Synergistic Effect of Bupivacaine and Meloxicam in HTX-011 Across Multiple Doses and Surgeries

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INTRODUCTION

- The most severe pain after a surgery occurs within the first 72 hours[1-3]
- Inadequate pain management during this period can lead to adverse outcomes for patients and increased costs for the health care system[4,5]
- A local anesthetic such as bupivacaine is commonly used for surgical pain relief, but current formulations, including extended-release (ER) formulations, exhibit limited efficacy beyond 12-24 hours after surgery[6,7]
- The normal inflammatory process after acute injury (ie, surgical incision) impairs the ability of local anesthetics to block nociception[8,9]
- HTX-011 is an ER formulation of bupivacaine and meloxicam in our proprietary Biochronomer® technology that is applied into the wound site to coat the affected tissue during surgery
- HTX-011's unique formulation[10] is designed to overcome the challenges of the local inflammatory process, potentiating a synergistic reduction in postoperative pain through 72 hours

RESEARCH QUESTIONS

- **Synergy:** Are the pain relief effects of HTX-011 synergistic (ie, greater than the individual pain relief effects of bupivacaine ER and meloxicam ER)?
- **Efficacy:** Does HTX-011 provide better pain relief than bupivacaine HCl?

METHODS

Study Designs

- These analyses included 2 randomized, multicenter, double-blind, placebo-controlled, institutional review board–approved phase 2 trials involving subjects undergoing bunionectomy (NCT02762929) or herniorrhaphy (NCT02504580)
- Each analysis included subjects who were randomly assigned to receive one of the treatments described in **Table 1**; doses used in the efficacy study are being carried forward into phase 3 studies

Table 1. Study Treatments

	Bunionectomy	Herniorrhaphy
SYNERGY EVALUATION	• HTX-011 60 mg via injection or instillation • Bupivacaine ER 60 mg via injection or instillation • Meloxicam ER[a]	• HTX-011 200 mg via instillation • Bupivacaine ER 200 mg via instillation • Meloxicam ER[a]
EFFICACY EVALUATION	• HTX-011 60 mg via injection or instillation • Bupivacaine HCl 50 mg via injection • Saline placebo	• HTX-011 300 mg via instillation • Bupivacaine HCl 75 mg via injection • Saline placebo

ER, extended release.
[a]Higher dose than the meloxicam in HTX-011.

- After eligible subjects provided informed consent and underwent surgery, each was kept in the hospital for 72 hours for assessments of postoperative pain and opioid rescue medication use (**Table 2**)

Table 2. Study Design

Eligibility

Key Inclusion Criteria:
- Male or female ≥18 years old
- Planning to undergo one of the following:
  - Primary unilateral first metatarsal bunionectomy repair
  - Unilateral inguinal herniorrhaphy

Key Exclusion Criteria:
- ASA Physical Status classification system category ≥4
- Clinically significant renal (creatinine ≥2× ULN) or hepatic (AST or ALT ≥3× ULN) abnormalities
- Current use of analgesics for a chronic pain condition, use of long-acting opioids within 3 days of surgery, or use of any opioids within 24 hours of surgery

Key Efficacy Endpoint (assessed through 72 hours)
- AUC of pain intensity score[a]
- Total postoperative opioid rescue medication (MME)[b]
- Proportion of opioid-free subjects

ALT, alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, aspartate aminotransferase; AUC, area under the curve; ER, extended release; MME, intravenous morphine milligram equivalent; ULN, upper limit of normal.
[a]Pain intensity scores were assessed using an 11-point (0, no pain-10, worst pain imaginable) numeric rating scale.
[b]Opioid rescue medication was available as needed; total opioids consumed were converted to MMEs and summed for analysis.

RESULTS

Baseline Population Characteristics

- These analyses included 234 bunionectomy and 179 herniorrhaphy subjects; demographic characteristics were comparable across cohorts for each study (**Table 3**)

Table 3. Demographic and Baseline Characteristics[a]

	Bunionectomy					Herniorrhaphy					
	HTX-011 60 mg n = 52	Bupivacaine HCl 50 mg n = 25	Bupivacaine ER 60 mg n = 23	Meloxicam ER n = 30	Saline Placebo n = 104	HTX-011 300 mg n = 16	HTX-011 200 mg n = 16	Bupivacaine HCl 75 mg n = 32	Bupivacaine ER 200 mg n = 12	Meloxicam ER n = 18	Saline Placebo n = 85
Female, n (%)	45 (86.5)	22 (88.0)	21 (91.3)	27 (90.0)	91 (87.5)	0	0	1 (3.1)	1 (8.3)	1 (5.6)	1 (1.2)
Male, n (%)	7 (13.5)	3 (12.0)	2 (8.7)	3 (10.0)	13 (12.5)	16 (100)	16 (100)	31 (96.9)	11 (91.7)	17 (94.4)	84 (98.8)
Mean age, years (SD)	52.2 (15.13)	52.7 (11.81)	50.2 (12.89)	49.9 (13.41)	50.0 (13.46)	46.3 (11.28)	42.6 (12.26)	41.7 (12.74)	49.8 (16.56)	49.8 (10.73)	46.0 (12.40)
Mean BMI, kg/m^2 (SD)	29.20 (5.89)	31.75 (5.83)	29.39 (5.54)	29.2 (6.11)	30.26 (6.75)	26.58 (3.74)	29.58 (2.99)	26.0 (3.60)	28.85 (3.10)	27.50 (4.96)	27.79 (4.14)
Race, n (%)											
Asian	2 (3.8)	0	2 (8.7)	2 (6.7)	3 (2.9)	0	0	1 (3.1)	0	0	1 (1.2)
Black or African American	17 (32.7)	7 (28.0)	3 (13.0)	10 (33.3)	37 (35.6)	2 (12.5)	1 (6.3)	4 (12.5)	0	4 (22.2)	14 (16.5)
White	33 (63.5)	17 (68.0)	18 (78.3)	17 (56.7)	61 (58.7)	14 (87.5)	15 (93.8)	27 (84.4)	12 (100)	13 (72.2)	70 (82.4)
Other	0	1 (4.0)	0	1 (3.3)	3 (2.9)	0	0	0	0	1 (5.6)	0

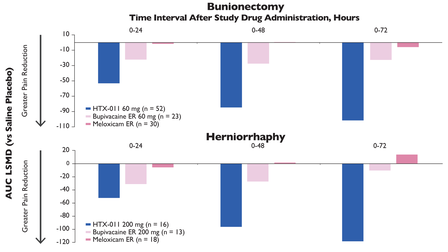
BMI, body mass index; ER, extended release; SD, standard deviation.
[a]Numbers of subjects represent those in the safety population. Slight differences in numbers of subjects from those in the efficacy results are due to mis-dosed subjects.

SYNERGY

Synergy of HTX-011 is Apparent Across Surgical Models

- HTX-011 exhibited a synergistic effect compared with bupivacaine ER and meloxicam ER given individually after bunionectomy and herniorrhaphy (**Figure 1**)

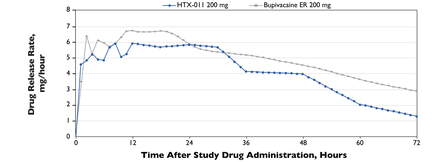
Figure 1. Analgesic effects[a] of HTX-011, bupivacaine ER and meloxicam ER[b] after bunionectomy or herniorrhaphy.



AUC, area under the curve; LSMD, least squares mean difference.
[a]Pain was assessed using an 11-point (0, no pain-10, worst pain imaginable) numeric rating scale.
[b]Higher dose than the meloxicam in HTX-011.

- HTX-011's synergistic formulation demonstrated greater pain relief, despite exhibiting a similar release profile to bupivacaine ER (**Figure 2**)
  - The release rate of bupivacaine from HTX-011 was calculated from the plasma concentration-time profile using deconvolution analysis using literature values for the pharmacokinetics of bupivacaine HCl[11]

Figure 2. In vivo drug release profile for the 200 mg herniorrhaphy groups in Figure 1

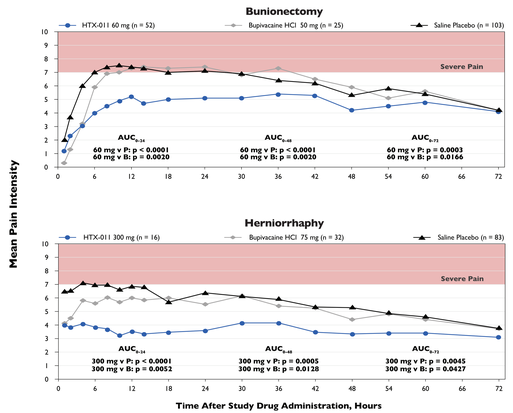


EFFICACY

Postoperative Pain Relief

- HTX-011 provided significantly better pain relief than either bupivacaine HCl or saline placebo after bunionectomy (60 mg) or herniorrhaphy (300 mg) through 72 hours (**Figure 3**)
- Mean pain scores after surgery remained well below the severe pain threshold after treatment with HTX-011, whereas scores after treatment with bupivacaine and saline placebo (bunionectomy only) both crossed the threshold for severe pain and remained higher than HTX-011-treated patients for the majority of the 72-hour assessment period (**Figure 3**)

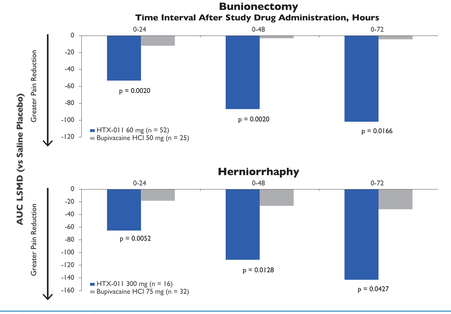
Figure 3. Mean pain intensity[a] through 72 hours after bunionectomy or herniorrhaphy.



AUC_{0-x}, area under the curve from 0 to x hours after surgery; B, bupivacaine HCl; P, saline placebo.
[a]Pain was assessed using an 11-point (0, no pain-10, worst pain imaginable) numeric rating scale.

- In an analysis of AUC least squares mean difference vs saline placebo, HTX-011 produced greater reductions in pain vs saline placebo than did bupivacaine HCl in both bunionectomy (HTX-011 60 mg) and herniorrhaphy (HTX-011 300 mg) surgical models (**Figure 4**)

Figure 4. Pain reduction[a] with HTX-011 and bupivacaine HCl compared with saline placebo through 72 hours after bunionectomy or herniorrhaphy.



AUC, area under the curve; LSMD, least squares mean difference.
[a]Pain was assessed using an 11-point (0, no pain-10, worst pain imaginable) numeric rating scale.

Postoperative Opioid Rescue Medication

- HTX-011 subjects required significantly less opioid rescue medication (21.73 intravenous morphine milligram equivalents [MMEs]) than subjects receiving bupivacaine HCl (32.28 MMEs, p = 0.0382) or saline placebo (32.67 MMEs, p = 0.0047) after bunionectomy through 72 hours
- Total rescue opioid consumption was numerically lower after herniorrhaphy with HTX-011 (18.38 MMEs) compared with bupivacaine HCl (25.09 MMEs, p = 0.3324) and saline placebo (32.28 MMEs, p = 0.0815)
- A greater proportion of herniorrhaphy and bunionectomy subjects were opioid-free through 72 hours with HTX-011 treatment than with bupivacaine HCl (H: 50.0% vs 12.5%, p = 0.0108; B: 17.3% vs 8.0%, p = 0.4877) or saline placebo (H: 50.0% vs 7.2%, p = 0.0001; B: 17.3% vs 3.9%, p = 0.0106)

CONCLUSIONS

- HTX-011 provided a synergistic analgesic effect that was greater than that of either bupivacaine ER or meloxicam ER administered alone, resulting in a >20-fold pain reduction compared with saline placebo through 72 hours
- HTX-011 reduced pain intensity through the first 72 hours after surgery compared with bupivacaine ER, bupivacaine HCl, or saline placebo in both surgical models
  - HTX-011 subjects also remained well below the threshold for severe pain throughout the 72-hour study period
- HTX-011 significantly reduced the amount of opioid rescue medication used after bunionectomy and significantly increased the number of subjects not requiring opioid rescue medication through 72 hours after herniorrhaphy compared with bupivacaine or saline placebo
- The unique synergistic formulation in HTX-011, delivered into the surgical site over 72 hours using Biochronomer technology, may represent a significant advance in the prevention and treatment of postoperative pain

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DISCLOSURES

EO, AC, SP, TO, CW, and BQ are all employees of Heron Therapeutics, Inc.

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