P0162

Opioid-Free Postoperative Pain Management in Patients Undergoing Bunionectomy With the Extended-Release Analgesic HTX-011

Gwo-Chin Lee, MD,[1] Danlin Cai, PhD[2]

[1]University of Pennsylvania, Philadelphia, PA, USA; [2]Heron Therapeutics Inc, San Diego, CA, USA

INTRODUCTION

- Despite the widespread use of multimodal analgesia (MMA), most patients still require opioids for pain management following bunionectomy[1]
- HTX-011 is an extended-release, dual-acting local anesthetic (DALA) comprising bupivacaine and low-dose meloxicam in a novel polymer that allows for the controlled diffusion of active ingredients over 72 hours
  - HTX-011 works synergistically to treat postoperative pain through 72 hours: meloxicam reduces the local inflammatory response to injury, thereby normalizing local pH and increasing penetration of bupivacaine across the neural membrane, where it can bind voltage-gated sodium channels and prevent pain signal transmission[2]
- In a controlled phase 3 study of patients undergoing unilateral bunionectomy with osteotomy (EPOCH-1) with no scheduled postoperative MMA, HTX-011 60 mg bupivacaine/1.8 mg meloxicam, when compared to saline placebo or bupivacaine hydrochloride (HCl) 50 mg[3]:
  - Provided superior pain relief through 72 hours
  - Significantly reduced the incidence of severe pain
  - Significantly reduced opioid use
  - Allowed significantly more subjects to recover opioid-free through 72 hours, 91% and 82% of whom remained opioid-free through postsurgical day 10 and 28, respectively
  - Exhibited a similar safety profile and had no impact on bone healing at 6 weeks per follow-up X-rays

OBJECTIVES

- This EPOCH-1 follow-on study (NCT03718039) was designed to assess postoperative pain intensity and opioid-free recovery rates achieved with HTX-011 when used as the foundation of non-opioid MMA following bunionectomy with osteotomy

METHODS

Study Design

- Inclusion criteria are outlined in **Table 1**
- Patients received HTX-011 intraoperatively and a scheduled non-opioid MMA regimen for the first 72 hours postoperatively, including:
  - HTX-011 was administered to the surgical field without a needle using a syringe and Luer lock applicator (**Figure 1**)
  - HTX-011 doses: up to 60 mg bupivacaine/1.8 mg meloxicam (2.3 mL), so that surgeons coated all pain-generating tissues without excess
  - MMA regimen: 600 mg PO ibuprofen alternating with 1 g PO acetaminophen every 3 hours (such that each was taken at 6-hour intervals)
- Patients remained hospitalized for 72 hours for study assessments
  - Rescue opioid medication: PO immediate-release oxycodone (up to 10 mg every 4 hours) and/or intravenous (IV) morphine (up to 10 mg every 2 hours)
- Upon discharge, patients were instructed to continue ibuprofen as needed, followed by acetaminophen if necessary, and record opioid medication use through Day 28 in a daily diary
  - Patients who received <10 mg immediate-release oxycodone PO within 12 hours before discharge were *not to be* provided an opioid prescription
- Patients returned on Days 7, 28, and 42 for postoperative assessments including review of opioid diary and pain and safety assessments

Figure 1. HTX-011 Is Administered Without a Needle

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 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.

Outcome Measures

- Primary endpoint: mean area under the curve (AUC) of the Numeric Rating Scale (NRS) of pain intensity scores through 72 hours
- Secondary endpoints:
  - Proportion of patients opioid-free (requiring no opioids) through 72 hours
  - Proportion of those opioid-free through 72 hours who remained opioid-free through Days 7 and 28
  - Safety and tolerability of HTX-011 with scheduled MMA
- Other: proportion of patients who experienced severe pain (NRS ≥7)

Safety Assessments

- Safety was assessed based on AEs, surgical wound healing assessments, vital signs, and clinical laboratory tests (hematology and serum chemistry)
  - Opioid-related AEs were prespecified as: nausea, vomiting, constipation, pruritus, pruritus generalized, somnolence, respiratory depression, and urinary retention
  - Nonsteroidal anti-inflammatory drug (NSAID)-related AEs were determined from a customized literature-based NSAID-related toxicity list of preferred terms[4]

Statistical Analysis

- Pain intensity analyses were adjusted for opioid use
- Opioid-free was defined as no postoperative opioids (0 MME)
- Continuous data are presented using descriptive statistics; categorical data are summarized by the number and percentage of patients

RESULTS

- Results of the EPOCH-1 follow-on study of HTX-011 as the foundation of MMA are presented alongside the EPOCH-1 study, which did not include a scheduled postoperative MMA regimen

Baseline Population Characteristics

- 31 patients underwent bunionectomy with osteotomy in the follow-on study; none discontinued (**Table 2**)
  - Mean (SD) dose administered was 58.71 (3.02) mg bupivacaine/1.76 (0.091) mg meloxicam

Table 2. Patient Demographics and Baseline Characteristics

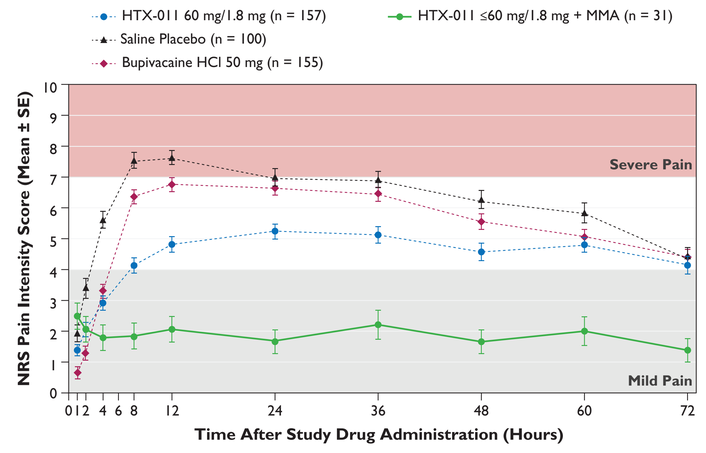
	EPOCH-1[3]			Follow-on
	HTX-011 60 mg/1.8 mg n=157	Saline Placebo n=100	Bupivacaine HCl 50 mg n=155	HTX-011 ≤60 mg/1.8 mg + MMA n=31
Age, mean (SD), years[a]	48.0 (14.47)	47.3 (12.83)	45.5 (14.79)	49.1 (12.66)
Female Sex, n (%)	138 (87.9)	86 (86.0)	132 (85.2)	29 (93.5)
Hispanic or Latino, n (%)	47 (29.9)	32 (32.0)	49 (31.6)	15 (48.4)
White, n (%)	123 (78.3)	86 (86.0)	128 (82.6)	27 (87.1)
BMI, mean (SD), kg/m^2	27.31 (4.793)	27.91 (5.050)	27.15 (4.376)	28.09 (3.818)

BMI, body mass index; HCl, hydrochloride; MMA, multimodal analgesia; SD, standard deviation.
[a]Age was calculated relative to the date of informed consent.

Pain Intensity

- Mean pain intensity remained within the mild range (NRS <4) at all time points through 72 hours in the follow-on study (**Figure 2**)
  - The mean (SD) AUC of pain intensity through 72 hours (**Figure 2**) was 126.9 (129.8)

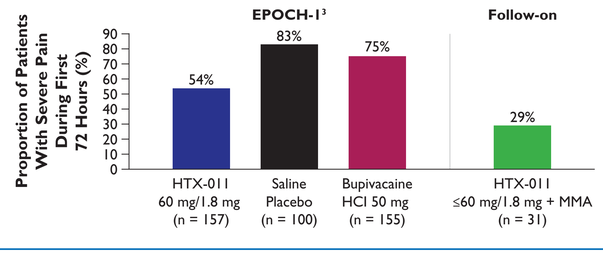
Figure 2. HTX-011 + Non-Opioid MMA Maintained Mean Pain Scores in the Mild Range Through 72 Hours



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

- 71% of patients had no severe pain (NRS ≥7) in the follow-on study (**Figure 3**)

Figure 3. The Majority of Patients Receiving HTX-011 + Non-Opioid MMA Did Not Experience Severe Pain at Any Time Point Through 72 Hours

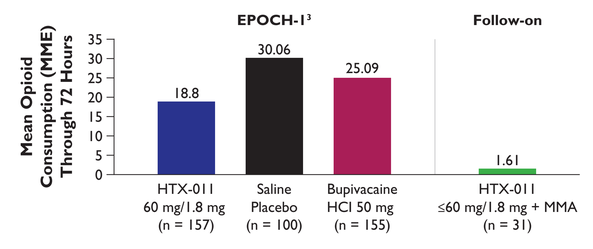


HCl, hydrochloride; MMA, multimodal analgesia.

Postoperative Opioid Use

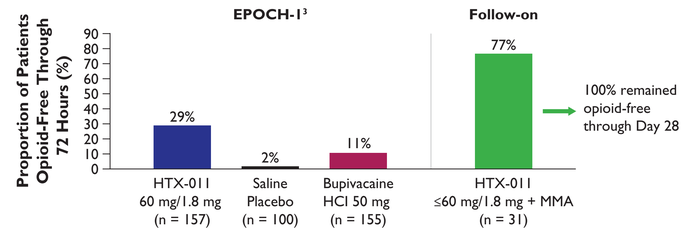
- Patients treated with HTX-011 and scheduled postoperative non-opioid MMA in the follow-on study received an average of 1.61 MME over 72 hours (**Figure 4**) and 77% remained opioid-free (**Figure 5**)

Figure 4. Mean Total Opioid Consumption Through 72 Hours Was Minimal in Patients Receiving HTX-011 + Non-Opioid MMA



HCl, hydrochloride; MMA, multimodal analgesia; MME, IV morphine milligram equivalents.

Figure 5. HTX-011 + Non-Opioid MMA Allowed the Majority of Patients to Remain Opioid-Free for 72 Hours Following Bunionectomy



HCl, hydrochloride; MMA, multimodal analgesia.

- Only 1 patient (3.2%) treated with HTX-011 and non-opioid MMA was prescribed an opioid at discharge
- All 24 patients in the follow-on study who did not require opioid rescue medication during the first 72 hours remained opioid-free (100%) through Day 28 (study end)

Safety

- Overall, 20 (64.5%) patients in the follow-on study reported at least one AE; none were severe or considered related to the study regimen (**Table 3**)

Table 3. Summary of Adverse Events

	EPOCH-1[3]			Follow-on
AE Categories, n (%)	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
Local inflammatory AEs[a]	45 (28.7)	20 (19.8)	34 (22.1)	1 (3.2)
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; HCl, hydrochloride; MMA, multimodal analgesia; SAE, serious adverse event.
[a]Local inflammatory AEs were prespecified as: blister, blood blister, cellulitis, erythema, impaired healing, events at the incision site (cellulitis, complication, erythema, hemorrhage, infection, edema, rash, swelling, vesicles), infection, postoperative wound complication or infection, postprocedural cellulitis, purulent discharge, and wound complication, dehiscence, infection, or secretion.

- There was no evidence of NSAID- or acetaminophen-related toxicity when HTX-011 was administered with the non-opioid MMA regimen per AE profiles and clinical laboratory tests
  - NSAID-related AEs were few and nonserious, occurring in 2 (6%) patients who received HTX-011 with the ibuprofen-containing MMA regimen (1 [3%] each: pruritus and hypertension)
- Opioid-related AEs occurred in 9 (29%) patients in the follow-on study (**Table 4**)

Table 4. Incidence of Opioid-Related Adverse Events

	EPOCH-1[3]			Follow-on
	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
Patients Reporting ≥1 ORAE, n (%)	69 (43.9)	54 (53.5)	78 (50.6)	9 (29.0)
Nausea	59 (37.6)	44 (43.6)	70 (45.5)	7 (22.6)
Vomiting	23 (14.6)	19 (18.8)	33 (21.4)	3 (9.7)
Constipation	9 (5.7)	7 (6.9)	18 (11.7)	2 (6.5)
Pruritus	8 (5.1)	6 (5.9)	1 (0.6)	1 (3.2)
Pruritus generalized	4 (2.5)	4 (4.0)	8 (5.2)	0

HCl, hydrochloride; MMA, multimodal analgesia; ORAE, opioid-related adverse event.

SUMMARY AND CONCLUSIONS

- A single ≤60 mg/1.8 mg intraoperative dose of HTX-011 used as the foundation of a scheduled non-opioid MMA regimen in patients undergoing bunionectomy with osteotomy:
  - Provided reliable pain relief
  - Maintained mean pain in the mild range (NRS <4) through 72 hours
  - Nearly eliminated the need for opioid prescriptions, allowing the majority of patients to recover opioid-free through Day 28
  - Was well tolerated with a low rate of ORAEs and no evidence of NSAID-related toxicities
- In these patients, HTX-011 allowed 77% of patients to recover opioid-free with a scheduled non-opioid MMA regimen, comparing favorably to the 25% of patients in a bunionectomy study using only ibuprofen and acetaminophen[1]
- These encouraging results demonstrate the safety and potential for opioid use reduction with HTX-011 as the foundation of non-opioid MMA in foot and ankle surgery

REFERENCES

1. Daniels SE et al. *Clin Ther*. 2019;41:1982-1995.
2. Ottoboni T et al. *Reg Anesth Pain Med*. 2019;45:117-123.
3. Viscusi E et al. *Reg Anesth Pain Med*. 2019;44:700-706.
4. Essex MN et al. *Expert Opin Drug Safety*. 2013;12:465-477.

ACKNOWLEDGMENTS

Funding for this research was provided by Heron Therapeutics, Inc. (San Diego, CA, USA). Medical writing assistance was provided by ApotheCom (San Francisco, CA, USA).

An electronic version of the poster can be viewed by scanning the QR code. The QR code is intended to provide scientific information for individual reference. The PDF should not be altered or reproduced in any way. All copyrights remain those of the copyright holder. This page will not be available after March 28, 2020. http://bit.ly/2Pz5zpH **(This URL is case sensitive.)**

HERON THERAPEUTICS

Presented at the American Academy of Orthopaedic Surgeons (AAOS) Congress; March 24-28, 2020; Orlando, FL