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HTX-011, a Proprietary, Extended-Release Synergistic Combination of Bupivacaine and Meloxicam for the Relief of Acute Postoperative Pain

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INTRODUCTION

- The most severe pain after a surgical procedure such as bunionectomy 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[4-6]
- Systemic opioids are commonly prescribed to manage postoperative pain, but this overreliance heightens the risk of opioid-related adverse events (AEs) for patients, increases costs for hospitals, and contributes to the wider societal risk for opioid addiction[7-9]
- A local anesthetic such as bupivacaine is commonly used for surgical pain relief, but current formulations, including long-acting formulations, exhibit limited efficacy beyond 24 hours[10,11]
- HTX-011 overcomes this limitation by combining the anti-inflammatory effect of meloxicam with the powerful local analgesic effect of bupivacaine over 72 hours via sustained delivery of both agents using Biochronomer® technology[12]
- HTX-011 has the potential to significantly advance the treatment of postoperative pain[13]

OBJECTIVES

- To evaluate the activity of HTX-011 for acute postoperative pain relief
- To assess whether the combination of long-acting bupivacaine and long-acting meloxicam demonstrates synergy by producing significantly greater benefit than is produced by the additive effects of the two components when administered individually

METHODS

Study Design

- The analgesic contribution of the two components of HTX-011 was investigated as part of a large IRB-approved, double-blind, randomized, dose-finding trial of subjects undergoing primary unilateral first metatarsal bunionectomy
- Each subject provided informed consent, was confined in the hospital for protocol-specified assessments for 72 hours postdose, and could receive opioid as rescue medication (converted to intravenous milligram morphine equivalents for analysis) for pain control as needed

Subjects

Key inclusion criteria

- Male or female ≥18 years of age
- Scheduled to undergo a primary unilateral first metatarsal bunionectomy under regional anesthesia without collateral procedures
- No contralateral bunionectomy in the nonstudy foot in the past 3 months

Key exclusion criteria

- Presence of clinically significant cardiac, renal, or hepatic abnormalities
- American Society of Anesthesiologists Physical Status classification system category ≥4
- Aspartate aminotransferase or alanine aminotransferase >3 times the upper limit of normal, creatinine >2 times the upper limit of normal, or both
- Preexisting painful condition or another surgery within 30 days of the procedure
- Current or recent opioid or analgesic use

Treatments

- Subjects were assigned a single-dose administration of one of the following:
  - 120 mg HTX-011 (Biochronomer bupivacaine and meloxicam; equivalent to 120 mg bupivacaine base)
  - Equipotent component dose of HTX-002 (Biochronomer bupivacaine only)
  - Equipotent component dose of HTX-009 (Biochronomer meloxicam only)
  - Saline placebo

Study Assessments

Primary end point

- Summed pain intensity score (SPI) over 24 hours (SPI_{0-24}); pain intensity scores were assessed using an 11-point (0, no pain—10, worst pain imaginable) numerical pain rating scale

Secondary end points

- SPI from 0 to 48 hours and from 0 to 72 hours
- Time to administration of first dose of narcotic rescue medication
- Total opioid rescue medication over 24, 48, and 72 hours after treatment, assessed using milligram morphine equivalent

Safety end point

- AEs recorded throughout the study

RESULTS

Subject Characteristics

- This interim analysis included 211 subjects; 85.8% were women, their average age was 50, and their mean body mass index was 30.5 kg/m² (**Table 1**)
- Subject characteristics were similar across cohorts (**Table 1**)

Table 1. Subject Characteristics

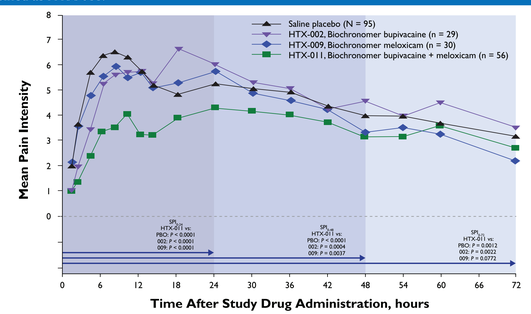
Parameter	HTX-011, Biochronomer Bupivacaine + Meloxicam n = 56	HTX-002, Biochronomer Bupivacaine n = 29	HTX-009, Biochronomer Meloxicam n = 30	Saline Placebo n = 96
Mean age, years (SD)	49.6 (12.51)	48.8 (12.73)	49.9 (13.41)	50.4 (13.64)
Female, n (%)	45 (80.4)	25 (86.2)	27 (90.0)	84 (87.5)
Mean BMI, kg/m² (SD)	31.4 (6.16)	29.6 (7.45)	29.2 (6.11)	30.6 (6.76)
Ethnicity, n (%)				
Hispanic or Latino	18 (32.1)	13 (44.8)	10 (33.3)	25 (26.0)
Not Hispanic or Latino	38 (67.9)	16 (55.2)	20 (66.7)	71 (74.0)
Race, n (%)				
White	38 (67.9)	20 (69.0)	17 (56.7)	55 (57.3)
Black or African American	17 (30.4)	7 (24.1)	10 (33.3)	35 (36.5)
Other	1 (1.8)	2 (6.9)	3 (10)	6 (6.2)

BMI, body mass index; SD, standard deviation.

Pain Relief

- HTX-011 recipients exhibited a significant reduction in mean SPI over the first 24 and 48 hours against all three comparators, with statistical significance maintained through 72 hours against saline placebo and Biochronomer bupivacaine (**Figure 1**)

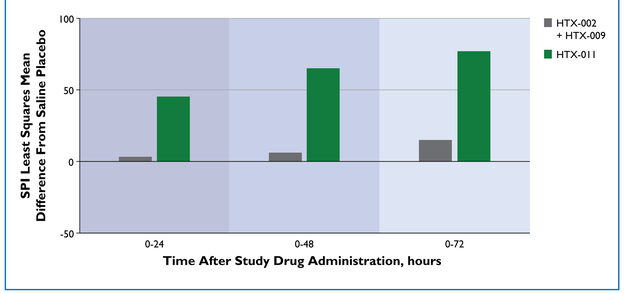
Figure 1. Mean pain intensity over time after administration of meloxicam and bupivacaine alone or combined as HTX-011.[a]



PBO, saline placebo; SPI, summed pain intensity.
[a]None of the SPI comparisons were adjusted for use of rescue medications.

- HTX-011 improved SPI scores to a much greater extent (indicating substantially better pain relief) than the sum of both of its components administered alone; these results demonstrate the true synergy of bupivacaine plus meloxicam in HTX-011 (**Figure 2**)

Figure 2. The least squares mean difference in SPI between saline placebo and each cohort reveals a synergistic effect of combined meloxicam and bupivacaine in HTX-011.



SPI, summed pain intensity.

Opioid Use

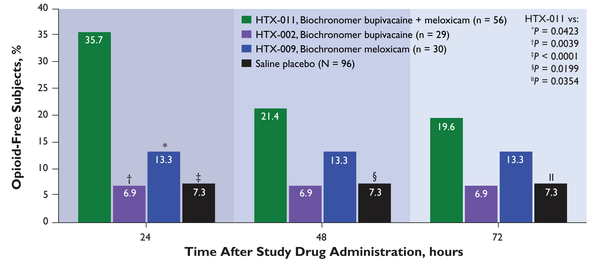
- HTX-011 recipients showed a significantly longer median time to first opioid rescue medication use (13 hours) than did subjects who received HTX-002 (7 hours), HTX-009 (4 hours), or saline placebo (4 hours) (**Table 2**)
- Subjects who received HTX-011 used fewer total rescue opioids within the first 24 hours than did subjects who received HTX-002, HTX-009, or saline placebo ($P \leq 0.001$ for all); significant differences compared with saline placebo were maintained through 72 hours (**Table 2**)
- A significantly greater percentage of subjects who received HTX-011 remained opioid free over the first 24 hours after surgery (36%) than did those who received HTX-002 (7%), HTX-009 (13%), or saline placebo (7%); this significance between HTX-011 and saline placebo recipients was maintained through 72 hours (**Figure 3**)

Table 2. Rescue Opioid Medication Administration

Parameter	HTX-011, Biochronomer Bupivacaine + Meloxicam n = 56	HTX-002, Biochronomer Bupivacaine n = 29	HTX-009, Biochronomer Meloxicam n = 30	Saline Placebo n = 96
Time to first opioid use, median hours (95% CI)	13.17 (7.87, 19.87)	6.63 (3.18, 8.22)	3.93 (2.80, 4.78)	3.78 (3.18, 4.23)
		$P = 0.0023$*‡	$P < 0.0001$*‡	$P < 0.0001$*‡
Total opioids used, mean MME (SD)				
24 hours after treatment	8.0 (8.10)	13.9 (6.61)	15.4 (10.63)	16.4 (8.66)
		$P = 0.001$*‡	$P < 0.001$*‡	$P < 0.001$*‡
48 hours after treatment	17.8 (13.95)	23.8 (14.05)	25.6 (17.67)	26.1 (15.10)
		$P = 0.066$*‡	$P = 0.028$*‡	$P < 0.001$*‡
72 hours after treatment	23.8 (19.72)	27.6 (17.44)	31.4 (21.92)	32.0 (21.19)
		$P = 0.379$*‡	$P = 0.105$*‡	$P = 0.019$*‡

CI, confidence interval; MME, milligram morphine equivalent; SD, standard deviation.
*Compared with HTX-011. †Wilcoxon test. ‡ANOVA.

Figure 3. Percentage of subjects who remained opioid free in the first 72 hours after study drug administration.



Safety

- No deaths were reported
- One subject (HTX-009) reported a serious AE of inflammation at the wound site that necessitated hospitalization
- One subject (saline placebo) discontinued prematurely because of an allergic reaction to morphine
- The differences in frequencies of the most commonly reported AEs among any of the HTX-011, HTX-009, and HTX-002 groups were not clinically meaningful

CONCLUSIONS

- Meloxicam and bupivacaine combined in a single long-acting formulation delivered at the wound site exhibited a synergistic analgesic effect up to 72 hours after surgery that was greater than the sum of the analgesic effect of either compound delivered alone
- HTX-011 significantly reduced the need for opioids more than did either of its components alone following unilateral bunionectomy
- HTX-011 was generally well tolerated after bunionectomy and had an AE profile similar to that of saline placebo
- The synergistic combination of meloxicam and bupivacaine in HTX-011 may represent a significant advance in the treatment of postoperative pain

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