Opioid-Free Hernia Recovery With HTX-011, the First Dual-Acting Local Anesthetic, as Foundation Therapy

Neil Singla, MD,[1] Jia Hu, PhD,[2] Jay Redan, MD[3]

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

INTRODUCTION

- Up to 70% of subjects experience moderate to severe pain after surgery, with the greatest degree of pain occurring within the first 72 hours[1,2]
- HTX-011 is a novel, dual-acting, extended-release (ER), fixed-dose combination local anesthetic comprising bupivacaine and low-dose meloxicam, incorporated in a proprietary Biochronomer® polymer
- In a phase 3 herniorrhaphy study, treatment with HTX-011 300 mg without background multimodal analgesics (MMA) significantly reduced total opioid consumption, provided superior pain relief, and resulted in more opioid-free subjects (51%) through 72 hours than that achieved with either placebo or bupivacaine hydrochloride 75 mg[3]
- This trial was designed to be a follow-on study to the prior phase 3 study

OBJECTIVES

- To evaluate the efficacy and safety of HTX-011 as the foundation of an opioid-free hernia recovery MMA regimen that includes nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen
- To determine whether the addition of intravenous (IV) ketorolac to an over-the-counter MMA regimen provides additional benefit

METHODS

- This study included 2 cohorts. Both cohorts received a single dose of HTX-011 300 mg administered via needle-free application to the surgical site during surgery as well as a nonopioid background MMA regimen; Cohort 2 also received IV ketorolac intraoperatively (**Table 1**)
  - Nonopioid preoperative MMA therapy comprised oral acetaminophen 1000 mg; nonopioid postoperative MMA therapy comprised oral ibuprofen 600 mg and oral acetaminophen 1000 mg administered every 6 hours (alternating every 3 hours) throughout the 72-hour inpatient postoperative period
  - IV ketorolac 15 mg was administered for subjects ≥65 years old with serum creatinine >1.5 mg/dL and/or weight <50 kg or 30 mg for subjects <65 years old and/or weight ≥50 kg
- Subjects were kept in the hospital for 72 hours for assessments of postoperative pain and opioid rescue medication

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 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 NSAIDs, long-acting opioids, any opioids, bupivacaine, or any local anesthetic for ≤10 days, ≤3 days, ≤24 hours, ≤5 days, or ≤72 hours prior to scheduled surgery, respectively • BMI >39 kg/m^2

ASA, American Society of Anesthesiologists; BMI, body mass index; NSAIDs, nonsteroidal anti-inflammatory drugs.

Outcome Measures

- The primary efficacy endpoint was the proportion of subjects who remained opioid-free through 72 hours after surgery
- Secondary efficacy endpoints included:
  - Total opioid consumption (IV morphine milligram equivalents [MME]) through 72 hours after surgery
  - Proportion of subjects remaining opioid-free through 72 hours and days 10 and 28 after surgery
  - Proportion of subjects in severe pain (numeric rating scale [NRS] ≥7) at any time through 72 hours after surgery
- Safety endpoints included incidence of treatment-emergent adverse events (TEAEs), serious adverse events, and change from baseline in clinical laboratory results through day 28

Assessments

- Opioid rescue medication taken from time 0 (start of HTX-011 administration) to 72 hours postsurgery were recorded; subjects completed a daily diary to record opioid use (yes/no) from 72 hours through day 28
- Pain level was evaluated at 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 adverse events (AEs) and safety laboratory tests

Statistical Analysis

- Opioid-free through 72 hours was defined as 0 IV 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; subjects who had a missing report or withdrew from the study were not considered to be opioid-free
- For analysis of pain intensity, NRS endpoints were adjusted for the duration of effect of opioid rescue medication using the windowed worst observation carried forward method

RESULTS

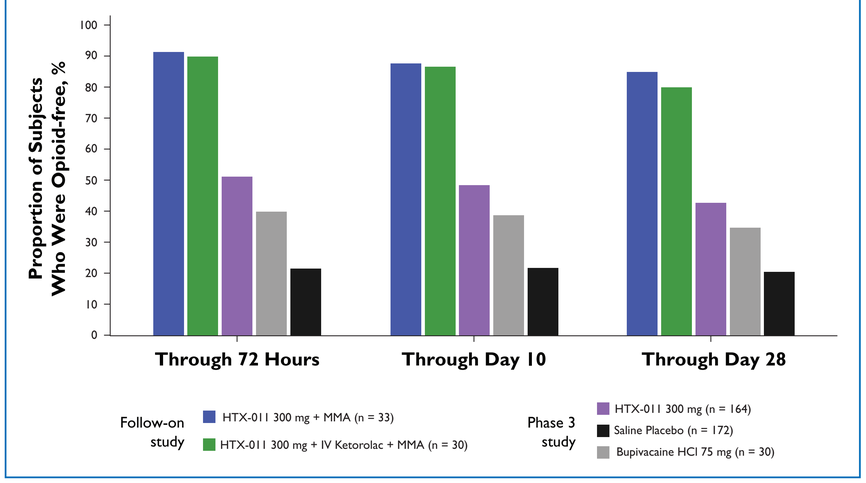
Baseline Population Characteristics

- A total of 63 subjects (Cohort 1: 33; Cohort 2: 30) received treatment at 3 sites across the United States, of which 61 completed the 72-hour inpatient postoperative period and 58 completed the study through day 28
- The baseline characteristics were generally well-balanced across the follow-on and phase 3 studies; 93.7% and 94.5% of subjects were male, average age was 48.7 and 48.9 years, and average body mass index was 27.6 and 27.2 kg/m^2 among all subjects in the follow-on and phase 3 studies, respectively

Postoperative Opioid Use

- More than 90% of subjects who received HTX-011 and a nonopioid MMA regimen did not require opioids to manage their postoperative pain for 72 hours after surgery. In comparison, 51%, 40%, and 22% of subjects were opioid-free when receiving HTX-011, bupivacaine, and placebo, respectively, in the prior phase 3 study (**Figure 1**)
  - Among the subjects who were opioid-free through 72 hours, 96.5% remained opioid-free through Day 10 and 91.2% remained opioid-free through Day 28
- All 6 subjects who took an opioid during the 72-hour inpatient postoperative period had an NRS score ≥ 6 within the first 2 hours and/or had received an opioid within the first 2 hours
- Mean ± SE total postoperative opioid consumption was 0.9 ± 0.41 MME overall (0.6 ± 0.37 MME for cohort 1 and 1.3 ± 0.77 MME for cohort 2)

Figure 1. More Than 90% of Subjects Opioid-free Through 72 Hours with HTX-011 and MMA.

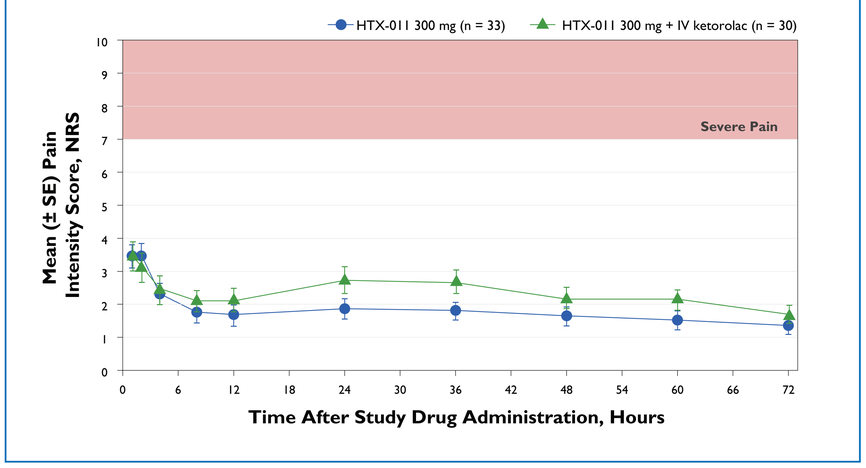


IV, intravenous; MMA, multimodal analgesics.

Pain Intensity

- Mean NRS never rose above the mild pain range (<4) throughout the 72-hour postoperative period for either cohort (**Figure 2**); the addition of IV ketorolac did not demonstrate additional pain relief
- The proportion of subjects with severe pain during the 72-hour postoperative period was 17.5% across both cohorts
  - Severe pain almost always occurred during the first 24 hours; if severe pain was not reported during the first 24 hours, none of these subjects subsequently reported severe pain

Figure 2. Mean Pain Intensity Through 72 Hours After Herniorrhaphy



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

Safety

- Overall, 24 (38.1%) subjects experienced a TEAE; there was little difference between the rates of TEAEs observed in the two cohorts; however, the incidence of TEAEs was much lower in the current study than in the prior phase 3 study, predominantly due to the lower rates of opioid-related adverse events (ORAEs) (**Table 2**)
- There was no evidence of NSAID-related cardiovascular, gastrointestinal, or renal toxicity

Table 2. Summary of TEAEs, n (%)

	Follow-on Study		Phase 3
Category	Cohort 1 HTX-011 n = 33	Cohort 2 HTX-011 + IV ketorolac n = 30	HTX-011 n = 163
Any TEAE	12 (36.4)	12 (40.0)	119 (73.0)
Severe TEAE	0	1 (3.3)	3 (1.8)
TEAE possibly related to study drug	2 (6.1)	1 (3.3)	41 (25.2)
Opioid-related TEAE	2 (6.1)	5 (16.7)	53 (32.5)
SAE	0	0	2 (1.2)
Fatal SAE	0	0	0
TEAE leading to premature withdrawal from the study	0	0	0

IV, intravenous; SAE, serious adverse event; TEAEs, treatment-emergent adverse events.

SUMMARY AND CONCLUSIONS

- HTX-011 is a novel, dual-acting local anesthetic that when used as foundation therapy enables opioid-free hernia recovery
- More than 90% of subjects were opioid-free through 72 hours with HTX-011 and over-the-counter analgesics
  - Among the subjects who were opioid-free through 72 hours, 96.5% remained opioid-free through Day 10 and 91.2% remained opioid-free through Day 28
  - The use of IV ketorolac did not provide additional benefit
- HTX-011 was well tolerated; co-administration with IV and oral NSAIDs did not affect the safety profile of HTX-011

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. Viscusi ER et al. Manuscript submitted to *Hernia*. 2019.

ACKNOWLEDGMENTS

Funding for this research and medical writing assistance by Andrew Occiano, PharmD, was provided by Heron Therapeutics, Inc. (San Diego, CA).

HERON THERAPEUTICS

Presented at the American Society for Enhanced Recovery and Perioperative Medicine (ASER) 2019 Congress; April 25-27, 2019; Washington, DC.