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

David Leiman, MD;[1] Harold S. Minkowitz, MD;[1] Sanjay S. Patel, PhD;[2] Guy Boccia;[2] Alice Chu, MA;[2] Linda Heiner;[2] Mary Rose Keller;[2] Erol Onel, MD;[2] Tom Ottoboni, PhD;[2] Barry Quart, PharmD[2]

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- After surgery such as abdominoplasty, pain is typically most severe within the first 72 hours[1-3]
- Adequate management of postoperative pain not only increases patient comfort, but also prevents a cascade of adverse clinical outcomes for patients and increased costs for the health care system[4,5]
- Systemic opioids are often relied upon to manage postoperative pain, increasing the risk of opioid-related adverse events and the potential for drug abuse and addiction, as well as diversion of unused opioids[6-8]
- The normal inflammatory process after acute injury (ie, surgical incision) impairs the ability of local anesthetics to block nociception[9,10]; available local anesthetics, including extended-release formulations, have demonstrated limited effect beyond 12-24 hours[11,12]
- HTX-011's long-acting formulation, using bupivacaine, meloxicam, and proprietary Biochronomer® technology,[13] is applied into the wound site to coat the affected tissue during surgery; the active ingredients in HTX-011's unique formulation work synergistically to overcome the challenges of the local inflammatory process, potentiating a reduction in postoperative pain through 72 hours
- Results in subjects undergoing inguinal herniorrhaphy[14] and bunionectomy[15] indicate that HTX-011 significantly reduces pain intensity and the need for rescue opioids; here, we describe the efficacy of HTX-011 in abdominoplasty, a procedure involving larger incisions

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- This analysis includes a cohort of subjects participating in a randomized, multicenter, double-blind, placebo- and active-controlled, phase 2 institutional review board–approved clinical trial (clinicaltrials.gov, NCT02689258)
- Subjects were randomly assigned to receive HTX-011 400 mg via a combination of injection and instillation, bupivacaine HCl 100 mg, or saline placebo
- After signing informed consent, subjects were administered study drug during surgery and evaluated postoperatively for pain and opioid rescue medication use through 72 hours

Table 1. Clinical Study Design

ELIGIBILITY	
Key Inclusion Criteria • Male or female ≥18 years old • BMI ≤30 kg/m^2 • ASA Physical Status classification system category 1 or 2 • Planning to undergo complete abdominoplasty (may involve umbilical repositioning)	**Key Exclusion Criteria** • Clinically significant renal (creatinine ≥2× ULN) or hepatic (AST or ALT ≥3× ULN) 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
END POINTS	
Efficacy End Points (assessed through 72 hours) • AUC of pain intensity score[a] • Total rescue opioid use (MME)[b] • Proportion of opioid-free subjects	**Safety End Points** • TEAEs, serious TEAEs • Vital signs, clinical laboratory evaluations, ECG

ALT, alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, aspartate aminotransferase; AUC, area under the curve; BMI, body mass index; ECG, electrocardiography; MME, intravenous morphine milligram equivalent; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

[a]Pain intensity was assessed on a visual analog scale (100-mm line anchored by "no pain" to "worst pain imaginable") by measuring the distance from 0 (no pain) to the subject's mark; mean pain scores were adjusted for opioid use using the windowed worst observation carried forward procedure.

[b]Rescue pain medication was available as needed; total rescue opioid medication consumed was converted to MMEs and summed for analysis.

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Introduction

Methods

Results: Baseline Characteristics

Results: Pain Reduction

Results: Opioid Use

Results: Safety

Conclusions

References

Baseline Population Characteristics

- This analysis included a total of 74 females who underwent complete abdominoplasty; demographics were comparable across cohorts (**Table 2**)

Table 2. Demographics and Baseline Characteristics

	HTX-011 400 mg n = 25	Bupivacaine 100 mg n = 17	Saline Placebo n = 32
Mean age, years (SD)	42.6 (8.71)	40.6 (6.38)	43.2 (8.53)
Mean BMI, kg/m^2 (SD)	26.89 (2.06)	26.54 (2.70)	27.34 (1.57)
Race, n (%)			
White	19 (76.0)	13 (76.5)	23 (71.9)
Black or African American	5 (20.0)	4 (23.5)	9 (28.1)
Other	1 (4.0)	0	0

BMI, body mass index; SD, standard deviation.

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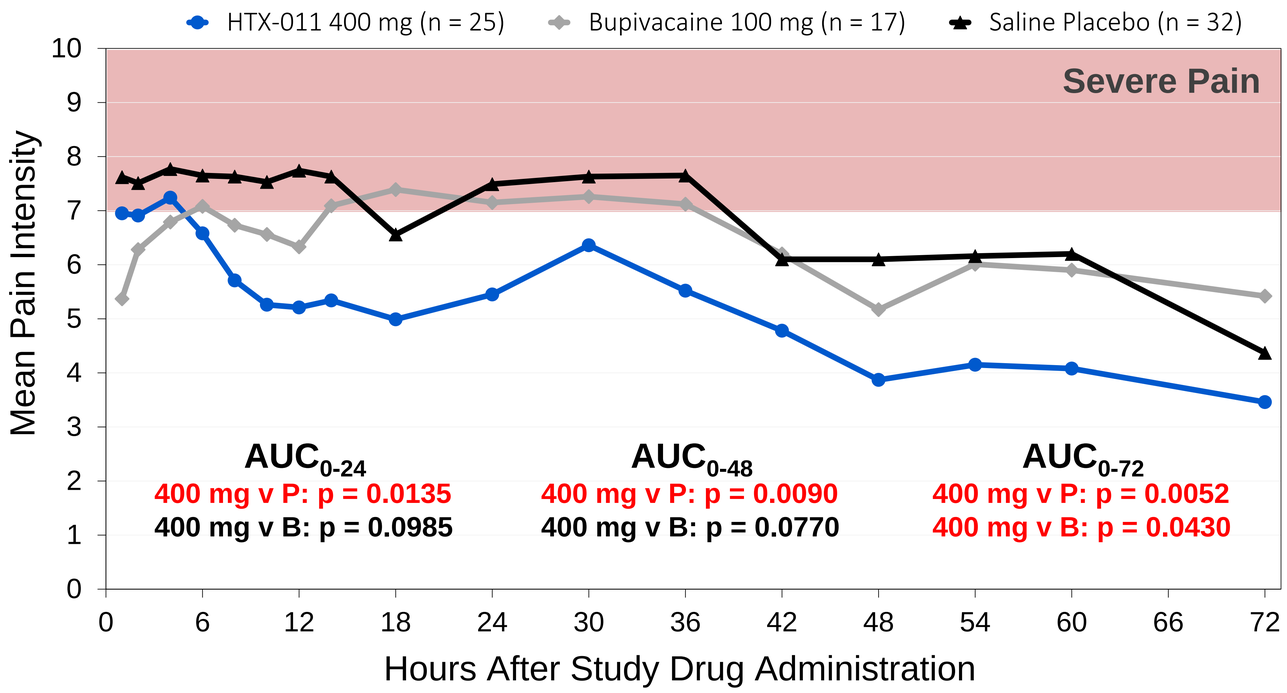
Efficacy – Pain Reduction

- Subjects treated with HTX-011 experienced significantly less pain (as measured by AUC of mean pain intensity scores) at all time points through 72 hours compared with subjects who received saline placebo; HTX-011 resulted in significantly less pain compared with bupivacaine during the 0-72 hour window (**Figure 1**)

Figure 1. Mean pain intensity[a] over time following complete abdominoplasty.



AUC_{0-x}, area under the curve from 0 to x hours after study drug administration; B, bupivacaine; P, saline placebo.
[a]Pain was assessed on a visual analog scale (100-mm line anchored by "no pain" to "worst pain imaginable") by measuring the distance from 0 (no pain) to the subject's mark

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Efficacy – Postoperative Opioid Rescue Medication Use

- Subjects receiving HTX-011 required significantly less opioid rescue medication through 72 hours than did those receiving bupivacaine or saline placebo (**Figure 2**)
- Treatment with HTX-011 led to a greater percentage of opioid-free subjects on each study day (**Figure 3**), indicating that subjects were able to stop opioid rescue medication sooner after receiving HTX-011

Figure 2. Total opioid rescue medication use over time.

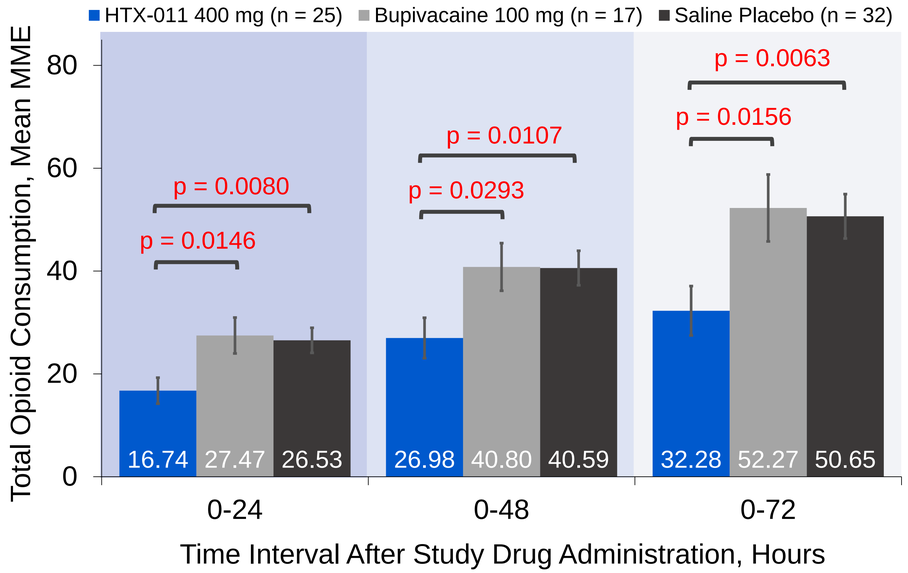
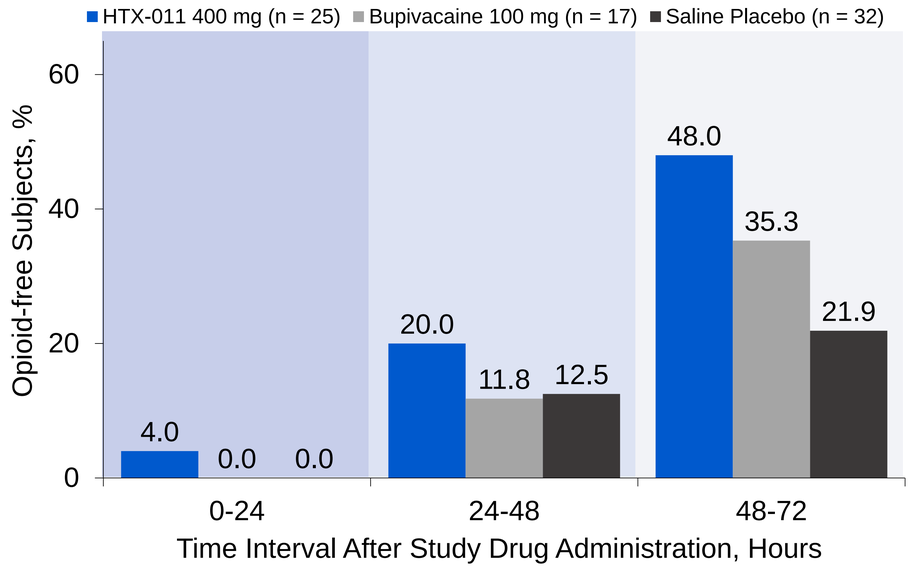


Figure 3. Percentage of subjects who were opioid-free each postoperative day.



MME, intravenous morphine milligram equivalent.

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Safety

- The incidence of adverse events in subjects treated with HTX-011, bupivacaine, and saline placebo are presented in **Table 3**
- Differences in adverse event rates between the treatment groups were not clinically meaningful

Table 3. Treatment-Emergent Adverse Events Occurring in >2 Subjects in Any Group

TEAE, n (%)	HTX-011 400 mg n = 25	Bupivacaine 100 mg n = 17	Saline Placebo n = 32
Any TEAE	20 (80.0)	15 (88.2)	28 (87.5)
Nausea	17 (68.0)	12 (70.6)	14 (43.8)
Constipation	7 (28.0)	7 (41.2)	10 (31.3)
Headache	7 (28.0)	2 (11.8)	11 (34.4)
Pruritus	4 (16.0)	2 (11.8)	7 (21.9)
Vomiting	3 (12.0)	1 (5.9)	3 (9.4)
Wound dehiscence	2 (8.0)	2 (11.8)	4 (12.5)
Dizziness	2 (8.0)	4 (23.5)	3 (9.4)
Hypotension	2 (8.0)	1 (5.9)	3 (9.4)
Seroma	1 (4.0)	0	3 (9.4)
Pyrexia	0	2 (11.8)	3 (9.4)

TEAE, treatment-emergent adverse event.

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- The unique formulation of HTX-011 was well tolerated and significantly reduced postoperative pain intensity through 72 hours compared with saline placebo, and during the 0-72 hour window compared with bupivacaine
- HTX-011 significantly reduced the need for opioid rescue medication through 72 hours compared with bupivacaine and placebo
- Taken with previous reports in herniorrhaphy[14] and bunionectomy,[15] these abdominoplasty data suggest that HTX-011 is well tolerated and effective across a range of surgical models with different incision sizes
- HTX-011 may represent a significant advance in postoperative pain management

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