HTX-011, a Proprietary, Unique, Long-Acting Local Anesthetic, Reduces Acute Postoperative Pain Intensity and Opioid Consumption Following Bunionectomy

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Disclosures

- Erol Onel is an employee of Heron Therapeutics, Inc.

HTX-011, a Novel, Long-Acting Local Analgesic for Non-Opioid Postoperative Pain Management

Postoperative Pain and the Opioid Crisis

- Overreliance on opioids for postoperative pain can lead to increased:
  - Risk of opioid-related adverse events for patients[1]
  - Costs for hospitals[2]
  - Societal impact of opioid addiction[3]

Current Local Analgesic Options Have Limited Efficacy in Postoperative Pain

- Bupivacaine is commonly used; however, even ER formulations have limited efficacy beyond 12-24 hours after surgery[4,5]
- The normal postoperative inflammatory process impairs the ability of local anesthetics to block sensory nerve conduction[6,7]

HTX-011

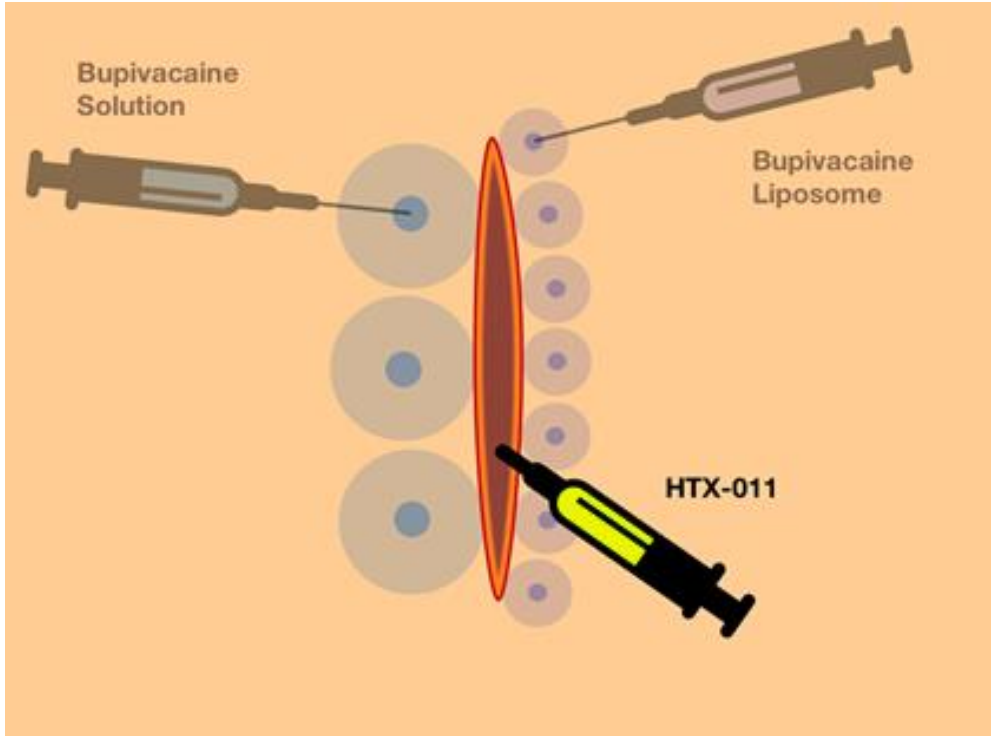
- HTX-011's unique formulation of ER bupivacaine and meloxicam in proprietary Biochronomer® technology is designed to overcome the challenges of the local inflammatory process, potentiating a synergistic pain reduction effect postoperatively through 72 hours

ER, extended-release.

1. Ramachandran SK et al. *J Clin Anesth*. 2011;23:207-213. 2. Kessler ER et al. *Pharmacotherapy*. 2013;33:383-391. 3. Alam A et al. *Arch Intern Med*. 2012;172:425-430.
4. Miller RD, ed. *Miller's Anesthesia,* 8th ed. Philadelphia, PA: Elsevier/Saunders; 2015. 5. Golf M et al. *Adv Ther*. 2011;28:776-788. 6. Ueno T, et al. *J Inflamm Res*. 2008;1:41-48.
7. Becker DE Reed KL. Anesth Prog. 2006;53:98-108.

Although it Can Be Injected Like Bupivacaine, HTX-011 is Ideally Suited for Needle-Free Administration

- HTX-011 is easy to apply and stays in place at the surgical site after application
- HTX-011 releases its active ingredients simultaneously
- HTX-011's release is controlled by diffusion from the polymer, not modulated by the environment
- Compared to injection, simply coating the affected tissue without using a needle:
  - Is easier to administer and less invasive
  - Avoids up to 120 needle sticks
  - Reduces the risk of inadvertent intravascular puncture and accidental needle sticks



Bunionectomy Study: Phase 2 Clinical Study Design

Screening

Key Inclusion Criteria

- Male or female ≥18 years old
- Able to undergo a lidocaine Mayo block for primary unilateral first metatarsal bunionectomy repair

Key Exclusion Criteria

- ASA Physical Status classification category ≥4
- Clinically significant renal or hepatic abnormalities
- Current use of analgesics for a chronic pain condition, use of long-acting opioids within 3 days of surgery, or use of any opioids within 24 hours of surgery

Study Treatments

- HTX-011 200 mg
- HTX-011 120 mg
- HTX-011 60 mg[a]
- HTX-011 30 mg
- Bupivacaine HCl 50 mg
- Saline Placebo
- Bupivacaine ER 60 mg
- Meloxicam ER

Endpoints

Efficacy Endpoints (assessed through 72 hours)

- AUC of mean pain intensity score
- Total opioid rescue medication used (MME)
- Proportion of opioid-free subjects

Safety Endpoints

- TEAEs, serious TEAEs
- Vital signs, clinical laboratory evaluations, ECG

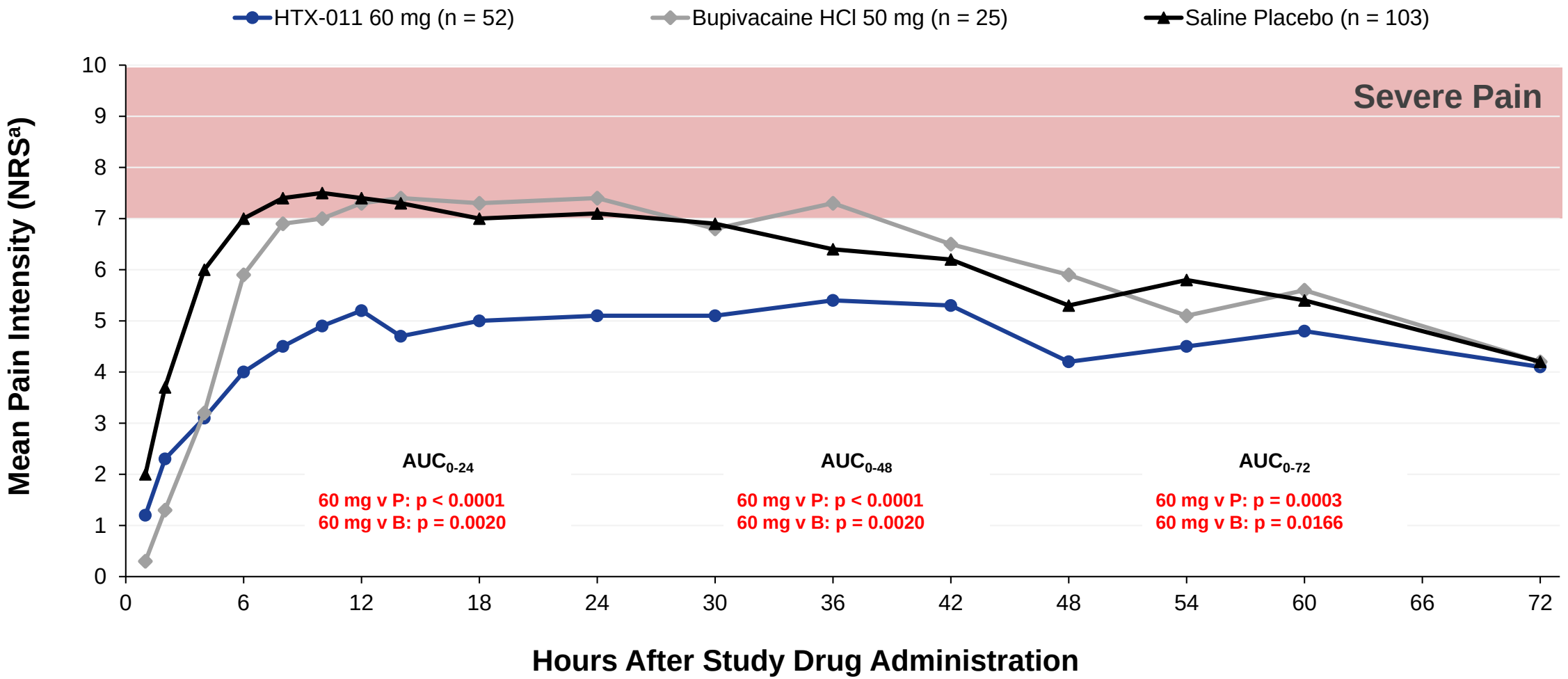
ASA, American Society of Anesthesiologists; AUC, area under the curve; ECG, electrocardiograph; MME, intravenous morphine milligram equivalent; TEAE, treatment-emergent adverse event.
[a]Dose being carried forward in Phase 3 studies.

Bunionectomy Study: Baseline Demographics and Characteristics Comparable Across Cohorts

	HTX-011 60 mg[a] n = 52	Bupivacaine HCl 50 mg n = 25	Bupivacaine ER 60 mg n = 23	Meloxicam ER n = 30	Saline Placebo n = 104[b]
Female, n (%)	45 (86.5)	22 (88.0)	21 (91.3)	27 (90.0)	91 (87.5)
Male, n (%)	7 (13.5)	3 (12.0)	2 (8.7)	3 (10.0)	13 (12.5)
Mean age, years (SD)	52.2 (15.13)	52.7 (11.81)	50.2 (12.89)	49.9 (13.41)	50.0 (13.46)
Mean BMI, kg/m^2 (SD)	29.20 (5.89)	31.75 (5.83)	29.39 (5.54)	29.20 (6.11)	30.26 (6.75)
Race, n (%)					
Asian	2 (3.8)	0	2 (8.7)	2 (6.7)	3 (2.9)
Black or African American	17 (32.7)	7 (28.0)	3 (13.0)	10 (33.3)	37 (35.6)
White	33 (63.5)	17 (68.0)	18 (78.3)	17 (56.7)	61 (58.7)
Other	0	1 (4.0)	0	1 (3.3)	3 (2.9)

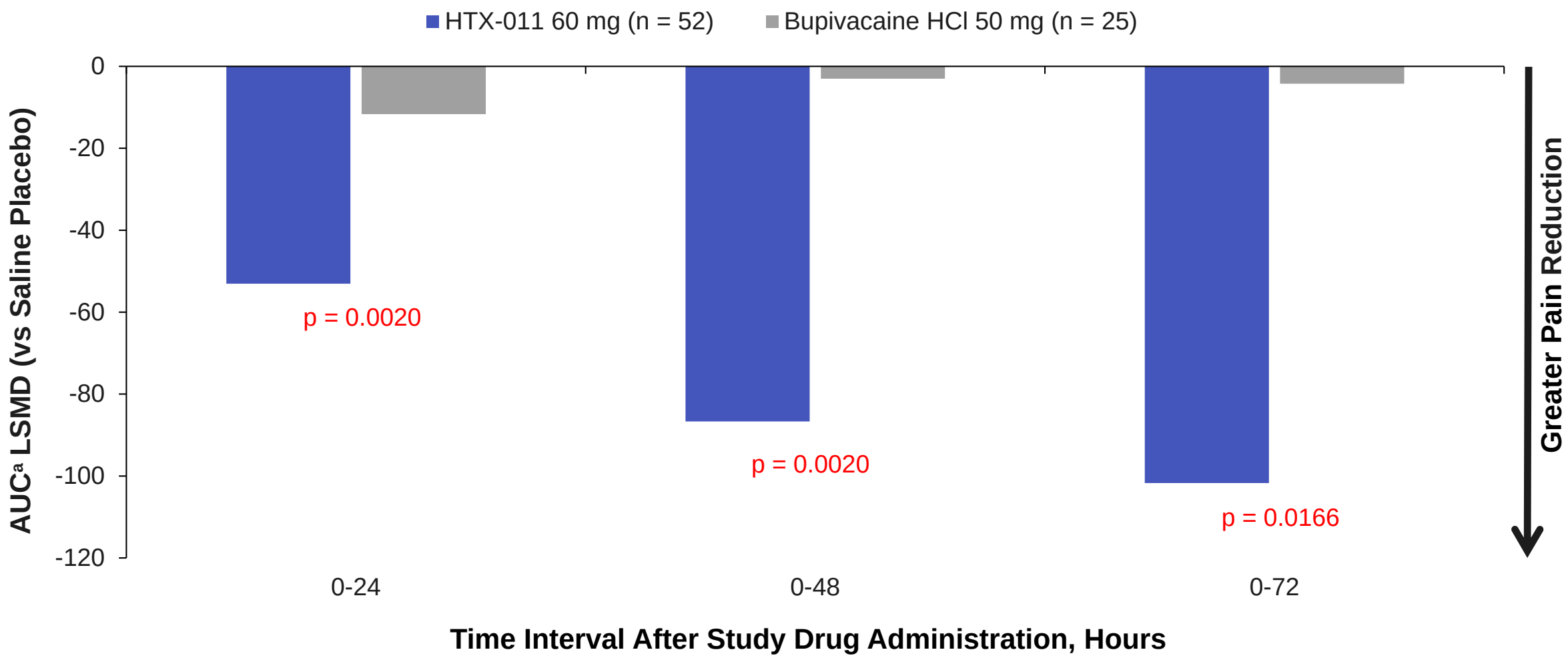
BMI, body mass index, SD, standard deviation.
[a]Dose being carried forward in Phase 3 studies.
[b]Numbers of subjects represent those in the safety population. Slight differences in numbers of subjects from those in the efficacy results are due to mis-dosed subjects.

Bunionectomy Study: HTX-011 Significantly Reduced Pain Compared with Bupivacaine or Saline Placebo Through 72 Hours



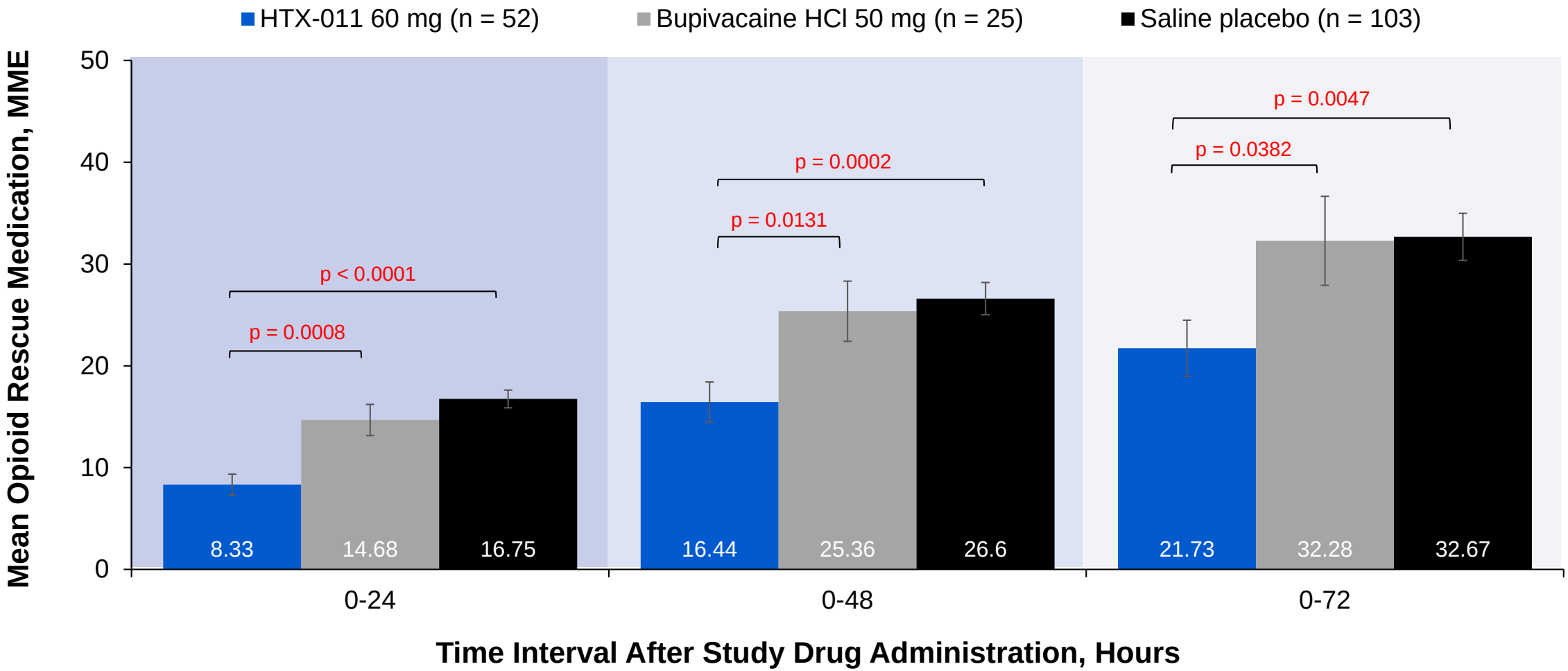
AUC_{0-x}, area under the curve from 0 to x hours after study drug administration; B, bupivacaine; NRS, numeric rating scale; P, placebo.
[a]Pain was assessed using an 11-point (0, no pain-10, worst pain imaginable) numeric rating scale

Bunionectomy Study: HTX-011 60 mg Significantly Reduced Pain Through 72 Hours Compared with Bupivacaine

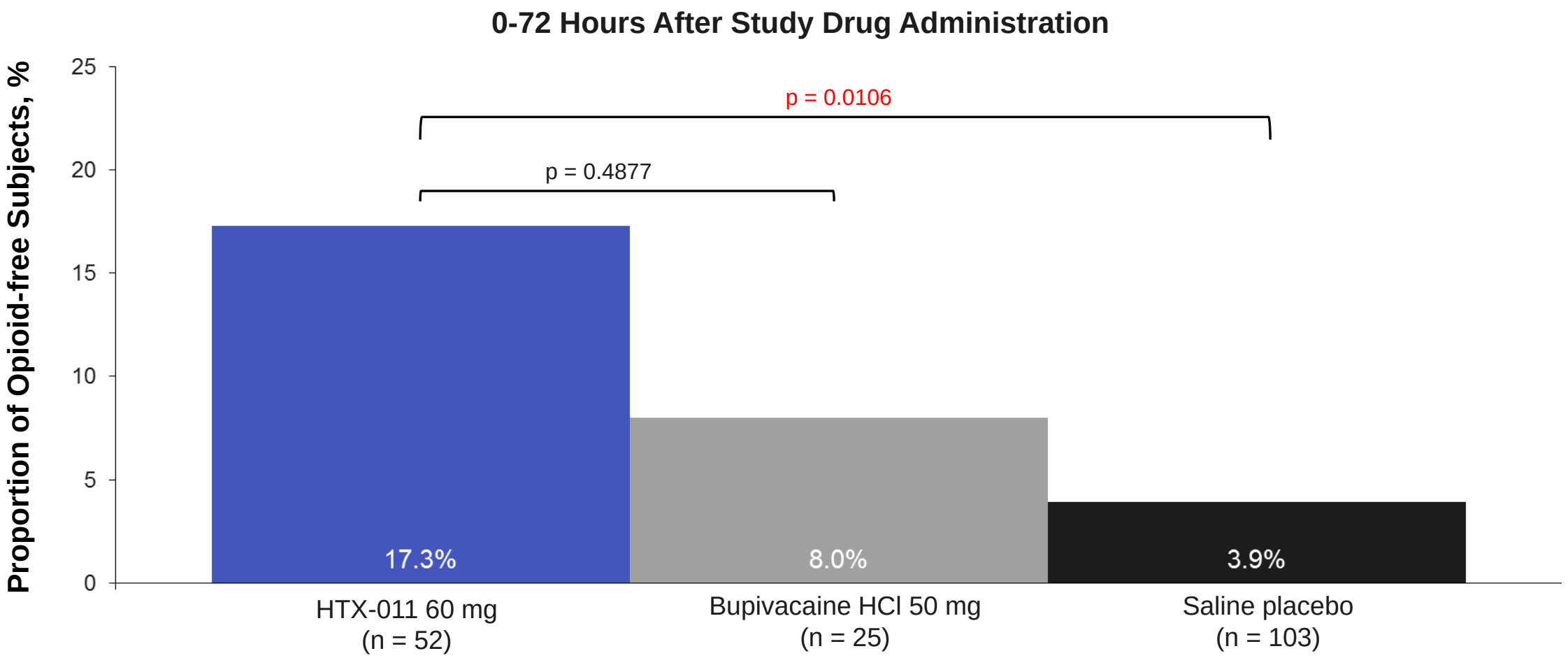


LSMD, least squares mean difference.
[a]Pain was assessed using an 11-point (0, no pain-10, worst pain imaginable) numeric rating scale.

Bunionectomy Study: HTX-011 Significantly Reduced the Use of Opioid Medication Through 72 Hours Compared with Bupivacaine or Saline Placebo



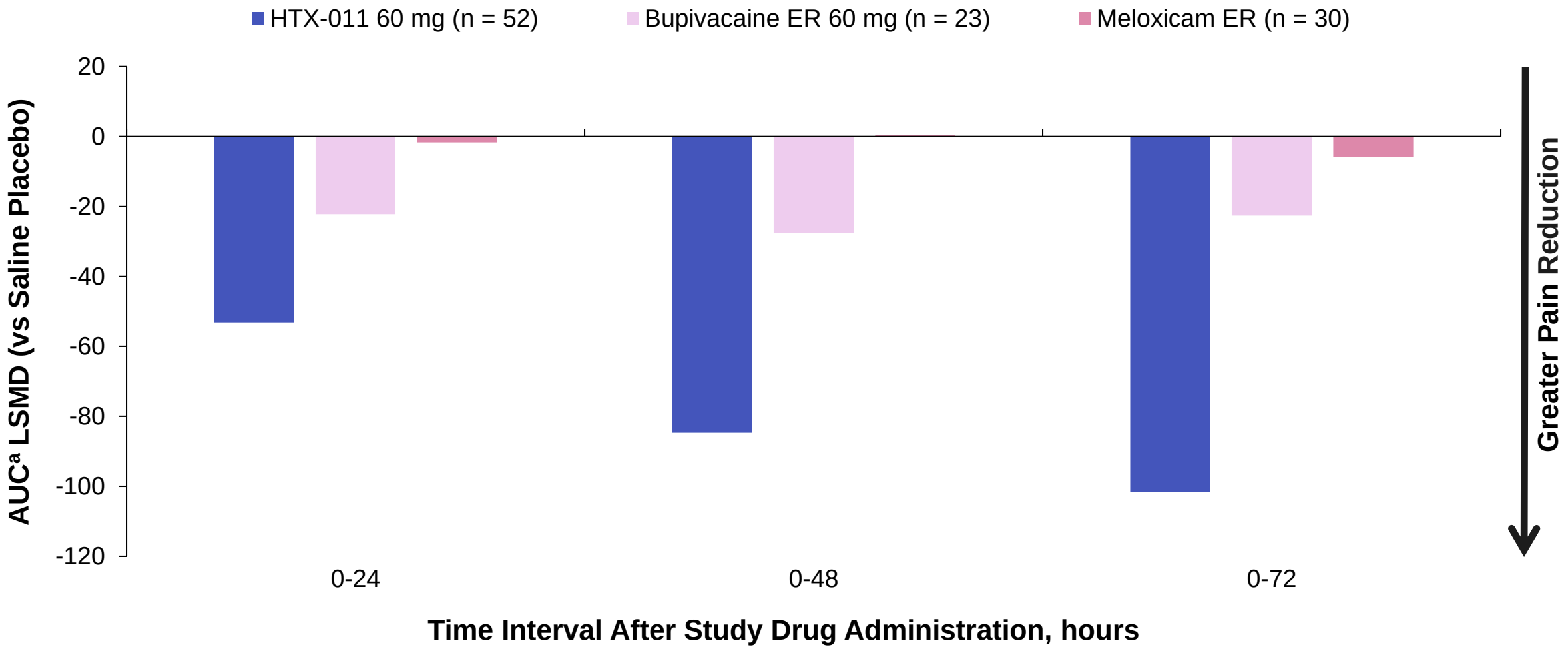
HTX-011 Significantly Increased the Proportion of Opioid-Free Subjects vs Saline Placebo



Bunionectomy Study: Summary of TEAEs

TEAEs Occurring in >10% of Subjects in Any Group, n (%)			
	HTX-011 60 mg (n = 52)	Bupivacaine HCl 50 mg (n = 25)	Saline Placebo (n = 104)
At least one TEAE	33 (63.5%)	20 (80.0%)	76 (73.1%)
Nausea	16 (30.8%)	11 (44.0%)	44 (42.3%)
Vomiting	8 (15.4%)	5 (20.0%)	27 (26.0%)
Pruritus	7 (13.5%)	4 (16.0%)	8 (7.7%)
Headache	5 (9.6%)	5 (20.0%)	19 (18.3%)
Constipation	4 (7.7%)	1 (4.0%)	20 (19.2%)

Bunionectomy Study: A Synergistic Effect on Pain Reduction Was Observed with HTX-011



[a]Pain was assessed using an 11-point (0, no pain-10, worst pain imaginable) numeric rating scale.

Conclusions

- HTX-011's unique formulation significantly reduced pain intensity through the first 72 hours after bunionectomy compared with either bupivacaine HCl or saline placebo
  - Mean pain scores remained well below the severe pain threshold through the entire 72-hour study period after treatment with HTX-011
- HTX-011 significantly reduced opioid use following bunionectomy and increased the number of opioid-free subjects through 72 hours
- HTX-011 had an adverse event profile similar to that of bupivacaine HCl or saline placebo
- HTX-011 provided a synergistic effect, demonstrating greater pain reduction than its individual components (bupivacaine ER plus meloxicam ER)
- HTX-011 may represent a significant advance in the treatment of postoperative pain