HTX-011, a Locally Administered Analgesic, Reduces Postoperative Pain Intensity and Opioid Use Through 72 Hours Across Bony and Soft Tissue Surgical Models

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INTRODUCTION

- Surgery causes pain that is most severe 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]
- Systemic opioids are commonly prescribed to manage postoperative pain, but overreliance on these drugs heightens the risk for opioid-related adverse events for patients, increases costs for hospitals, and contributes to the wider societal risk for opioid addiction[6-8]
- A local anesthetic such as bupivacaine is commonly used for postoperative pain relief, but current formulations, including extended-release formulations, exhibit limited efficacy beyond 12-24 hours after surgery[9,10]
- HTX-011 (extended-release bupivacaine + meloxicam) leverages meloxicam in a unique combination with bupivacaine to potentiate a powerful local analgesic effect, delivered over 72 hours, with the use of Biochronomer® technology[11]
- HTX-011 has the potential to significantly advance the treatment of postoperative pain and reduce the need for opioid analgesics across bony and soft tissue surgical models within the first 72 hours after surgery[12]

OBJECTIVE

- To assess the safety and efficacy of HTX-011 in reducing pain intensity and opioid rescue medication use in subjects undergoing bunionectomy and herniorrhaphy

METHODS

- This analysis included 2 randomized, multicenter, double-blind, placebo-controlled, phase 2 institutional review board–approved clinical trials involving subjects undergoing bunionectomy (NCT02762929) or herniorrhaphy (NCT02504580)
- In this subset, subjects were randomly assigned to receive one of the treatments described in **Table 1**

Table 1. Study Treatments

Bunionectomy	Herniorrhaphy
HTX-011 60 mg via injection or instillation	HTX-011 300 mg via instillation
Bupivacaine 50 mg via injection	Bupivacaine 75 mg
Saline placebo	Saline placebo

- After signing informed consent and undergoing surgery, subjects were evaluated for postoperative pain and opioid rescue medication use (**Table 2**)

Table 2. Clinical 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
Endpoints	
Efficacy Endpoints (assessed through 72 hours) • AUC of pain intensity score[a] • Total opioid consumption (MME)[b] • Proportion of opioid-free subjects	**Safety Endpoints[c]** • TEAEs, serious TEAEs • Vital signs, clinical laboratory evaluations, ECGs

ALT, alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, aspartate aminotransferase; AUC, area under the curve; ECGs, electrocardiographs; MME, milligram morphine equivalent; TEAE, treatment-emergent adverse event; ULN, upper limit of normal. [a]Pain was assessed using an 11-point (0-10) numerical pain rating scale, with 0 indicating no pain experienced and 10 indicating the worst pain imaginable. [b]Rescue pain medication was available as needed; total opioids consumed were converted to MMEs and summed for analysis. [c]For herniorrhaphy, the safety population also included all subjects who have received HTX-011 400 mg via injection and/or instillation.

RESULTS

- This analysis included 181 bunionectomy and 133 herniorrhaphy subjects; demographic characteristics were comparable across cohorts for each study (**Table 3**)

Table 3. Demographics and Baseline Characteristics

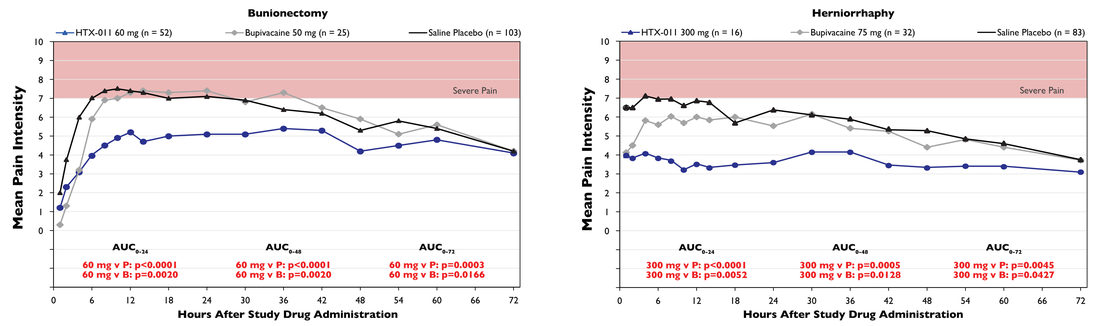
	Bunionectomy			Herniorrhaphy		
	HTX-011 60 mg n = 52	Bupivacaine 50 mg n = 25	Saline Placebo n = 104	HTX-011 300 mg n = 16	Bupivacaine 75 mg n = 32	Saline Placebo n = 85
Female, n (%)	45 (86.5)	22 (88.0)	91 (87.5)	0 (0.0)	1 (3.1)	1 (1.2)
Male, n (%)	7 (13.5)	3 (12.0)	13 (12.5)	16 (100)	31 (96.9)	84 (98.8)
Mean age, years (SD)	52.2 (15.13)	52.7 (11.81)	50.0 (13.46)	46.3 (11.28)	41.7 (12.74)	46.0 (12.40)
Mean BMI, kg/m^2 (SD)	29.20 (5.89)	31.75 (5.83)	30.26 (6.75)	26.58 (3.74)	25.99 (3.60)	27.79 (4.14)
Race, n (%)						
Asian	2 (3.8)	0 (0.0)	3 (2.9)	0 (0.0)	1 (3.1)	1 (1.2)
Black/African American	17 (32.7)	7 (28.0)	37 (35.6)	2 (12.5)	4 (12.5)	14 (16.5)
White	33 (63.5)	17 (68.0)	61 (58.7)	14 (87.5)	27 (84.4)	70 (82.4)
Other	0 (0.0)	1 (4.0)	3 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)

RESULTS

Efficacy

- Subjects treated with HTX-011 experienced significantly less pain (as measured by AUC of pain intensity scores adjusted for opioid use) than did subjects who received bupivacaine or saline placebo through 72 hours after bunionectomy or herniorrhaphy (**Figure 1**)

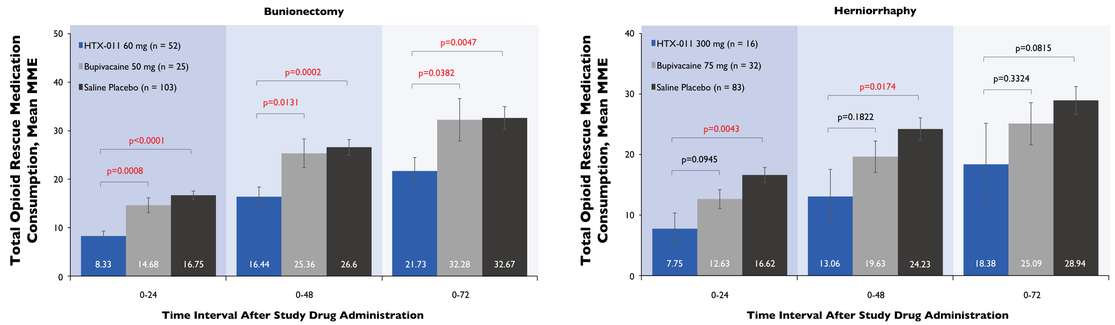
Figure 1. Mean pain score and AUC through 72 hours after bunionectomy or herniorrhaphy.



AUC_{0-x}, area under the curve from 0 to x hours after study drug administration; B, bupivacaine; P, placebo.
AUC_{0-72} for HTX-011 versus saline placebo was also statistically significant without adjustment for opioids.

- HTX-011 subjects required significantly less opioid rescue medication than subjects receiving bupivacaine or saline placebo after bunionectomy. Total opioid consumption was numerically lower after herniorrhaphy (**Figure 2**)

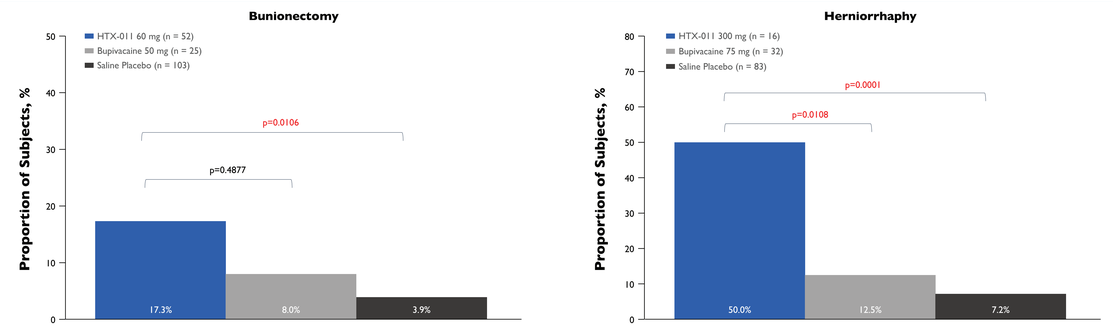
Figure 2. Total postoperative opioid rescue medication consumption over time.



MME, milligram morphine equivalent.

- A greater proportion of herniorrhaphy and bunionectomy subjects were opioid free through 72 hours with HTX-011 treatment than with bupivacaine or saline placebo (**Figure 3**)

Figure 3. Percentage of subjects who were opioid free through 72 hours.



Safety

- The incidences of adverse events in subjects treated with HTX-011, bupivacaine, and saline placebo are presented in **Table 4**

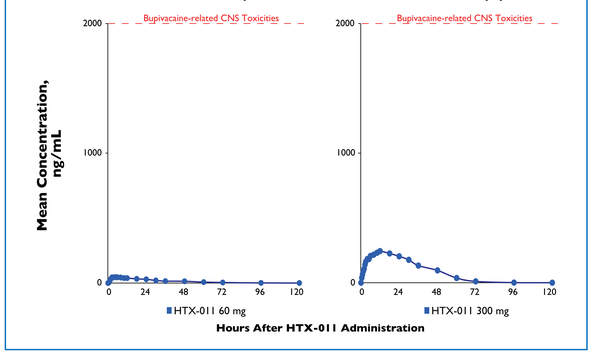
Table 4. Treatment-Emergent Adverse Events Occurring in >10% of subjects

TEAEs, n (%)	HTX-011	Bupivacaine	Saline Placebo
	60 mg	50 mg	
Bunionectomy	**n = 52**	**n = 25**	**n = 104**
Any TEAE	33 (63.5)	20 (80.0)	76 (73.1)
Nausea	16 (30.8)	11 (44.0)	44 (42.3)
Vomiting	8 (15.4)	5 (20.0)	27 (26.0)
Pruritus	7 (13.5)	4 (16.0)	8 (7.7)
Headache	5 (9.6)	5 (20.0)	19 (18.3)
Constipation	4 (7.7)	1 (4.0)	20 (19.2)
	300/400 mg	**75 mg**	
Herniorrhaphy	**n = 99**	**n = 32**	**n = 85**
Any TEAE	72 (72.7)	21 (65.6)	56 (65.9)
Constipation	26 (26.3)	8 (25.0)	28 (32.9)
Nausea	24 (24.2)	6 (18.8)	19 (22.4)
Headache	18 (18.2)	4 (12.5)	7 (8.2)

TEAE, treatment-emergent adverse event.

- HTX-011 primarily exerts its analgesic effect locally, lowering the risk for systemic toxicities from local anesthetic; serum bupivacaine levels are well below the thresholds for cardiac and neurologic adverse events[13-17] (**Figure 4**)

Figure 4. Serum bupivacaine levels after HTX-011 administration.



CNS, central nervous system.
The threshold for bupivacaine-related cardiovascular toxicities is 4000 ng/mL.

CONCLUSIONS

- HTX-011's unique formulation was well tolerated after bunionectomy and herniorrhaphy and significantly reduced pain intensity through 72 hours
- HTX-011 significantly reduced the amount of opioid rescue medication used after bunionectomy and significantly lowered the number of subjects requiring any opioid rescue medication through 72 hours after herniorrhaphy compared with bupivacaine or saline placebo
- These results confirm the efficacy of HTX-011 across both bony and soft tissue surgical models
- HTX-011 may represent an important advance in the prevention and treatment of postoperative pain

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ACKNOWLEDGMENTS

We thank the patients for their participation in this clinical trial. Medical writing assistance was provided by ApotheCom (San Francisco, CA) and was funded by Heron Therapeutics, Inc.

Presented at the 36th Annual ESRA Congress 2017; September 13-16, 2017; Lugano, Switzerland.