Synergistic Effect of Bupivacaine and Meloxicam in HTX-011: Animal and Clinical Studies

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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[4-6]
- Systemic opioids are commonly prescribed to manage postsurgical pain, but an overreliance on these drugs heightens the risk of opioid-related adverse events 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 postsurgical pain relief, but current long-acting formulations exhibit limited efficacy beyond 24 hours[10, 11]
- HTX-011 leverages meloxicam in a unique combination with bupivacaine to potentiate a powerful local analgesic effect, delivered over 72 hours using Biochronomer® technology[12] for extended release (ER)

OBJECTIVES

- To assess in a preclinical setting whether the ER combination of bupivacaine with meloxicam demonstrates significantly greater benefit than that produced by the additive effects of the two components when administered individually in the same ER formulation, and to confirm this synergy assessment in a clinical setting

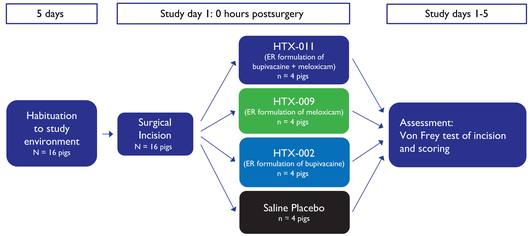
PRECLINICAL PIG POSTOPERATIVE PAIN MODEL[13]

Preclinical Methods

Preclinical Study Design (Figure 1)

- After 5 days of habituation to the study environment, male pigs (N = 16, pooled across 3 studies) underwent surgical incisions and dosing with either HTX-011, HTX-002 (bupivacaine ER), HTX-009 (meloxicam ER), or saline placebo (n = 4/cohort) (**Figure 1; Figure 2A**)

Figure 1. Preclinical Pig Postoperative Pain Model Study Design*.

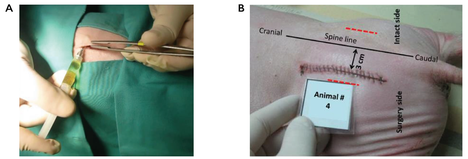


ER, extended release.
*Data used for HTX-011, HTX-009, and HTX-002 were collected as part of 3 separate studies that each followed this study design.

Assessments

- Pain near the surgical incision (**Figure 2B**) was measured with a Von Frey test (filaments are applied until the animal withdraws from the stimuli up to a maximal force of 60 g) at 24 hours pre-dose, at incision and dosing, and at 1, 3, 5, 24, 48, 72, 96, and 120 hours after dosing

Figure 2. A) Application of HTX-011 at the Incision Site. B) Locations of Surgical Incision and Von Frey Assessment.

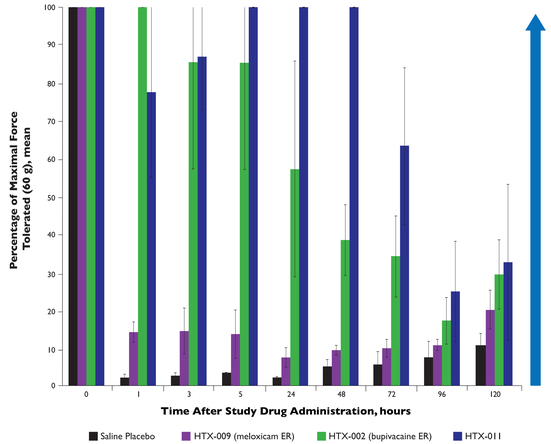


Preclinical Results

Pain Sensitivity Following Surgical Incision in Pigs

- Within the first 5 hours postdose, pigs treated with HTX-011 tolerated a similar percentage of maximal force in the Von Frey test (78.3%-100%) as pigs treated with HTX-002 (bupivacaine ER) (85.5%-100%) (**Figure 3**)
- By contrast, the effect of HTX-009 (meloxicam ER) within the first 5 hours postdose was minimal (**Figure 3**)
- In the longer term—24-72 hours postdose—pigs that received HTX-011 tolerated a greater percentage of maximal force (63.3%-100%) than pigs that received HTX-002 (bupivacaine ER) (34.2%-57.3%) or saline placebo (2.2%-5.7%) (**Figure 3**)
- During this extended timeframe, the analgesic effects of HTX-009 (meloxicam ER) (7.5%-10.0% percentage of maximal force) were still minimal (**Figure 3**)
- HTX-011 maintained a larger analgesic effect over time than either HTX-009 or HTX-002; in the extended timeframe, only at 72 hours postdose did pigs treated with HTX-011 show any increased sensitivity to pain (**Figure 3**). At 96-120 hours postdose, all treatments showed similar percentages of maximal force tolerated (**Figure 3**)

Figure 3. Pig Postoperative Pain Study: Analgesia after surgical incision lasts for a longer time period after administration of HTX-011 than after HTX-002 (bupivacaine ER), HTX-009 (meloxicam ER), or saline placebo.



ER, extended release.

Preclinical Conclusions

- In this preclinical model of postsurgical pain, HTX-011 demonstrated long-lasting analgesia beyond either of its components alone, suggesting that bupivacaine and meloxicam may have a synergistic effect when combined in HTX-011
- These synergistic preclinical results were validated in humans as part of a phase 2 clinical study with patients undergoing bunionectomy

PHASE 2 BUNIONECTOMY CLINICAL STUDY

Clinical Methods

Clinical Study Design

- The analgesic contribution of bupivacaine (120 mg) and meloxicam combined (HTX-011), as well as the analgesic contribution of each component alone within the same ER technology (HTX-002, bupivacaine ER; HTX-009, meloxicam ER), was investigated as part of a large Institutional Review Board-approved, randomized, blinded, dose-finding trial in which subjects underwent primary unilateral first metatarsal bunionectomy (**Table 1**)
- Each subject provided informed consent, was confined in the hospital for protocol-specified assessments for 72 hours postdose, and received opioid as rescue medication (converted to intravenous milligram morphine equivalents [MME] for analysis) for pain control as needed

Table 1. Clinical Study Elements

Key Criteria	**Inclusion**	**Exclusion**
	• Adults (≥18 years of age) scheduled to undergo primary unilateral first metatarsal bunionectomy under regional anesthesia without collateral procedures • No contralateral bunionectomy in the non-study foot in the past 3 months	• Clinically significant cardiac, renal, or hepatic abnormalities • ASA physical status classification system category ≥4 • AST or ALT >3 times the ULN, creatinine >2 times the ULN, or both • Preexisting painful condition or another surgery within 30 days of the procedure • Current or recent opioid or analgesic use
Key Endpoints	**Primary[a]**	**Secondary[a]** / **Safety**
	• SPI_{0-24}	• SPI_{0-48} and SPI_{0-72} • Time to administration of first dose of opioid rescue medication • Total opioid rescue medication used over 24 hours posttreatment[b] • Percentage of subjects who remained opioid-free in the first 72 hours post-surgery **Safety** • AEs recorded throughout the study

AE, adverse event; ALT, alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, aspartate aminotransferase; SPIx-y, summed pain intensity from x to y hours after study drug administration; ULN, upper limit of normal.
[a]Pain intensity scores were assessed utilizing an 11-point (0, no pain-10, worst pain imaginable) numerical pain rating scale.
[b]Assessed using milligram morphine equivalent.

- Additional analyses included area under the mean pain intensity curve (AUC) up to 24, 48, and 72 hours postdose

Clinical Results

Clinical Subject Characteristics

- This bunionectomy study interim analysis included 237 subjects (**Table 2**)
- Subject characteristics were similar across cohorts (**Table 2**)

Table 2. Clinical Subject Characteristics

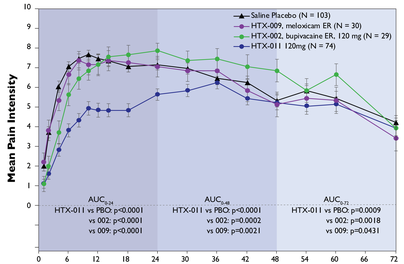
Parameters	HTX-011, 120mg (n = 74)	HTX-002, bupivacaine ER, 120 mg (n = 29)	HTX-009, meloxicam ER, (n = 30)	Saline Placebo (n = 104)
Mean age, years (SD)	49.7 (12.72)	48.8 (12.73)	49.9 (13.41)	50.3 (13.39)
Female, n (%)	61 (82.4)	25 (86.2)	27 (90.0)	91 (87.5)
Mean BMI, kg/m² (SD)	31.1 (5.97)	29.6 (7.45)	29.2 (6.11)	30.3 (6.70)
Ethnicity, n (%)				
Hispanic or Latino	26 (35.1)	13 (44.8)	10 (33.3)	28 (26.9)
Race, n (%)				
White	51 (68.9)	20 (69.0)	17 (56.7)	62 (59.6)
Black or African American	21 (28.4)	7 (24.1)	10 (33.3)	36 (34.6)
Other	2 (2.7)	2 (6.9)	3 (10)	6 (5.8)

BMI, body mass index; ER, extended release; SD, standard deviation.

Pain Relief After Bunionectomy Surgery

- HTX-011 120 mg recipients exhibited a significant reduction in AUC over the first 24 and 48 hours against all three comparators, with statistical significance maintained through 72 hours against saline placebo and HTX-002 120 mg (bupivacaine ER) (**Figure 4**)

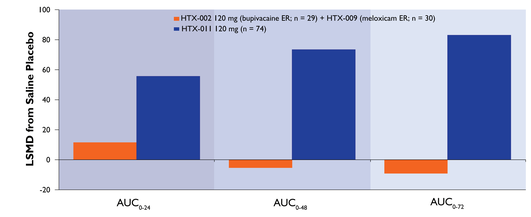
Figure 4. Mean pain intensity over time after administration of meloxicam ER, bupivacaine ER, or both combined within HTX-011 after bunionectomy.



AUC, area under the mean pain intensity curve; ER, extended release; PBO, saline placebo.

- HTX-011 improved AUC to a much greater extent (indicating substantially better pain relief) than did the sum of both of its components administered alone; these results demonstrate the synergy of bupivacaine plus meloxicam in HTX-011 (**Figure 5**)

Figure 5. The least squares mean difference in AUC from placebo reveals a synergistic effect of combined meloxicam and bupivacaine in HTX-011.



AUC_{x-y}, area under the mean pain intensity curve from x to y hours postdose; ER, extended release; LSMD, least squares mean difference.

Opioid use

- Subjects who received HTX-011 required less total rescue opioid consumption than did subjects who received HTX-002 (bupivacaine ER), HTX-009 (meloxicam ER), or saline placebo and demonstrated a longer median time to first opioid rescue medication use (11 hours vs 7, 4, or 4 hours, respectively)
- A significantly greater percentage of subjects who received HTX-011 remained opioid-free over the first 24 hours after surgery (30%) than did those who received HTX-002 (bupivacaine ER) (7%), HTX-009 (meloxicam ER) (13%), or saline placebo (4%)

Safety

- No deaths, serious adverse events, or discontinuations due to AEs were reported for HTX-011 120 mg

Clinical Conclusions

- HTX-011 significantly reduced mean pain intensity more than saline placebo, bupivacaine ER alone, or meloxicam ER alone
- HTX-011 120 mg allowed a significantly greater percentage of subjects to remain opioid free over the first 24 hours after surgery
- HTX-011 120 mg not only delayed but also significantly reduced the need for opioids more than either of its components alone following unilateral bunionectomy
- HTX-011 120 mg was generally well tolerated after bunionectomy and had an AE profile similar to that of saline placebo

CONCLUSIONS

- Meloxicam and bupivacaine combined in a single extended-release formulation (HTX-011) delivered at the wound site in a preclinical postsurgical pain model in pigs exhibited greater analgesia than either compound delivered alone within the same extended-release formulation; this finding was confirmed in an initial clinical trial in bunionectomy
- The synergistic combination of meloxicam and bupivacaine in HTX-011, delivered over 72 hours using Biochronomer technology, may represent a significant advance in the treatment of postoperative pain
- This clinical benefit is being validated in other surgical models and across dose levels
- HTX-011 has the potential to significantly advance the treatment of postoperative pain and reduce the need for opioid analgesics

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