Synergistic Effect of the Active Components in HTX-011, a Novel Fixed-ratio Formulation of Bupivacaine and Meloxicam, Across Multiple Doses and Surgical Models

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INTRODUCTION

- The most severe pain after a surgery occurs within the first 72 hours[1-3]
- Adequate non-opioid postoperative pain management during this period is crucial to preventing adverse outcomes and reducing over-reliance on systemic opioids, which are contributing to the opioid epidemic in the United States [4,5]
- Bupivacaine is a common local anesthetic used for surgical pain relief[6]; however, available formulations including extended-release (ER) formulations of bupivacaine alone have limited efficacy beyond 12-24 hours after surgery[7]
- The normal inflammatory process after acute injury (eg, surgical incision) creates an acidic environment that may impair the ability of local anesthetics to block nociception,[8,9] possibly explaining the lack of efficacy of available local anesthetics beyond 12-24 hours
- HTX-011 is a novel, extended-release (ER), non-opioid, fixed-ratio formulation of bupivacaine and meloxicam in proprietary Biochronomer® technology that is designed to overcome the challenges of the local inflammatory process, with meloxicam potentiating the analgesic effect of bupivacaine for 72 hours
- HTX-011 is a viscous solution administered as a single-dose application via needle-free syringe to directly coat the affected tissue within the surgical site prior to suturing

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

Synergy Evaluation	
Bunionectomy	**Herniorrhaphy**
• 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	
Bunionectomy	**Herniorrhaphy**
• 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]Contains a higher dose of meloxicam than that used 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	**Key Exclusion Criteria:**
• Male or female ≥18 years old • Planning to undergo one of the following: – Primary unilateral first metatarsal bunionectomy repair – Unilateral inguinal herniorrhaphy	• 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 Endpoints (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)	47.8 (9.82)	41.7 (12.74)	49.8 (16.56)	49.8 (10.73)	46.0 (12.40)
Mean BMI, kg/m² (SD)	29.20 (5.89)	31.75 (5.83)	29.39 (5.54)	29.23 (6.11)	30.26 (6.75)	26.58 (3.74)	26.38 (4.33)	25.99 (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

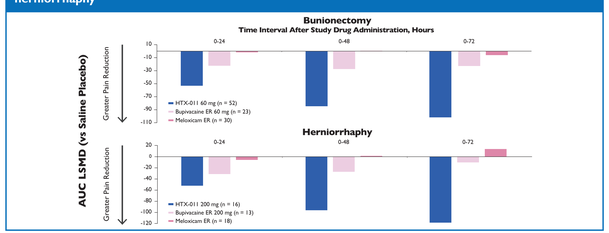
BMI, body mass index; ER, extended release; SD, standard deviation.
[a]Numbers of subjects represent those in the safety population. Slight differences from those in the efficacy results are due to mis-dosed subjects.

SYNERGY

Synergy of HTX-011 Is Demonstrated Across Surgical Models

- HTX-011 exhibited a synergistic effect compared with bupivacaine ER and meloxicam ER given individually, or the sum of the two components after bunionectomy or herniorrhaphy (**Figure 1**)

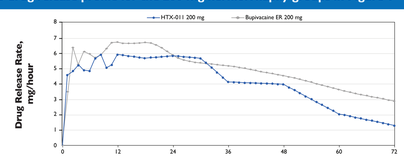
Figure 1. Analgesic effects[a] of HTX-011, bupivacaine ER, and meloxicam ER[b] after bunionectomy or herniorrhaphy



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]Contains a higher dose of meloxicam than that in HTX-011.

- HTX-011's synergistic combination 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[11]

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

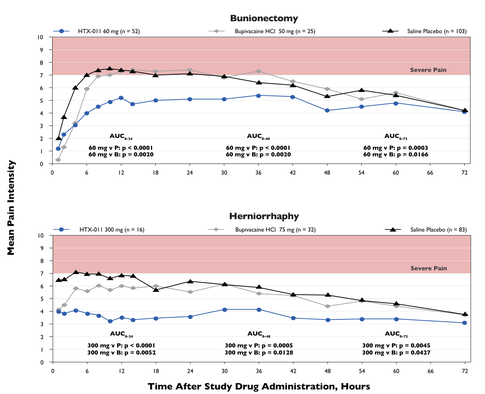


EFFICACY

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 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 (**Figure 3**)

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

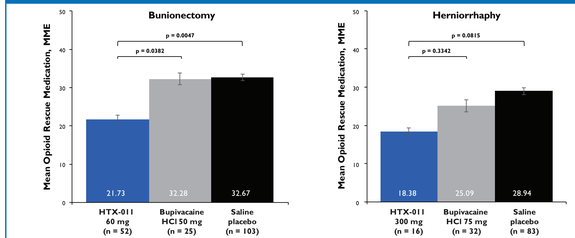


AUC_{0-x}, area under the curve from 0 to x hours after surgery; B, bupivacaine HCl; P, saline placebo.
[a]None of the AUC comparisons were adjusted for use of rescue medications.

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 (32.65 MMEs, p = 0.0047) after bunionectomy through 72 hours (**Figure 4**)
- Total opioid rescue medication 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 (28.94 MMEs, p = 0.0815) through 72 hours (**Figure 4**)
- A greater proportion of herniorrhaphy (H) and bunionectomy (B) 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)

Figure 4. Use of opioid medication through 72 hours



Safety

- The adverse event profile of HTX-011 was not clinically meaningfully different from the adverse event profile of the comparators in either study
- The mean bupivacaine plasma concentration after needle-free application of HTX-011 reached a C_{max} of 271 ng/mL after a 300-mg dose in herniorrhaphy and 53.6 ng/mL after a 60-mg dose in bunionectomy

CONCLUSIONS

- Across multiple clinical studies, HTX-011 provided a synergistic analgesic effect that was greater than that of either bupivacaine ER or meloxicam ER administered alone or the sum of the two individual components, and than 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
  - The mean pain intensity for 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 that remained opioid free through 72 hours after herniorrhaphy compared with bupivacaine or saline placebo
- The non-opioid formulation in HTX-011, applied into the surgical site, may represent a significant advance in prevention and treatment of postoperative pain

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