Reduction in Proportion of Patients With Severe Pain Following Herniorrhaphy Using HTX-011 as the Foundation of a Non-Opioid Multimodal Analgesic Regimen

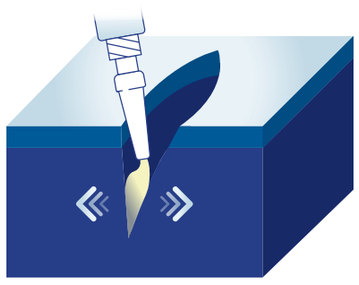
Neil Singla, MD,[1] Barry Quart, PharmD,[2] Jackie Evans-Shields, PharmD,[2] Jia Hu, PhD,[2] Jay Redan, MD[3]

[1]Lotus Clinical Research, Pasadena, CA, USA; [2]Heron Therapeutics, San Diego, CA, USA; [3]AdventHealth Celebration, Celebration, FL, USA

INTRODUCTION

- After surgery, up to 70% of patients experience moderate to severe postoperative pain within the first 72 hours[1,2]
- Current analgesic treatments include local anesthetics, which provide pain relief for 6 to 12 hours,[3] and opioid medicines, which are indicated for acute severe pain but can result in serious, even life-threatening adverse events (AEs)[4,5]
- Evidence-based guidelines recommend the use of multimodal analgesia (MMA) to manage postoperative pain[6,7]
- HTX-011 is an investigational extended-release, dual-acting local anesthetic (DALA) that combines bupivacaine and low-dose meloxicam in a proprietary Biochronomer (Heron Therapeutics, San Diego, CA, USA) extended-release polymer
  - HTX-011 is administered via needle-free instillation (**Figure 1**) to the surgical site

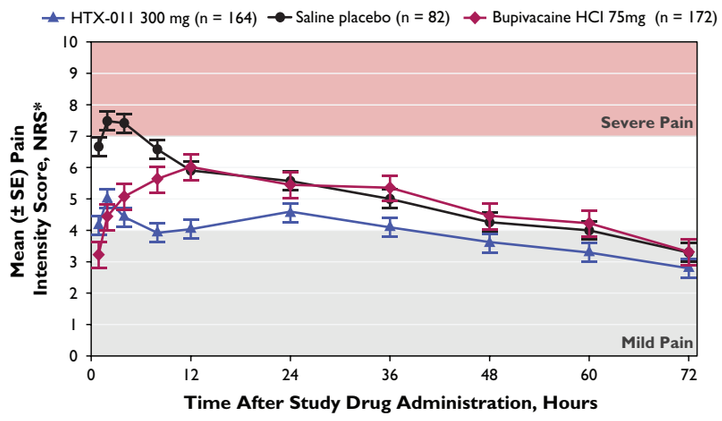
Figure 1. Needle-Free Instillation of HTX-011



HTX-011 is instilled into the surgical site prior to wound closure using a syringe (without a needle) and a Luer lock applicator.

- In a phase 3 herniorrhaphy study, HTX-011 300 mg/9 mg (bupivacaine/meloxicam) alone (without a scheduled MMA regimen) (**Figure 2**)[8]:
  - Relieved severe pain significantly better than either bupivacaine HCl or saline placebo
  - Resulted in significantly fewer patients requesting opioid medication
  - Demonstrated a clinically similar safety profile to bupivacaine HCl

Figure 2: HTX-011 Without MMA Significantly Reduced Pain Compared With Bupivacaine and Placebo[8]



*Using numeric rating scale with windowed worst observation carried forward.
MMA, multimodal analgesia; NRS, numeric rating scale; SE, standard error.

OBJECTIVES

- The study described herein is a follow-on study to the phase 3 herniorrhaphy study and was designed to:
  - Evaluate the efficacy of HTX-011 with a non-opioid MMA regimen for postoperative pain, including severe pain, in patients receiving open inguinal herniorrhaphy with mesh
  - Determine the proportion of opioid-free patients (and total opioid use) after postoperative treatment with HTX-011 as the foundation of a non-opioid MMA regimen
  - Assess the relationship between severe pain and the use of opioid medication
  - Evaluate the safety and tolerability of HTX-011 with a non-opioid MMA regimen for postoperative pain

METHODS

- In this open-label study, patients scheduled to undergo open inguinal herniorrhaphy with mesh who met the study entry criteria (**Table 1**) were enrolled into one of two sequential cohorts. Both cohorts received a single dose of HTX-011 300 mg/9 mg (bupivacaine/meloxicam) during surgery as the foundation of a scheduled non-opioid background MMA regimen
  - Cohort 2 also received a single dose of intravenous (IV) ketorolac intraoperatively (15 mg or 30 mg, per product labeling)
  - Non-opioid preoperative MMA therapy comprised oral acetaminophen 1000 mg; non-opioid postoperative MMA therapy comprised oral ibuprofen 600 mg and oral acetaminophen 1000 mg every 6 hours, alternating the 2 medications so that an analgesic was administered every 3 hours throughout the 72-hour inpatient postoperative period
- Patients were kept in the hospital for 72 hours for administration of the scheduled MMA regimen and for assessments of postoperative pain. Opioid rescue medication was available upon request for inadequate pain control independent of pain score

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 • Provided written informed consent • Scheduled to undergo unilateral open inguinal herniorrhaphy with mesh under general anesthesia • ASA Physical Status Classification System category I-III	• Pre-existing concurrent acute or chronic painful/restrictive condition (unrelated to the hernia) that may require analgesia during the postoperative period • Use of the following within a defined time period prior to 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; NSAIDs, nonsteroidal anti-inflammatory drugs.

Outcome Measures

- The primary endpoint was the proportion of patients who did not receive opioid rescue medication (ie, remained opioid-free) through 72 hours after surgery
- Secondary endpoints included:
  - Proportion of patients in severe pain (numeric rating scale [NRS] ≥7) at any time through 72 hours after surgery
  - Total opioid consumption (IV morphine milligram equivalents [MME]) through 72 hours after surgery
  - Proportion of patients receiving no opioid rescue from 0 through 72 hours who did not require opioid pain medication through day 10 and day 28 recovery
- Safety endpoints included incidence of AEs, serious AEs, opioid-related AEs, and change from baseline in clinical laboratory results through day 28

Assessments

- Opioid rescue medication taken from time 0 (start of HTX-011 instillation) to 72 hours postsurgery were recorded; patients completed a daily diary to record opioid use (yes/no) from 72 hours through day 28
- Pain level was evaluated at various timepoints using an 11-point NRS, where 0 represents "no pain" and 10 represents "worst pain imaginable"
- Safety was primarily assessed by recording AEs and safety laboratory tests

Statistical Analysis

- Opioid-free through 72 hours was defined as 0 MME during the 72-hour postoperative period
- Opioid-free from 72 hours through day 10 or 28 was defined as answering "no" to the question "Did you take any opioid medication?" on a daily basis from 72 hours through day 10 or 28; patients who reported "yes" or had a missing report were not considered to be opioid-free during the period of interest
- Pain-intensity observations made for a windowed period after use of opioid rescue medication were replaced by the highest pain score recorded before the opioid was given

RESULTS

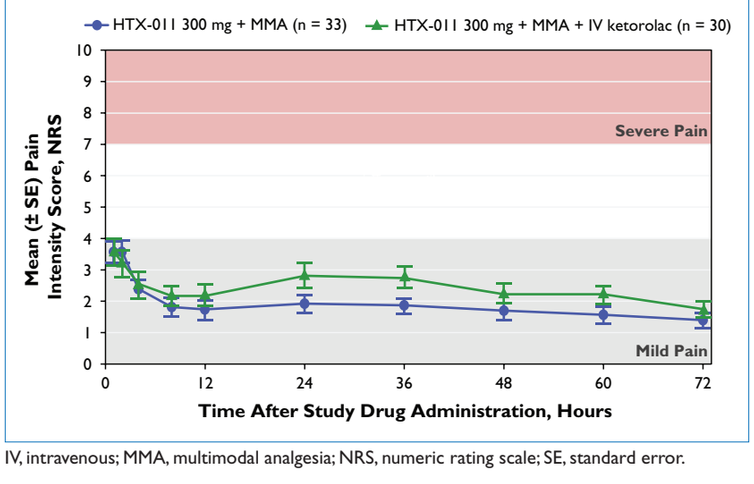
Baseline Population Characteristics

- Sixty-three patients (cohort 1: 33 patients; cohort 2: 30 patients) were treated with HTX-011 across multiple study sites; 61 (97%) completed the 72-hour inpatient postoperative period and 58 (92%) completed the study through day 28
- Baseline characteristics were well-balanced between cohorts; most patients were male (94%) and the mean BMI was 28 kg/m^2

Pain Intensity

- The addition of an intraoperative dose of IV ketorolac did not demonstrate additional benefit; therefore, results for the total study population are presented
- Throughout the 72-hour inpatient period, the mean pain intensity score never rose above the mild pain range (NRS <4) for either cohort (**Figure 3**)
- The proportion of patients with severe pain (NRS ≥7) at any time was low (17.5%) across both cohorts during the 72-hour postoperative period; most severe pain occurred during the first 24 hours
- The proportion of patients with severe pain was lower in this follow-on study, in which HTX-011 was used as the foundation of a scheduled non-opioid MMA regimen compared with the precedent phase 3 study[8]

Figure 3. HTX-011 With MMA Kept Mean Pain Intensity in the Mild Range Through 72 Hours

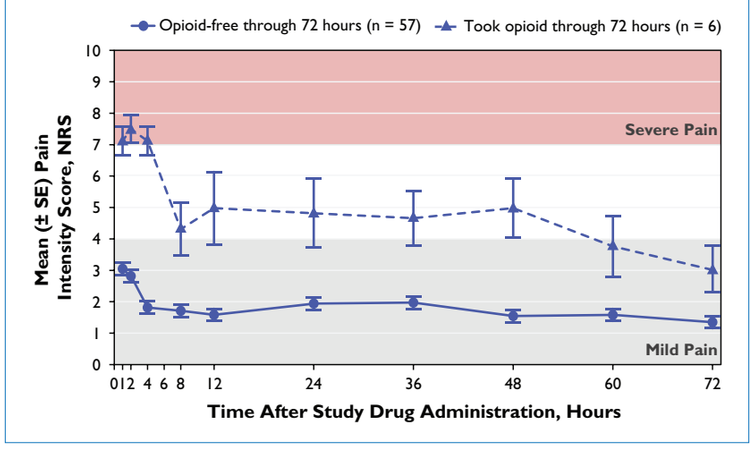


IV, intravenous; MMA, multimodal analgesia; NRS, numeric rating scale; SE, standard error.

Postoperative Opioid Use

- 90% of patients (57/63) did not require opioids to manage pain at any time during the 72-hour inpatient period
- Mean total opioid consumption during the 72-hour postoperative period was <1 MME in the overall study population and <10 MME in the subset of patients who took an opioid during that period
- All 6 patients who required opioid rescue medication could be identified early; they reported an NRS score of ≥6 and/or received an opioid within the first 2 hours
- The small subset of patients requiring opioid rescue immediately exhibited a distinct pain intensity profile and could be easily identified within the first 2 hours (**Figure 4**)

Figure 4. Patients Requiring Opioids Have A Distinct Mean Pain Intensity Profile and Can Be Identified Early*



*Combined data from both cohorts.
NRS, numeric rating scale; SE, standard error.

Safety

- Overall, 24 (38%) patients experienced an AE; the rates of AEs in the two cohorts were similar (**Table 2**)
- The scheduled use of nonsteroidal anti-inflammatory drugs (NSAIDs) did not demonstrate an increase in NSAID-related toxicity
- The incidence of TEAEs was much lower in the current study than in the prior phase 3 study, likely due to the lower rates of opioid-related AEs observed in this follow-on study[8]

Table 2. Summary of AEs, n (%)

Category	Cohort 1 HTX-011 n = 33	Cohort 2 HTX-011 + IV ketorolac n = 30	Total n = 63
Any AE	12 (36.4)	12 (40.0)	24 (38.1)
AE possibly related to HTX-011	2 (6.1)	1 (3.3)	3 (4.8)
Opioid-related AE*	2 (6.1)	5 (16.7)	7 (11.1)
AE leading to premature withdrawal	0	0	0
Fatal or other SAE	0	0	0

*Opioid-related AEs observed in the study included constipation, nausea, pruritus, and vomiting.
AE, adverse event; IV, intravenous; SAE, serious adverse event.

SUMMARY AND CONCLUSIONS

- HTX-011, in combination with a scheduled regimen of non-opioid over-the-counter analgesics, eliminated severe postoperative pain in 82.5% of patients
  - The mean pain intensity score did not rise above the mild range at any time during the 72-hour inpatient period
  - Patients who experienced severe pain did so within the first 2 hours after surgery
- Pain intensity and opioid use were similar between cohorts, and no additional benefit of IV ketorolac was observed
- The majority (90%) of patients did not require opioids to manage pain at any time during the 72-hour inpatient period; of these patients, most (91%) remained opioid-free through recovery at day 28
  - Based on these results, the following algorithm was developed to determine who should receive a discharge prescription for opioids in future studies
  - Patients who receive an opioid rescue or have a NRS pain score of ≥6 within the first 2 hours after surgery
- The combination of HTX-011 and the scheduled non-opioid MMA regimen was well tolerated, and use of NSAIDs did not increase NSAID-related toxicity
- These data demonstrate that HTX-011 could be the foundation for an opioid-free post-operative recovery

REFERENCES

1. Lynch EP et al. *Anesth Analg*. 1997;85:117-123.
2. Svensson I et al. *J Pain Symptom Manage*. 2000;20:193-201.
3. Kehlet H et al. *Acta Anaesthesiol Scand*. 2011;55:778-784.
4. Kessler ER et al. *Pharmacotherapy*. 2013;33:383-391.
5. Ramachandran SK et al. *J Clin Anesthesia*. 2011;23:207-213.
6. American Society of Anesthesiologists. *Anesthesiology*. 2012;116:248-273.
7. Chou R et al. *J Pain*. 2016;17:131-157.
8. Viscusi E et al. *Hernia*. 2019. https://doi.org/10.1007/s10029-019-02023-6.

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 September 14, 2019. http://bit.ly/2MlcYDd **(This URL is case sensitive.)**

Presented at the European Society of Regional Anaesthesia & Pain Therapy (ESRA) 2019 Congress; September 11-14, 2019; Bilbao, Spain