Opioid-free Postoperative Recovery in Patients Undergoing Bunionectomy With HTX-011, an Extended-Release Local Anesthetic

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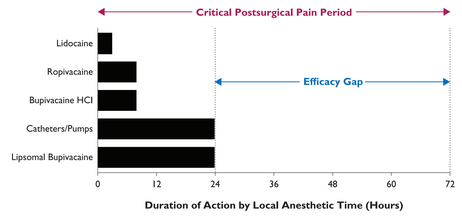
INTRODUCTION

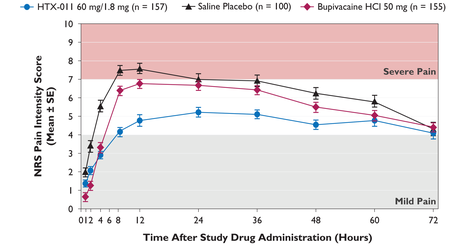
- Up to 70% of patients experience moderate to severe postoperative pain during the first 72 hours following surgical procedures[1,2]
- Current postoperative analgesic options include local anesthetics (eg, bupivacaine hydrochloride [HCl]) that are effective for 6 to 12 hours[3-7] (**Figure 1**) and opioid medications, which are indicated for severe pain but are also associated with serious, sometimes life-threatening adverse events (AEs)[8,9]

Figure 1. There Is an Unmet Need for Postsurgical Pain Control Through 72 Hours



- Evidence-based guidelines recommend MMA regimens to manage postoperative pain[10,11]
- HTX-011 is an extended-release dual-acting local anesthetic comprising bupivacaine and low-dose meloxicam in a proprietary Biochronomer™ polymer that allows for the diffusion of active ingredients over 72 hours (Heron Therapeutics, Inc., San Diego, CA)
  - HTX-011 is administered via needle-free application to the surgical site prior to closure using a syringe and a Luer-lock applicator.
- In a prior phase 3 bunionectomy study (EPOCH-1; NCT03295721)[12] comparing HTX-011 60 mg/1.8 mg (bupivacaine/meloxicam) without a scheduled over-the-counter (OTC) multimodal analgesia (MMA) regimen vs bupivacaine HCl 50 mg and saline placebo, HTX-011:
  - Provided superior pain relief over the first 72 hours (**Figure 2**)
  - Significantly reduced incidence of severe pain at any time over the first 72 hours
  - Significantly reduced total opioid consumption through 72 hours following surgery
  - Allowed 90% of patients who were opioid-free during the 72-hour postoperative period to remain opioid-free through Day 10

Figure 2. HTX-011 Without Multimodal Analgesia Significantly Reduced Postoperative Pain Compared With Bupivacaine and Saline Placebo in the EPOCH-1 Study[12]



HCl, hydrochloride; NRS, numeric rating scale; SE, standard error.

OBJECTIVES

- The objectives of this follow-on study were to:
  - Assess the efficacy and safety of HTX-011 as the foundation of a scheduled non-opioid OTC MMA regimen to manage postoperative pain following bunionectomy
  - Demonstrate the opioid-sparing potential of HTX-011 as the foundation of a scheduled non-opioid OTC MMA regimen

METHODS

Study Design

- The EPOCH 1 Follow-on Study enrolled patients undergoing unilateral bunionectomy who met study criteria (**Table 1**)
  - As the superiority of HTX-011 to bupivacaine HCl was previously demonstrated in 2 phase 3 studies in the same treatment population,[12] an active control was not included in this study

Table 1. Key Inclusion and Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Males and females who are not pregnant or lactating • Age ≥18 years • Provide written informed consent • Scheduled to undergo primary unilateral, distal, first metatarsal bunionectomy with osteotomy and internal fixation under regional anesthesia • ASA Physical Status classification system category I-III	• Contralateral foot bunionectomy in the past 3 months or planned concurrent surgical procedure • Pre-existing concurrent acute or chronic painful/restrictive condition that may require analgesia during postoperative period • Use of the following within a defined time period before surgery: NSAIDs (10 days), long-acting opioids (3 days), any opioid (24 hours), bupivacaine (5 days), or any local anesthetic (72 hours) • BMI >39 kg/m^2

ASA, American Society of Anesthesiologists; BMI, body mass index; NSAID, non-steroidal anti-inflammatory drugs.

- Patients received HTX-011 intraoperatively and a scheduled non-opioid OTC MMA regimen for 72 hours following surgery
  - HTX-011 doses were individualized; surgeons coated all pain-generating tissues but did not allow excess that could be expressed onto the skin
    - The maximum allowed HTX-011 dose was 2.1 mL (60 mg bupivacaine/1.8 mg meloxicam)
    - Syringes containing HTX-011 were weighed before and after administration to determine the volume applied
  - A scheduled non-opioid OTC MMA regimen was taken postoperatively for 72 hours: ibuprofen 600 mg every 6 hours (q6h) orally (PO) alternated every 3 hours with acetaminophen 1 g q6h PO
- Patients remained in the hospital for 72 hours after surgery to capture study assessments
  - Rescue opioid treatment with PO immediate-release oxycodone (≤10 mg within a 4-hour period) and/or intravenous (IV) morphine (≤10 mg within a 2-hour period) was available only upon request
- At discharge, patients were provided a daily diary to record whether they took an opioid medication between 72 hours and Day 28 and instructed to continue their MMA regimen as needed (ibuprofen for initial rescue supplemented with acetaminophen if pain persisted)
  - Patients who received <10 mg immediate-release oxycodone PO within 12 hours before discharge were not provided an opioid prescription
- Patients returned to the study site for follow-up assessments on Days 7, 28, and 42

Outcome Measures

- The primary endpoint was analgesic efficacy (based on patient-reported pain scores) through the first 72 hours after unilateral bunionectomy
- Secondary endpoints included:
  - Proportion of patients who required no opioids (opioid-free) through the first 72 hours
  - Proportion of patients who were opioid-free through 72 hours and who remained opioid-free through Days 7 and 28 of recovery
  - Safety and tolerability of HTX-011 in combination with MMA

Assessments

- Efficacy was assessed based on:
  - Pain intensity measured using the 11-point numeric rating scale (NRS), where 0 indicates "no pain" and 10 indicates "worst pain imaginable"
    - NRS score classification: mild pain, <4; moderate pain, 4-6; severe pain, ≥7
  - Opioid use during the 72-hour inpatient postoperative period
  - Patients' daily diaries recording opioid use (yes/no) after discharge through Day 28 recovery after surgery
- Safety was assessed based on:
  - AEs at any time during the study period
  - Surgical wound healing assessments and vital signs
  - Clinical laboratory tests (hematology and serum chemistry)

Statistical Analysis

- Pain intensity observations made during a windowed period after use of rescue opioid medication were replaced by the highest NRS score recorded before the opioid was given (windowed worst observation carried forward [wWOCF])
- Opioid-free through 72 hours was defined as 0 IV morphine milligram equivalents administered during the inpatient postoperative period
- Patients who were considered opioid-free from 72 hours through Day 7 or 28 responded "no" to the question "Did you take any opioid medication?" on a daily basis; patients who responded "yes" or had a missing report were not considered to be opioid-free during the period in question

RESULTS

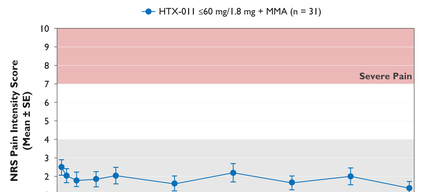
Baseline Population Characteristics

- Thirty-one patients underwent unilateral bunionectomy and received HTX-011 with a scheduled ibuprofen and acetaminophen regimen; all eligible dosed patients completed the study
- Baseline characteristics (mean age, 49 years; 94% female; 87% white) were similar to those of patients who received HTX-011 in the prior phase 3 study[12]

Pain Intensity

- Mean pain intensity remained within the mild range (NRS <4) at all times through 72 hours (**Figure 3**)

Figure 3. HTX-011 With a Non-Opioid OTC MMA Regimen Maintained Pain Scores in the Mild Range Through the 72-hour Postoperative Period

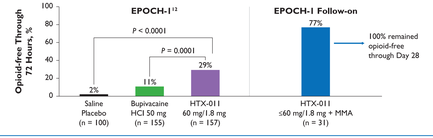


MMA, multimodal analgesia; NRS, numeric rating scale; SE, standard error.
Mean NRS scores computed with the windowed worst observation carried forward (wWOCF).

Postoperative Opioid Use

- Twenty-four (77.4%) patients treated with HTX-011 and non-opioid MMA required no opioids through 72 hours after surgery (**Figure 4**)

Figure 4. HTX-011 With a Non-Opioid OTC MMA Regimen Managed Pain Without Any Opioid Rescue Medication Through 72 Hours in the Majority of Patients Undergoing Bunionectomy



HCl, hydrochloride; MMA, multimodal analgesia.

- Only one (3.2%) patient who received HTX-011 with MMA in this study was discharged with an opioid prescription
- Of the 24 patients who did not take opioids during the first 72 hours, all (100%) remained opioid-free through Day 28 of recovery

Safety

- The mean dose of HTX-011 administered was 58.71 mg/1.76 mg (bupivacaine/meloxicam) in a volume of 1.97 mL
- Overall, 20 (64.5%) patients reported at least one AE, none of which were severe or considered related to study drug (**Table 2**)
  - The most common AEs were nausea (22.6%) and vomiting (9.7%)
  - There was one local inflammatory AE (impaired healing), which was mild in severity and resolved
  - Opioid-related AEs (ORAEs) occurred in 9 (29%) patients; in the prior phase 3 study, >50% of patients treated with bupivacaine HCl or saline placebo and 44% of those receiving HTX-011 without a scheduled MMA regimen experienced ORAEs[12]
  - There were no reports of cardiac, renal, or hepatobiliary AEs in the EPOCH-1 Follow-on study
  - There was no evidence of NSAID- or acetaminophen-related toxicity when HTX-011 was administered with the MMA regimen as determined from AEs and clinical laboratory tests
    - NSAID-related AEs were few and nonserious, occurring in 2 (6.5%) patients who received HTX-011 with a non-opioid OTC MMA regimen

Table 2. Overall Summary of Adverse Events, n (%)

	EPOCH-1[12]			EPOCH-1 Follow-on
AE Categories	HTX-011 60 mg/1.8 mg n = 157	Saline Placebo n = 101	Bupivacaine HCl 50 mg n = 154	HTX-011 ≤60 mg/1.8 mg + MMA n = 31
Any AEs	131 (83.4)	79 (78.2)	131 (85.1)	20 (64.5)
AEs possibly related to study drug	29 (18.5)	21 (20.8)	35 (22.7)	0
Severe AEs	5 (3.2)	3 (3.0)	7 (4.5)	0
ORAEs	69 (43.9)	54 (53.5)	78 (50.6)	9 (29.0)
AEs leading to study withdrawal	1 (0.6)	0	0	0
SAEs	3 (1.9)	1 (1.0)	3 (1.9)	0
SAEs possibly related to study drug	0	0	0	0
Fatal AE	0	0	1 (0.6)	0

AE, adverse event; MMA, multimodal analgesia; ORAE, opioid-related adverse event; SAE, serious adverse event.

SUMMARY AND CONCLUSIONS

- HTX-011, when used as the foundation of a scheduled non-opioid OTC MMA regimen following bunionectomy:
  - Maintained average pain in the mild range
  - Eliminated the need for opioid rescue medication in 77% of patients through recovery in the 28-day postoperative period
  - Nearly eliminated the need for opioid prescriptions at discharge (1/31 patients, 3.2%)
  - Was well tolerated with no evidence of NSAID-related toxicity
- These data indicate that HTX-011 has the potential to allow for opioid-free recovery following bunionectomy

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