158.0, 183.80)	(-152.70, 177.60)	(-156.60, 188.10)

p-value vs Saline Placebo	0.0002
p-value vs Bupivacaine Hcl	0.0001

Source: CSR Section 11.4.1.3.3, Table 14.2.4. CI: confidence interval.

Similar to Study HTX-011-301, I re-analyzed all primary and key secondary endpoints by excluding site 001 which was closing due to financial instability. All re-analysis results reached statistical significance, except that there was no statistical significance in the proportion of opioid-free subjects during the first 72 hours between HTX-011 and bupivacaine (p-value = 0.0717). However, as site 001 had the most enrollment (19% of the ITT population), excluding it would decrease the power of the statistical test. Moreover, the proportion of opioid-free subjects was numerically higher in the HTX-011 group (55%) compared with the bupivacaine group (44%). Therefore, in my opinion, the exclusion of the data from site 001 would not change the overall conclusions.

3.2.3 Study HTX-011-209

3.2.3.1 Study Design and Endpoints

Study HTX-011-209 was a Phase 2b, R, DB, MC, placebo- and active-controlled study. The study was designed to compare the efficacy and duration of analgesia following periarticular infiltration of HTX-011 with that of placebo in subjects undergoing primary unilateral total knee arthroplasty. The study included two cohorts where Cohort 1 was a dose-finding cohort, and Cohort 2 was an adequate and well-controlled cohort. The review will focus on Cohort 2.

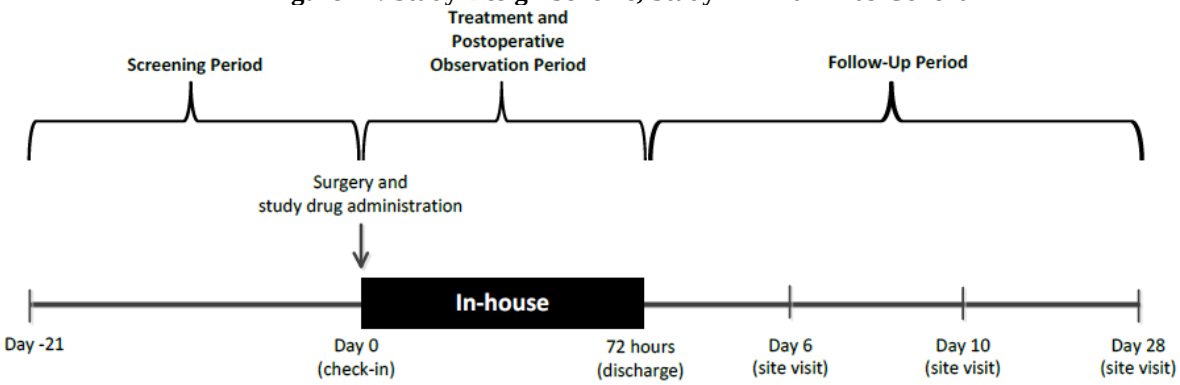
The study design scheme for Cohort 2 is presented in Figure 11. Subjects were screened within 21 days prior to surgery. On the day of surgery (Day 0), a single dose of study drug was administered into the surgical site and the start of study drug administration was considered Time 0. Eligible subjects were randomized equally to one of the following four treatment groups:

- HTX-011, 400 mg/12 mg (bupivacaine/meloxicam doses), 13.7 mL, via periarticular instillation into the surgical site
- HTX-011, 400 mg/12 mg (bupivacaine/meloxicam doses), 13.7 mL, via periarticular instillation into the surgical site and ropivacaine 0.5% (50 mg, 10 mL) via periarticular injection into the surgical site (posterior capsule)
- Saline placebo, 13.7 mL, via periarticular injection into the surgical site
- Bupivacaine HCl without epinephrine 0.25%, 125 mg (50 mL), via periarticular injection into the surgical site

A low-dose ropivacaine (50 mg) was injected into the posterior capsule in one of the two HTX-011 groups to evaluate if administration of local anesthetic can contribute to the treatment of postoperative pain. Subjects undergoing surgery remained in the hospital for a minimum of 72 hours after the start of study drug administration to evaluate postoperative assessments. PI scores were assessed at baseline (before surgery) and at 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours after surgery using an 11-point NRS. During the 72-hour postoperative period, subjects with inadequately controlled pain could request only opioid rescue medication as needed. The rescue medication consisted of IV morphine (up to 10 mg within a 2-hour period) and/or oral immediate-release oxycodone (up to 10 mg within a 4-hour period). After 72 hours, subjects

could be discharged and the rescue analgesic regimen could be adjusted individually by the physician.

Figure 11: Study Design Scheme, Study HTX-011-209 Cohort 2



Source: Study HTX-011-209 CSR Figure 1

The applicant's primary efficacy endpoint was the mean AUC_{0-48} of the NRS-R (assessed while the subject was either seated comfortably or lying down) PI scores. The applicant's key secondary efficacy endpoint was mean AUC_{0-72} of the NRS-R PI scores. Additional secondary endpoints were also explored. These included:

- Mean total postoperative opioid consumption (in morphine equivalents) through 24, 48, and 72 hours
- Median time in hours to first opioid rescue administration
- Proportion of subjects who are opioid-free through 24, 48, and 72 hours.

3.2.3.2 Statistical Methodologies

A total sample size of 200 patients was planned to provide 90% power to detect a mean difference of 60 and standard deviation of 90 in AUC_{0-48} between placebo and HTX-011 groups with a 2-sided test at the significance level of 0.05.

All the efficacy analyses were performed using the intent-to-treat (ITT) population which included all randomized patients who received study drug. The primary and key secondary efficacy endpoints were calculated using the trapezoidal rule and were analyzed using an ANOVA model with treatment as the main effect. For additional secondary endpoints, postoperative opioid consumption through 24, 48, and 72 hours was analyzed using a Wilcoxon rank sum test because the assumption of normality was not met; proportion of subjects who were opioid-free through 24, 48, and 72 hours was analyzed using Fisher's exact test; time to first opioid rescue administration was analyzed through 72 hours and treatment comparisons were performed using Wilcoxon test. Subjects who completed 72 hours without taking rescue medication or who withdrew from the study during the 72 hours had their times censored.

A strict hierarchical testing procedure was applied for multiple treatment comparisons to control the overall alpha level at 0.05 in the following order:

1. Mean AUC_{0-48} of the NRS-R pain intensity scores for HTX-011 and ropivacaine compared with saline placebo
2. Mean AUC_{0-48} of the NRS-R pain intensity scores for HTX-011 compared with saline placebo
3. Mean AUC_{0-72} of the NRS-R pain intensity scores for HTX-011 and ropivacaine compared with saline placebo
4. Mean AUC_{0-72} of the NRS-R pain intensity scores for HTX-011 compared with saline placebo

If the first treatment comparison was statistically significant, then the second treatment comparison was tested. Sequential testing continued in this manner down the hierarchical order until a treatment comparison failed to meet statistical significance. All subsequently non-significant treatment comparisons were considered exploratory.

Any missing pain intensity scores were imputed using LOCF. For subjects who had no post-dose value available prior to the first missing value, the median of observed values in the same treatment group at that timepoint was used. Following LOCF, the same wWOCF method as the primary analysis in the Phase 3 studies was used to replace the PI scores observed during the analgesic window of any opioid rescue medication. This method was used in the primary analysis for both primary and key secondary endpoints. As stated early, we do not recommend single imputation methods. But as there were very little missing data (<2%), handling of missing data was not a concern. Sensitivity analysis was performed on the primary and key secondary endpoints using LOCF only. The Silverman integrated analysis was performed on AUC (0-48 and 0-72 hours) of NRS-R scores and total opioid consumption while missing pain scores were imputed using LOCF.

3.2.3.3 Patient Disposition, Demographic and Baseline Characteristics

A summary of patient disposition is presented in Table 21. A total of 232 subjects (222 subjects in ITT population) were randomized. Ten withdrew prior to dosing including eight screening failures and two withdrawals for other seasons. Therefore, the remaining 222 subjects were randomized and received study drug. There were very few (< 2%) missing data overall. Four subjects withdrew from the study prior to Day 28. However, we still had the efficacy data. Three withdrew due to adverse event and the other subject withdrew consent.

Demographics and baseline characteristics are presented in the appendix (Table 32). Approximately half of the subjects were female (51%) and the majority were white (87%). The mean age was 62 years. The overall mean BMI was 32 kg/m^2. The demographics and baseline characteristics were comparable between treatment groups.

Table 21: Patient Disposition, Study HTX-011-209

	Saline Placebo n (%)	Bupivacaine HCl 125 mg n (%)	HTX-011 400 mg/12 mg n (%)	HTX-011 400 mg/12 mg + low-dose ropivacaine n (%)
Randomized	57	58	58	59
ITT Population	53	55	58	56
Completed the 72-hour Period[a, b]	50 (94.3%)	55 (100%)	58 (100%)	53 (94.6%)
Completed the Study[a, c]	51 (96.2%)	55 (100%)	58 (100%)	54 (96.4%)
Reasons for Study Withdrawal[a]				
Adverse event	1 (1.9%)	0	0	2 (3.6%)
Withdrawal by subject	1 (1.9%)	0	0	0

Abbreviations: ITT, Intent-to-Treat.
Notes: HTX-011 (also referred to as HTX-011-56) is the intended commercial formulation. The ITT Population was defined as all subjects who were randomized and received study drug. Data presented are from the adequate and well controlled cohort (Cohort 2).
[a] The ITT Population was used as the denominator.
[b] Subjects who had a reported Numeric Rating Scale of pain intensity score at rest (NRS-R) at the nominal 72-hour postoperative timepoint were considered as completing the 72-hour postoperative observation period.
[c] Study completion was defined as completing the Day 28 Visit.
Source: SCE

3.2.3.4 Results and Conclusions

All efficacy analyses for this study were performed on the ITT population in Cohort 2.

The results from primary analysis are presented in Table 22. The results were consistent with the applicant's both the primary and key secondary endpoints. HTX-011 either with or without ropivacaine was statistically significantly superior (p-values < 0.001) to placebo with respect to AUC_{0-48} and AUC_{0-72}. Subjects who received HTX-011 with or without ropivacaine had less pain over the 48- and 72-hour postsurgical period compared with subjects who received placebo. Based on the combination rule and FDA's discussion with the applicant at the EOP2 meeting, the study is required to demonstrate the superiority of HTX-011 over bupivacaine in order to be included in the *Clinical Studies, Section 14* of the label. However, there was no meaningful difference between HTX-011 and bupivacaine groups with respect to AUC of NRS-R pain intensity scores from 0 through 48 and 72 hours.

Table 22: Primary Efficacy Analysis Using wWOCF, Study HTX-011-209

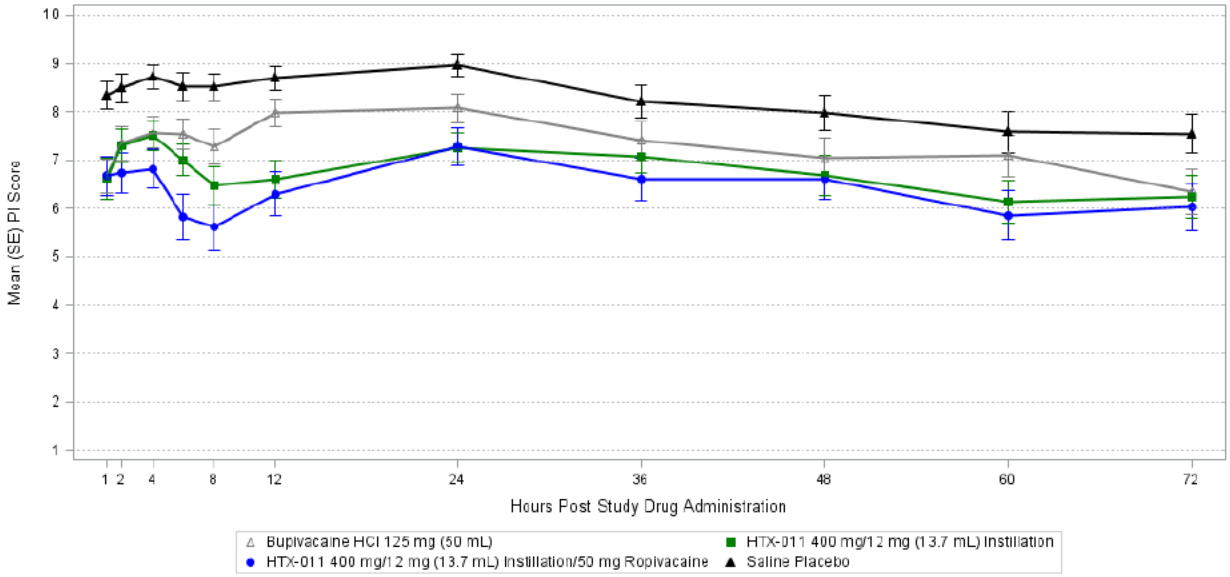
	HTX-011 400 mg/12 mg (N=58)	HTX-011 400 mg/12 mg + Ropivacaine (N=56)	Saline Placebo (N=53)	Bupivacaine HCl 125 mg (N=55)
AUC_{0-48} of NRS-R (Primary endpoint)				
Mean (SD)	322.08 (99.67)	307.25 (127.67)	396.36 (77.47)	352.74 (100.89)
LSMD (SE) vs PBO	-74.29 (19.62)	-89.11 (19.79)		
P-value vs PBO	0.0002	<0.0001		
LSMD (SE) vs BUPIV	-30.67 (19.44)	-45.50 (19.60)		

P-value vs BUPIV	0.1160	0.0212		
AUC_{0-72} of NRS-R (Key secondary endpoint)				
Mean (SD)	471.19 (149.44)	452.54 (194.10)	577.93 (125.10)	516.93 (152.51)
LSMD (SE) vs PBO	-106.73 (29.95)	-125.39 (30.20)		
P-value vs PBO	0.0004	<0.0001		
LSMD (SE) vs BUPIV	-45.73 (29.66)	-64.39 (29.92)		
P-value vs BUPIV	0.1246	0.0325		

Source: Reviewer's analyses

Figure 12 plots the mean (±SE) NRS-R pain intensity scores for all treatment groups over the 72-hour postoperative period. To adjust for the duration effect of rescue medication, pain scores observed during the rescue medication window were replaced using the wWOCF method as previously described. There was a clear separation of the pain curves between the HTX-011 groups and the placebo group over the entire time. However, the pain curves between HTX-011 and bupivacaine overlapped at many timepoints during the 72 hours.

Figure 12: Mean (SE) of NRS-R Pain Intensity Scores over 72 Hours Using wWOCF, Study HTX-011-209



Source: Reviewer's analyses

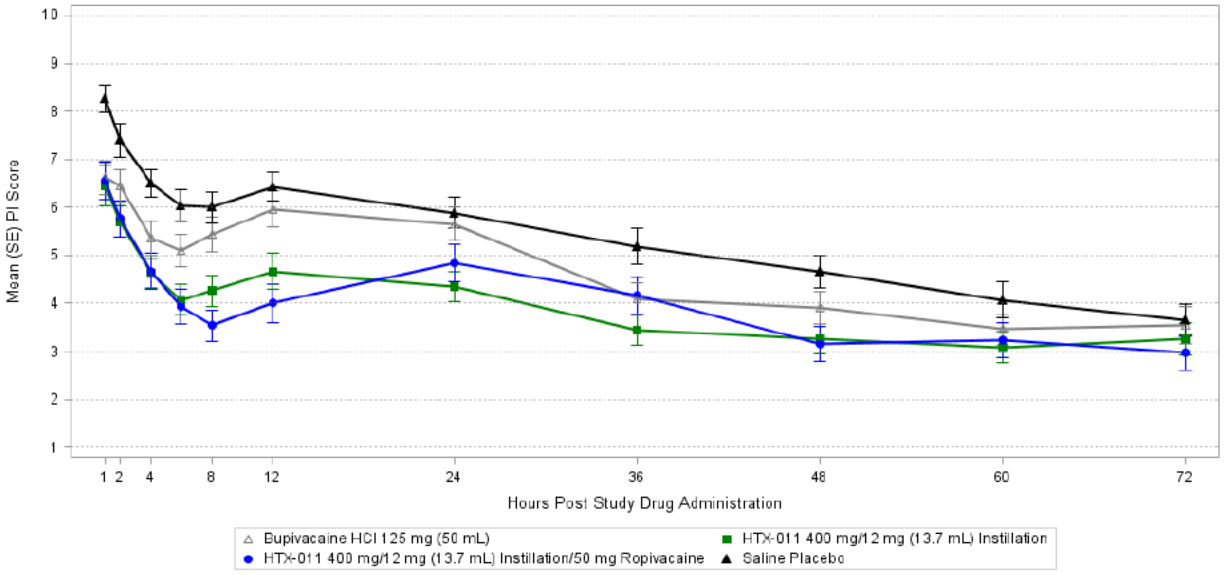
The results from sensitivity analyses on primary and key secondary endpoints are presented in Table 23. Without adjusting for use of rescue medication, the mean NRS-R PI scores decreased (approximately 100 in AUC_{0-48} and 200 in AUC_{0-72}) across all treatment groups compared with those from the primary analysis. While other results remained the same from the primary analysis, HTX-011 was now significantly superior (p-values < 0.05) to bupivacaine with respect to both endpoints. This was mainly attributed to high proportion of subjects who used opioid rescue medication in HTX-011 group. By taking into account the duration effect of opioid rescue medication, subjects who received HTX-011 with or without ropivacaine had less pain over the 48- or 72-hour postsurgical period compared with subjects who received placebo. Figure 13 illustrated the mean (±SE) NRS-R pain intensity scores over the 72-hour postoperative period from sensitivity analysis.

Table 23: Sensitivity Analysis Using LOCF, Study HTX-011-209

	HTX-011 400 mg/12 mg (N=58)	HTX-011 400 mg/12 mg + Ropivacaine (N=56)	Saline Placebo (N=53)	Bupivacaine HCl 125 mg (N=55)
AUC_{0-48} of NRS-R (Primary endpoint)				
Mean (SD)	188.91 (81.61)	194.54 (99.59)	267.28 (81.35)	233.72 (85.50)
LSMD (SE) vs PBO	-78.37 (16.60)	-72.74 (16.74)		
P-value vs PBO	<0.0001	<0.0001		
LSMD (SE) vs BUPIV	-44.81 (16.44)	-39.18 (16.59)		
P-value vs BUPIV	0.0070	0.0190		
AUC_{0-72} of NRS-R (Key secondary endpoint)				
Mean (SD)	264.56 (123.25)	269.51 (144.78)	365.41 (127.18)	319.58 (128.44)
LSMD (SE) vs PBO	-100.85 (24.93)	-95.90 (25.14)		
P-value vs PBO	<0.0001	0.0002		
LSMD (SE) vs BUPIV	-55.02 (24.69)	-50.07 (24.90)		
P-value vs BUPIV	0.0269	0.0456		

Source: Reviewer's analyses

Figure 13: Mean (SE) of NRS-R Pain Intensity Scores over 72 Hours Using LOCF, Study HTX-011-209



Source: Reviewer's analyses

To better evaluate the efficacy of HTX-011, the Silverman integrated analysis was performed on AUC (0-48 and 0-72 hours) of NRS-R scores and total opioid consumption. The highest score indicates the most pain despite the greatest use of opioid. Results in Table 24 showed that HTX-011 was statistically significant superior (p-values < 0.05) to saline placebo through 48 and 72 hours. However, by taking into account the use of opioid rescue analgesia, HTX-011 was not superior to bupivacaine through 72 hours.

Table 24: Silverman Integrated Rank Analysis Through 48 and 72 hours, Study HTX-011-209

	HTX-011 400 mg/12 mg	HTX-011 400 mg/12 mg	Saline Placebo (N=53)	Bupivacaine HCl 125 mg

	(N=58)	+ Ropivacaine (N=56)		(N=55)
0 – 48 Hours				
Mean (SD)	-25.68 (90.72)	-28.31 (106.20)	45.11 (92.81)	12.44 (97.16)
Median	-37.89	-27.35	47.98	8.97
Min, Max	-174, 186	-198, 167	-168, 187	-184, 166
P-value vs PBO	0.0001	0.0004		
P-value vs BUPIV	0.0284	0.0485		
0 – 72 Hours				
Mean (SD)	-19.97 (92.99)	-24.97 (110.68)	38.62 (91.78)	9.27 (96.90)
Median	-39.46	-25.34	35.43	-2.24
Min, Max	-169, 175	-198, 164	-170, 190	-184, 176
P-value vs PBO	0.0016	0.0024		
P-value vs BUPIV	0.0869	0.1106		

Source: Reviewer's analyses

Given that the study was designed to compare the efficacy and duration of analgesia, I also looked at the use of opioid rescue medication, including total postoperative opioid consumption up to 72 hours, time to first opioid rescue medication, and proportion of subjects who are opioid-free over time. Table 25 presents the total use of opioid rescue medication from 0 through 24, 48, and 72 hours in morphine milligram equivalency (MME).

Table 25: Total Use of Opioid Analgesia From 0 up to 72 Hours, Study HTX-011-209

	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: Study HTX-011-209 CSR Table 25

Median time to the first use of opioid rescue medication were 0.95, 1.04, 1.12, and 1.22 hours for subjects who received HTX-011, HTX-011 and ropivacaine, placebo, and bupivacaine, respectively. Surprisingly, subjects who received HTX-011 had a statistically significantly shorter time to use opioid analgesia compared with those who received placebo ($p = 0.021$) or bupivacaine ($p = 0.002$). There was no statistically significant difference between HTX-011 plus ropivacaine and placebo groups with respect to time to first use of opioid rescue medication.

In Cohort 2, 220 of the 222 treated subjects requested opioids within the first 24 hours after surgery. Only two subjects (one in HTX-011 with ropivacaine group and one in bupivacaine group) did not require any opioid rescue medication during the 24-hour postoperative period and remained opioid-free through 72 hours. Based on these results, Study HTX-011-209 failed to demonstrate a superiority of HTX-011 400 mg/12 mg over bupivacaine on both primary and key secondary endpoints during the 72-hour post-operative period in subjects undergoing TKA. Therefore, this study will not be included in the Clinical Studies, Section 14 of the label per the combination rule.

3.3 Evaluation of Safety

The safety database included all subjects in one Phase 1, three Phase 2a, two Phase 2b, two Phase 3 and 4-month safety studies. There was one death in the bupivacaine group and none in the study drug group. There were no serious adverse events (SAEs) associated with the study drug. The most commonly reported treatment emergent adverse events (TEAEs) for HTX-011 were nausea, constipation, dizziness, vomiting and headache. There did not appear to be a measurable increase in wound-related adverse events (AEs) after the treatment with HTX-011 in subjects undergoing bunionectomy. They were generally resolved by Day 42, mild in severity, and did not correlate with boney changes as assessed via post-operative x-rays. There was no apparent increase in cardiac conduction, disturbances or other signs/symptoms of local anesthetic systemic toxicity. There was also a trend in lower incidence of opioid related AEs. However, none of the trials that evaluated this drug were powered to specifically determine safety risk. The reader is referred to Dr. Renee Petit-Scott's review for detailed information regarding the adverse event profile.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

As Study HTX-011-209 failed to demonstrate a superiority of HTX-011 400 mg/12 mg over bupivacaine during the 72-hour postoperative period, subgroup analyses were only conducted in the two Phase 3 studies. Subgroup analyses were performed on the primary and key secondary efficacy endpoints using the predefined subgroups for sex (male and female), race (white and others) and ethnicity (Hispanic and not Hispanic). The applicant conducted subgroup analysis for four age groups: 18-44, 45-54, 55-64 and $\geq$ 65 years. After discussion with the clinical reviewer, subgroup analysis was conducted for two age groups: $<$ 65 and $\geq$ 65 years as this was deemed to be more clinically relevant.

In most circumstances, examining data from one subgroup in isolation (as done by the applicant) yields a less accurate estimate of the treatment effect in that subgroup. Moreover, estimates of

the treatment effect in subgroups with small sample size are often highly variable and biased. To reduce the overall estimation error, the Bayes shrinkage method were performed where data from all the groups were considered when trying to estimate the treatment effect of the individual groups. The concept of shrinkage is known as directly estimated subgroup treatment effects are shrunken towards the overall treatment effect. Relative to separate analyses of subgroups, shrinkage estimates tend to be more precise and provide narrower confidence/credible intervals.

4.1 Age, sex, race and ethnicity

Study HTX-011-301

In the subgroup analyses, the reviewer utilized the same ANOVA model as in the primary analyses with additional terms for each demographic variable and its interaction with treatment. There was no statistically significant interaction between the treatment and any of age, gender, race and ethnicity.

Results of the subgroup analyses are presented in Table 26 and 27, where PI scores after each of rescue use were handled by the wWOCF method listed in section 3.2.1 and 6-hour analgesic window was applied for all non-opioid rescue medication. Sample estimates were obtained from the ANOVA model with treatment as the main effect and shrinkage estimates were calculated by the Bayesian hierarchical modeling where the information of all the other subgroups were considered to estimate the mean $AUC_{0\text{-}72}$ of NRS-A for HTX-011 compared with saline placebo and bupivacaine. As seen in Table 26 and 27, shrinkage estimates were similar across all subgroups. Subgroups with small sample size (e.g. male, ≥ 65 years) were shrunk more towards the overall treatment effect. With smaller standard errors, shrinkage estimates had narrower credible intervals. Shrinkage estimates were consistent with the overall study population group, demonstrating that the mean $AUC_{0\text{-}72}$ of PI scores was reduced in subjects who received HTX-011 compared with saline placebo (Table 26) and bupivacaine (Table 27) irrespective of demographic factors. Different methods listed in Section 3.2.1 were tried to handle PI scores after each of rescue use, the results were robust regardless which method was used.

Subgroup analyses of total opioid consumption use and the proportion of opioid-free subjects were also consistent with the primary analyses.

Table 26: Subgroup Analyses for Study HTX-011-301 (ITT population)

mean $AUC_{0\text{-}72}$ of NRS-A PI scores for HTX-011 compared with saline placebo	**Sample size HTX-011 /PBO**	**Sample estimate**			**Shrinkage estimate**		
		LSMD	**SE**	**95% CI**	**MD**	**SE**	**95% CI***
Overall		-131.12	21.17	(-172.73, -89.51)			
Sex:							
Male	19/14	-118.84	64.33	(-247.87, 10.19)	-127.50	38.0	(-201.80, -42.68)
Female	138/86	-134.37	22.29	(-178.21, -90.54)	-132.30	21.39	(-174.50, -90.21)
Age: <65	133/92	-124.10	21.95	(-167.27, -80.93)	-121.0	21.0	(-162.30, -79.64)
≥65	24/8	-95.38	60.03	(-216.29, 25.54)	-112.10	37.46	(-180.80, -26.04)

Race: White	123/86	-130.88	22.51	(-175.15, -86.61)	-133.0	21.44	(-174.90, -90.81)
Others	34/14	-161.60	58.83	(-278.88, -44.32)	-141.0	36.90	(-226.60, -73.18)
Ethnicity:							
Not Hispanic	110/68	-138.78	25.49	(-188.95, -88.61)	-133.10	22.75	(-178.60, -88.88)
Hispanic	47/32	-115.37	38.25	(-191.07, -39.67)	-125.30	28.38	(-179.10, -65.58)

Source: Reviewer's analyses. *: credible interval. LSMD: least square mean difference; SE: standard error. CI: confidence interval. PBO: placebo.

Table 27: Subgroup Analyses for Study HTX-011-301 (ITT population)

mean AUC_{0-72} of NRS-A PI scores for HTX-011 compared with bupivacaine	**Sample size HTX-011 /Bupivacaine**	**Sample estimate**			**Shrinkage estimate**		
		LSMD	**SE**	**95% CI**	**MD**	**SE**	**95% CI***
Overall		-71.86	18.73	(-108.69, -35.04)			
Sex:							
Male	19/23	-96.79	56.62	(-210.36, 16.78)	-78.66	34.72	(-159.10, -14.61)
Female	138/132	-69.35	19.75	(-108.20, -30.50)	-71.04	18.98	(-108.20, -33.68)
Age: <65	133/139	-65.86	19.64	(-104.48, -27.24)	-65.18	18.56	(-101.60, -28.52)
≥65	24/16	-62.49	47.46	(-158.08, 33.10)	-63.89	29.91	(-125.0, -1.68)
Race: White	123/128	-81.99	20.22	(-121.76, -42.23)	-77.05	19.26	(-115.20, -39.16)
Others	34/27	-36.75	47.76	(-131.95, 58.45)	-61.48	34.21	(-119.50, 18.56)
Ethnicity:							
Not Hispanic	110/106	-76.81	22.49	(-121.07, -32.54)	-73.30	20.06	(-113.20, -34.18)
Hispanic	47/49	-61.60	34.07	(-129.04, 5.84)	-68.17	25.09	(-116.50, -16.14)

Source: Reviewer's analyses. *: credible interval. LSMD: least square mean difference; SE: standard error. CI: confidence interval.

Study HTX-011-302

Similar to Study HTX-011-301, the reviewer utilized the same ANOVA model as in the primary analyses with additional terms for each demographic variable and its interaction with treatment. There was no statistically significant interaction between the treatment and any of age, gender, race and ethnicity.

Results of the subgroup analyses are presented in Table 28 and 29, where sample estimates and shrinkage estimates were calculated using the same methods as in Study HTX-011-301. As seen in Table 28 and 29, shrinkage estimates had smaller standard errors and narrower credible intervals. Subgroups with small sample size (e.g. female, ≥ 65 years) were shrunk more towards the overall treatment effect. Shrinkage estimates were consistent with the overall study population group, demonstrating that the mean AUC_{0-72} of PI scores was reduced in subjects who received HTX-011 compared with saline placebo (Table 28) and bupivacaine (Table 29) irrespective of demographic factors. The results were robust no matter which method was used to handle PI scores after each of rescue use.

Subgroup analyses of total opioid consumption use and the proportion of opioid-free subjects were also consistent with the primary analyses.

Table 28: Subgroup Analyses for Study HTX-011-302 (ITT population)

mean AUC_{0-72} of NRS-A PI scores for HTX-011 compared with saline placebo	Sample size HTX-011 /PBO	Sample estimate LSMD	SE	95% CI	Shrinkage estimate MD	SE	95% CI*
Overall		-88.20	22.88	(-133.16, -43.23)			
Sex:							
Male	152/79	-83.08	23.48	(-129.25, -36.91)	-87.04	23.21	(-132.30, -41.56)
Female	12/3	-226.10	109.0	(-453.47, 1.26)	-127.2	75.65	(-326.0, -22.58)
Age: <65	149/77	-78.23	23.29	(-124.03, -32.43)	-83.03	22.56	(-127.10, -38.73)
≥65	15/5	-150.56	67.64	(-289.34, -11.78)	-104.7	46.78	(-221.90, -30.25)
Race: White	139/78	-92.89	23.85	(-139.79, -45.99)	-91.46	23.26	(-137.10, -45.69)
Others	25/4	-75.33	94.38	(-265.42, 114.76)	-86.21	50.16	(-187.40, 29.37)
Ethnicity:							
Not Hispanic	121/52	-77.14	28.65	(-133.53, -20.75)	-81.72	24.79	(-130.0, -32.26)
Hispanic	43/30	-98.15	38.03	(-173.45, -22.85)	-88.09	28.78	(-148.20, -33.55)

Source: Reviewer's analyses. *: credible interval. LSMD: least square mean difference; SE: standard error. CI: confidence interval. PBO: placebo.

Table 29: Subgroup Analyses for Study HTX-011-302 (ITT population)

mean AUC_{0-72} of NRS-A PI scores for HTX-011 compared with bupivacaine	Sample size HTX-011 /Bupivacaine	Sample estimate LSMD	SE	95% CI	Shrinkage estimate MD	SE	95% CI*
Overall		-72.43	18.47	(-108.73, -36.12)			
Sex:							
Male	152/164	-73.54	19.08	(-111.04, -36.04)	-72.26	18.66	(-108.9, -35.37)
Female	12/8	-51.45	77.07	(-212.22, 109.33)	-65.90	42.58	(-149.4, 33.86)
Age: <65	149/161	-57.49	18.87	(-94.59, -20.40)	-61.81	19.25	(-99.48, -24.01)
≥65	15/11	-214.52	52.31	(-321.85, -107.20)	-177.50	60.51	(-294.10, -64.74)
Race: White	139/153	-73.22	19.77	(-112.09, -34.35)	-73.47	18.86	(-110.3, -36.32)
Others	25/19	-80.29	53.34	(-187.73, 27.14)	-75.08	32.44	(-145.3, -9.41)
Ethnicity:							
Not Hispanic	121/121	-80.14	22.23	(-123.90, -36.39)	-73.81	20.06	(-114.1, -34.69)
Hispanic	43/51	-50.47	33.10	(-116.10, 15.06)	-63.17	25.62	(-110.5, -8.13)

Source: Reviewer's analyses. *: credible interval. LSMD: least square mean difference; SE: standard error. CI: confidence interval.

4.2 Other Special/Subgroup Populations

No other subgroup analyses were performed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

As bupivacaine is the disease-active ingredient and meloxicam enhances the effectiveness of bupivacaine, a factorial design study was not required. However, superiority to bupivacaine was required to satisfy the "combination rule" for fixed-combination products. Since the Phase 2b study (HTX-011-209) failed to demonstrate a superiority of HTX-011 400 mg/12 mg over bupivacaine on both endpoints during the 72-hour post-operative period, this study will not be included in the Clinical Studies, Section 14 of the label per the combination rule.

Another statistical issue identified during the review of the two Phase 3 studies submitted to support the efficacy of HTX-011 was that the applicant did not account for use of non-opioid rescue medication in their efficacy analyses. Sensitivity analyses were conducted that accounted for all recue medication including non-opioids. Sensitivity analyses were also performed using pain scores observed after rescue use. Moreover, an integrated assessment of pain scores and total amount of opioid rescue medication was conducted. All these analyses were supportive of the primary efficacy analysis in both studies and there was a statistically significant treatment effect noted in favor of HTX-011.

5.2 Collective Evidence

For the Phase 3 studies (HTX-011-301 and HTX-011-302), the efficacy of HTX-011 (60 mg bupivacaine/1.8 mg meloxicam and 300 mg bupivacaine/9 mg meloxicam) was evaluated by the area under the curve of NRS-A PI scores through 72 hours. The HTX-011 group had a statistically significant greater pain reduction compared to the bupivacaine and placebo group. The HTX-011 group also had a statistically greater reduction in total opioid consumption over 72 hours compared with the bupivacaine and placebo group. The proportion of subjects with opioid-free was statistically higher in the HTX-011 group compared with the bupivacaine group. However, a reduction in opioid analgesic use alone is not a clinically relevant finding without specifying clinically meaningful parameters that may result from a reduction in post-operative opioid analgesics use, such as a reduction in side effects related to opioid use.

5.3 Conclusions and Recommendations

Based on the analyses of the primary and key secondary efficacy endpoints in the two Phase 3 studies reviewed, there was substantial evidence that HTX-011 (60 mg bupivacaine/1.8 mg meloxicam and 300 mg bupivacaine/9 mg meloxicam) administered as a single dose reduces pain for up to 72 hours after unilateral bunionectomy and unilateral open herniorrhaphy surgery. Therefore, we recommend an approval to 60 mg bupivacaine/1.8 mg meloxicam and 300 mg bupivacaine /9 mg meloxicam from a statistical perspective.

5.4 Labeling Recommendations

We recommend only including the primary and key secondary efficacy endpoints in Section 14. (b) (4)

We also recommend removing Section 14.3 Study 3 (referring to the Phase 2b study) from the Clinical Studies, Section 14 of the label as this study failed to demonstrate that HTX-011 was significantly superior to bupivacaine in treating post-operative pain after total knee replacement. Per the combination rule, HTX-011 was required to be superior to placebo and bupivacaine.

6 Appendix

6.1 Demographic and Baseline Characteristics

Table 30: Demographic and Baseline Characteristics of Study HTX-011-301

Source: Clinical Study Report Section 11.2.1

	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/m^2)				
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.
Sources: Table 14.1.5.1, Listing 16.2.4.1.

Table 31: Demographic and Baseline Characteristics of Study HTX-011-302

Source: Clinical Study Report Section 11.2.1

	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/m^2)				
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: Table 14.1.5.1.

Table 32: Demographic and Baseline Characteristics of Study HTX-011-209 Cohort 2

Source: Study HTX-011-209 CSR Table 15

	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/m^2)					
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: Table 14.1.4.2.

6.2 Methodology of Shrinkage Analysis

The modeling assumptions are as follows:

For $i = 1, 2$, Y_i represents the sample estimate of LSMD for two subgroups

Assume:

$Y_i/72 \sim N(\mu_i, \sigma_i^2)$ where

- σ_i^2: variance of LSMD/72
- $\mu_i \sim N(\mu, \tau^2)$
- $\mu \sim N(0, SD=4)$, $1/\tau^2 \sim Gamma(0.001, 0.001)$

Note: the shrinkage analysis was performed for the transformed variable $Y_i/72$.

7 Reference

[1] Silverman DG, O'Conner TZ, Brull SJ. Intergrated assessment of pain scores and rescue morphine use during studies of analgesic efficacy. Anesth Analg 1993; 77:168-70

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/s/

YAN ZHOU
04/02/2019 03:41:15 PM

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DAVID M PETULLO
04/02/2019 06:11:42 PM
I concur.