

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

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## INTRODUCTION

- Despite the widespread use of multimodal analgesia (MMA), most patients still require opioids for pain management following bunionectomy<sup>1</sup>
- 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<sup>2</sup>
- In a controlled phase 3 study of patients undergoing unilateral bunionectomy with osteotomy (EPOCH-I) 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<sup>3</sup>:
  - 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

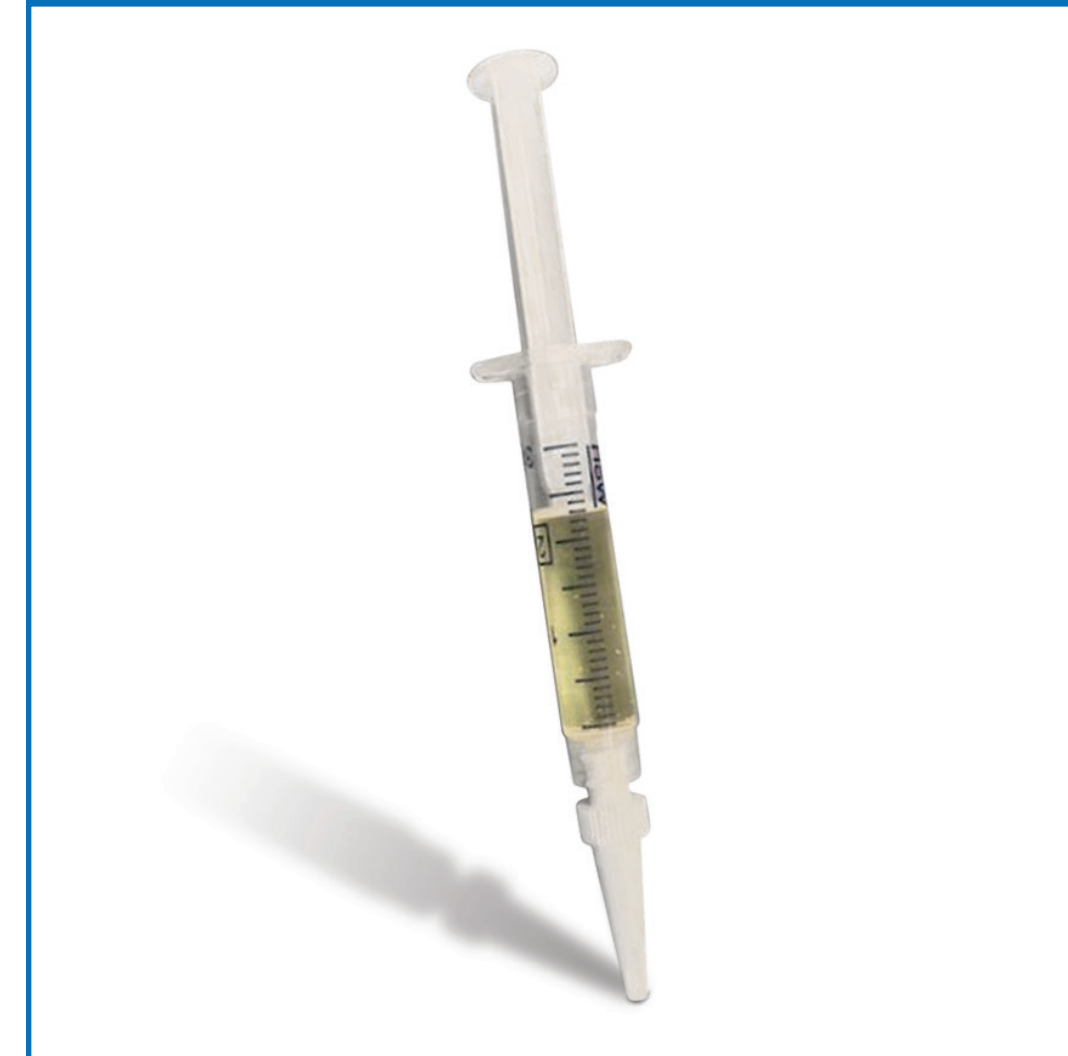
- This EPOCH-I follow-on study (NCT03718039) was designed to assess postoperative pain intensity and opioid-free recovery rates achieved with HTX-011 when used as the foundation of non-opioid MMA following bunionectomy with osteotomy

## 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
<ul style="list-style-type: none"> <li>Males and females who are not pregnant or lactating</li> <li>Age ≥18 years</li> <li>Provide written informed consent</li> <li>Scheduled to undergo primary unilateral, distal, first metatarsal bunionectomy with osteotomy and internal fixation under regional anesthesia</li> <li>ASA Physical Status classification system category I-III</li> </ul>	<ul style="list-style-type: none"> <li>Contralateral foot bunionectomy in the past 3 months or concurrent surgical procedure</li> <li>Pre-existing concurrent acute or chronic painful/restrictive condition that may require analgesia during postoperative period</li> <li>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)</li> <li>BMI &gt;39 kg/m<sup>2</sup></li> </ul>

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<sup>4</sup>

### 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-I follow-on study of HTX-011 as the foundation of MMA are presented alongside the EPOCH-I 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-I <sup>3</sup>			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 <sup>a</sup>	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 <sup>2</sup>	27.31 (4.793)	27.91 (5.050)	27.15 (4.376)	28.09 (3.818)

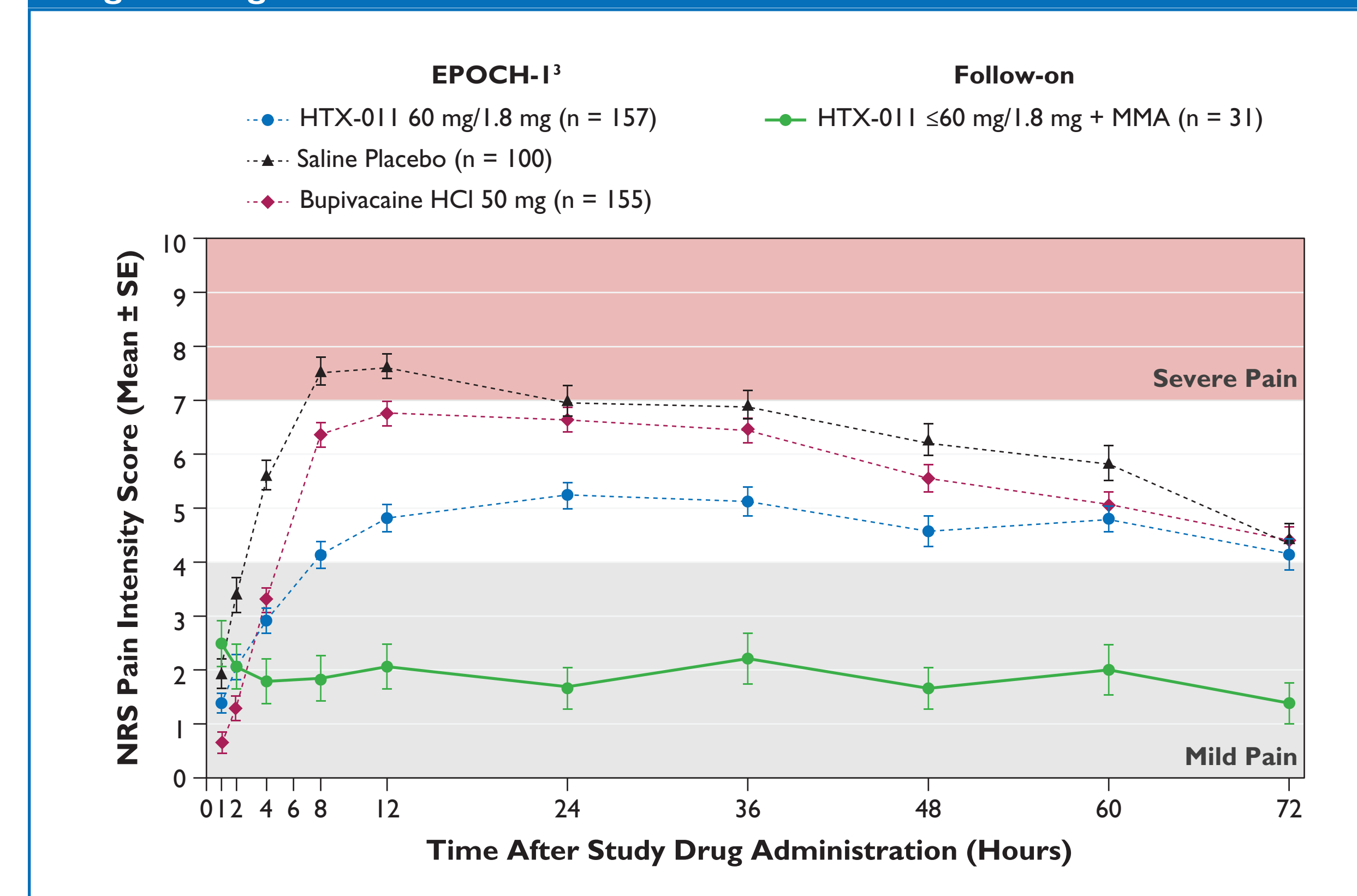
BMI, body mass index; HCl, hydrochloride; MMA, multimodal analgesia; SD, standard deviation.

<sup>a</sup>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**

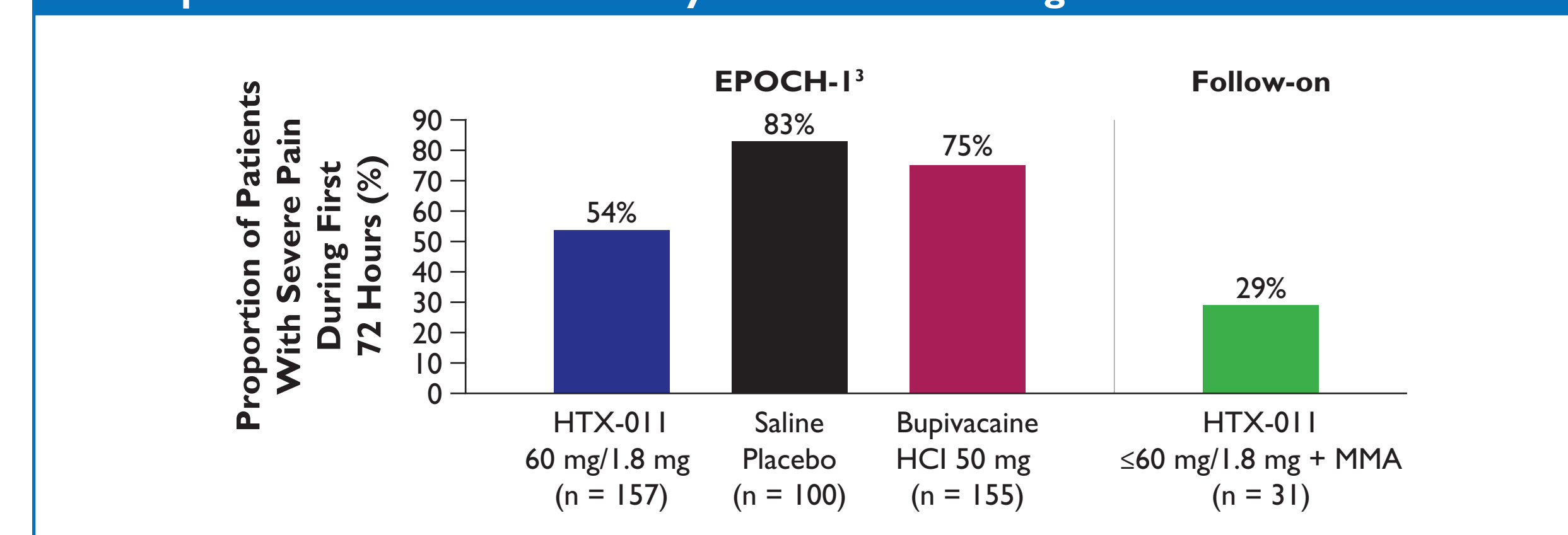


HCl, hydrochloride; MMA, multimodal analgesia; NRS, numeric rating scale; SE, standard error.

Mean NRS scores computed with the windowed worst observation carried forward (wWOOF).

- 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**

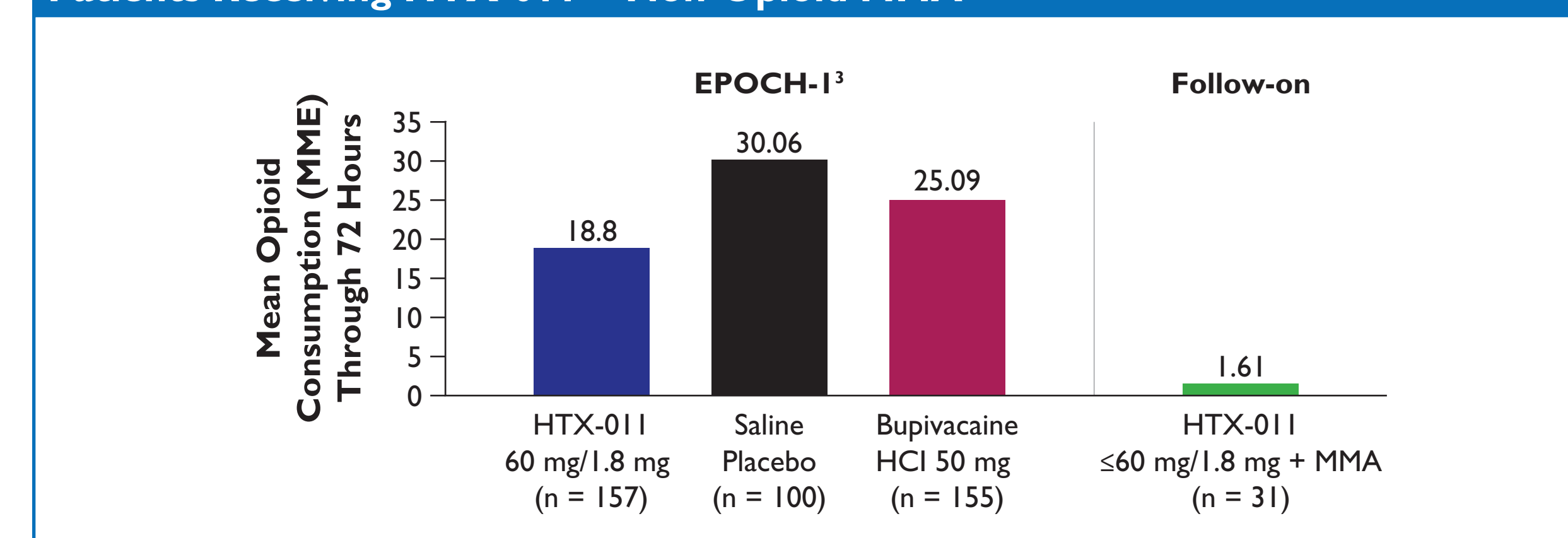


HCl, hydrochloride; MMA, multimodal analgesia.

### Postoperative Opioid Use

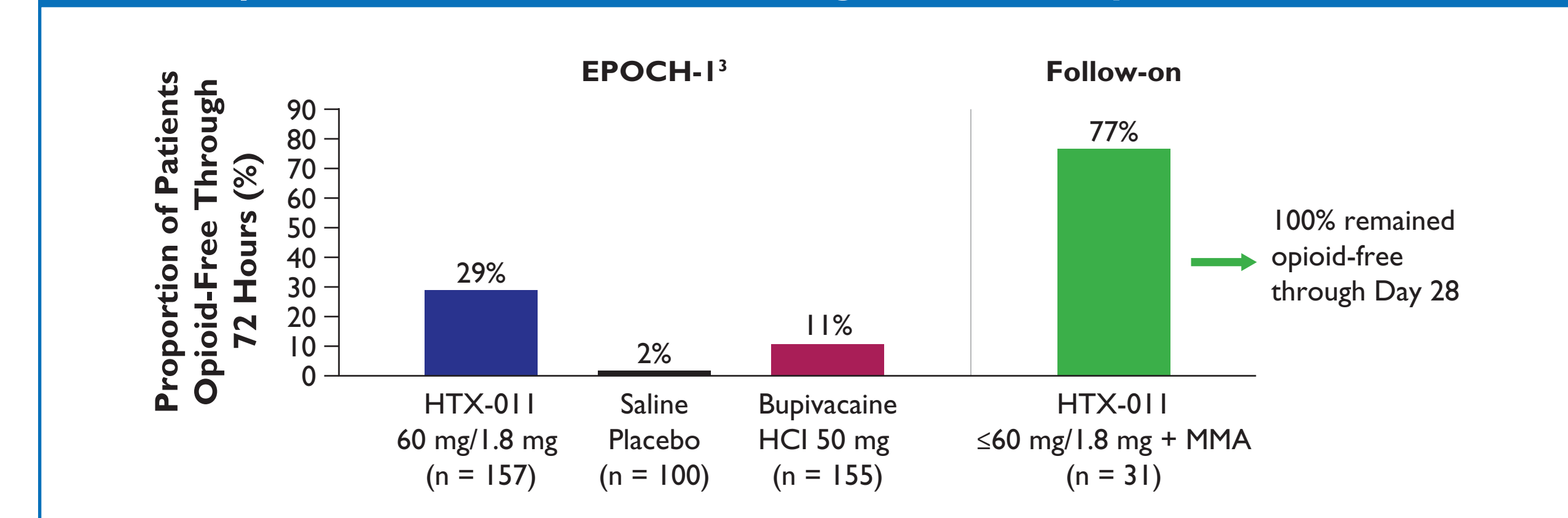
- Patients treated with HTX-011 and scheduled postoperative non-opioid MMA in the follow-on study received an average of 1.61 MME over 72 hours (**Figure 4**) and 77% remained opioid-free (**Figure 5**)

**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**

AE Categories, n (%)	EPOCH-I <sup>3</sup>			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
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 <sup>a</sup>	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.

<sup>a</sup>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-I <sup>3</sup>			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<sup>1</sup>
- 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

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