ePOSTER #48

Safety, Pharmacokinetics, and Analgesic Activity of HTX-011 in Spinal Surgery

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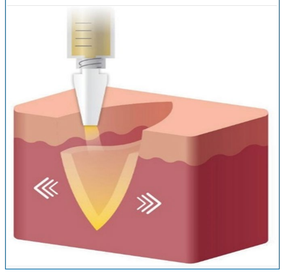
INTRODUCTION

- HTX-011 is a non-opioid, fixed-dose, extended-release local anesthetic containing bupivacaine and low-dose meloxicam formulated in a proprietary polymer.
- HTX-011 is applied as a single dose without a needle into the surgical site to coat the pain-generating tissues prior to wound closure (**Figure 1**).
- After administration, the polymer enables extended release of bupivacaine and meloxicam simultaneously for approximately 3 days[1,2].
- HTX-011 is approved as ZYNRELEF® for postsurgical analgesia for up to 72 hours after foot and ankle, small-to-medium open abdominal, and lower extremity total joint arthroplasty surgical procedures.
- Orthopedic surgery is painful with one of the highest rates of opioid prescribing. Reduced exposure to opioids and better pain management is associated with improved patient outcomes as well as reduced risk for developing persistent pain and chronic opioid use and abuse.
- This Phase 2, open-label study was conducted in patients undergoing open, lumbar spinal decompression surgery.

Figure 1. HTX-011 Administered Without Needle



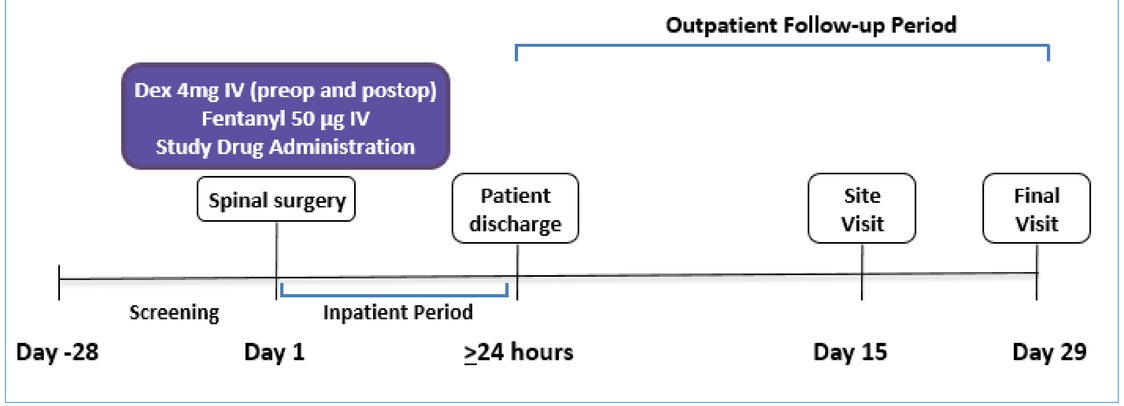
METHODS

- **Key Inclusion Criteria:** Adult patients (ASA I, II, III) scheduled to undergo open, 1- to 3-level lumbar decompression surgery with or without fixation under general anesthesia without neuraxial technique (eg, spinal, epidural, or regional nerve block).
- **Key Exclusion Criteria:** Pre-existing painful condition expected to require analgesic treatment, long-acting opioid use within 3 days before surgery.
- **Study Objectives**: Safety was the primary objective and the primary endpoint was the incidence of serious adverse events (SAEs). Pharmacokinetics (PK) and analgesic activity were secondary objectives.

METHODS (cont.)

- **Study Treatment:** Patients were to be enrolled into 1 of 3 cohorts
  - Cohort 1: Bupivacaine HCl 100 mg (20 mL) for 1- to 3-level surgery.
  - Cohort 2: Single individualized HTX-011 dose up to 200 mg/6 mg (7 mL) for 1-level surgery.
  - Cohort 3: Single individualized HTX-011 dose up to 200 mg/6 mg (7 mL) for 2- to 3-level surgery.
- Study drug was administered into the surgical site after paraspinal muscle closure. The surgeon determined the dose of HTX-011.
- Patients also received dexamethasone 4 mg IV before and after surgery, and fentanyl 50 µg IV at the end of surgery.
- Patients remained in house for ≥24 hours and were followed through Day 29.
- **Postoperative Rescue Medication:**
  - Through discharge: PO acetaminophen (≤1,000 mg within 6-hour period), PO immediate-release oxycodone (≤10 mg within 4 hour period), and/or IV morphine (≤10 mg within 2-hour period).
  - Discharge through Day 15: PO acetaminophen (≤1,000 mg within 6-hour period) recommended.

Figure 2. Study Design



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STUDY PATIENT CHARACTERISTICS

- 32 patients were dosed (6 in Cohort 1, 13 in Cohort 2, and 13 in Cohort 3) (**Table 1**). 31 (96.9%) patients completed the study.
- The mean dose of HTX-011 administered in Cohort 3 was ~twice that of Cohort 2 (**Table 1**) and likely reflects the difference in the size of the surgical space between 1-level and multi-level spinal decompression surgery.

Table 1. Baseline Characteristics and Surgical Details

	Cohort 1 Bupivacaine HCl 100 mg (N=6)	Cohort 2 HTX-011 up to 200 mg/6 mg (N=13)	Cohort 3 HTX-011 up to 200 mg/6 mg (N=13)
Age, mean (SD)	70.0 (6.54)	59.2 (15.84)	62.2 (7.24)
Male, n (%)	6 (100%)	7 (53.8%)	11 (84.6%)
Race, n (%)			
White	6 (100%)	10 (76.9%)	13 (100%)
Other[a]	0	3 (23.1%)	0
Type of surgical procedure			
Laminectomy/Laminotomy	2 (33.3%)	10 (76.9%)	12 (92.3%)
Other procedures	4 (66.7%)	3 (23.1%)	1 (7.7%)
Number of Levels Decompressed			
1 level	1 (16.7%)	13 (100%)	0
2-3 levels	5 (83.3%)	0	13 (100%)
Mean dose (vol) of study drug[b]	91.5 mg (18.3 mL)	91.9 mg/2.8 mg (3.1 mL)	190.8 mg/5.7 mg (6.5 mL)

[a] Other included Black/African Descent, Asian, and biracial.

[b] For HTX-011, the dose is bupivacaine mg/meloxicam mg and was determined based on syringe weight. The volume was calculated..

SAFETY RESULTS

- The incidence of any adverse event (AE) was lower for HTX-011 than bupivacaine HCl. No individual AE occurred in >1 HTX-011-treated patient.
- All AEs were mild or moderate in severity, and none were related to study drug.
- No SAEs or AEs leading to study withdrawal were reported for HTX-011. SAEs occurred in 2 bupivacaine-treated patients (dural tear, metabolic encephalopathy, and atrial fibrillation).
- There was no evidence of local anesthetic systemic toxicity (LAST).
- There were no AEs of bleeding or local inflammatory AEs.
- There were no meaningful differences across cohorts in hematology, chemistry, or vital signs.
- There was no meaningful difference across cohorts in motor or sensory function.
- Motor strength was ≥4 on a 0-5 scale for all muscle groups from 8 hours onwards.

Table 2. Summary of Adverse Events

Patients With AEs, n (%)	Cohort 1 Bupivacaine HCl 100 mg (N=6)	Cohort 2 HTX-011 up to 200 mg/6 mg (N=13)	Cohort 3 HTX-011 up to 200 mg/6 mg (N=13)
Any AE	5 (83.3%)	5 (38.5%)	6 (46.2%)
AEs related to study drug	0	0	0
Severe AEs	0	0	0
SAEs	2 (33.3%)	0	0
AEs leading to study withdrawal	0	0	0

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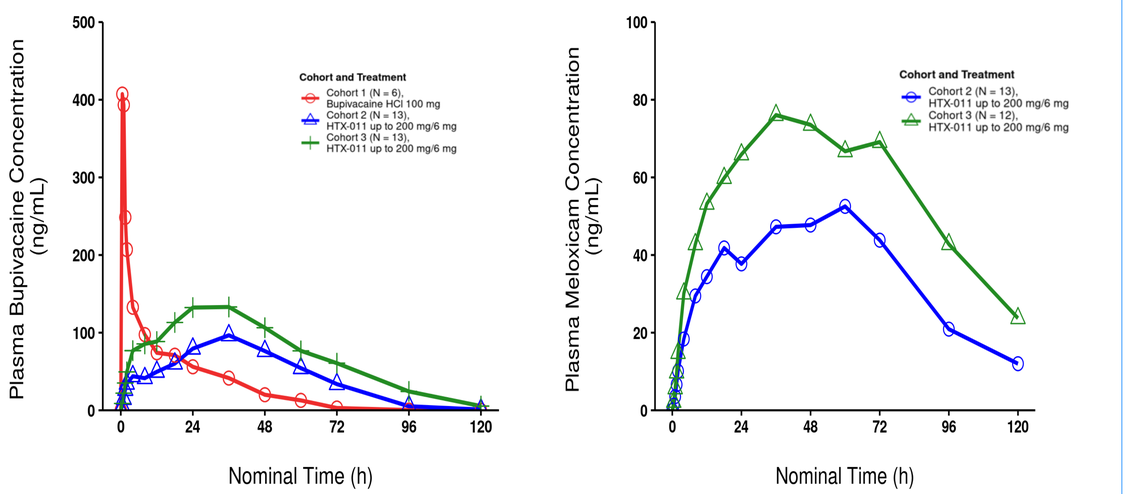
PK RESULTS

- HTX-011 demonstrated sustained plasma levels of bupivacaine and meloxicam (at least 4 to 5 days postdose, respectively) (**Figure 3**). The median bupivacaine T_{max} was ~23 hours postdose and the median meloxicam T_{max} ranged from ~18 to 43 hours postdose.
- A dose-proportional increase in bupivacaine and meloxicam exposure was generally observed for HTX-011.
- HTX-011 demonstrated a lower mean plasma bupivacaine C_{max} (94.9 ng/mL for Cohort 2 and 163 ng/mL for Cohort 3) compared with bupivacaine HCl (387 ng/mL for Cohort 1).
- No HTX-011-treated patient had a bupivacaine C_{max} >500 ng/mL.

Figure 3. Mean Bupivacaine and Meloxicam Plasma Concentrations Postdose



Note: 1 patient in Cohort 3 was excluded from meloxicam analysis because he had a predose meloxicam concentration >5% of C_{max}.

ANALGESIC RESULTS

- Pain scores adjusted for opioid use (using wWOCF) were similar for the HTX-011 cohorts over 72 hours, and both were lower than bupivacaine HCl (**Table 3**).
- Fewer HTX-011-treated patients experienced severe pain at any timepoint through 72 hours vs bupivacaine HCl (**Table 3**).
- Fewer HTX-011-treated patients missed ≥1 rehabilitation session due to pain vs bupivacaine HCl (7.7% and 0% for HTX-011 Cohorts 2 and 3, respectively, vs 33.3% for bupivacaine HCl Cohort 1).
- Almost all patients received postoperative opioids, but median total postoperative opioid consumption was lower for HTX-011 vs bupivacaine HCl (**Table 3**).

Table 3. Summary of Pain and Opioid Consumption Results

	Cohort 1 Bupivacaine HCl 100 mg (N=6)	Cohort 2 HTX-011 up to 200 mg/6 mg (N=13)	Cohort 3 HTX-011 up to 200 mg/6 mg (N=13)
Pain Analyses			
Mean AUC_{0-24} of NRS-R (wWOCF)	133.31	101.49	108.68
Mean AUC_{0-72} of NRS-R (wWOCF)	417.73	330.48	332.02
Patients with severe pain at any timepoint 0-72 h, n (%)	5 (83.3%)	7 (53.8%)	6 (46.2%)
Opioid Consumption			
Median total opioid consumption 0-24 h (IV MME)	14.25	9.50	7.50
Median total opioid consumption 0-72 h (IV MME)	28.00	23.75	22.00

Pain was assessed at rest using the validated 11-point numeric rating scale of pain intensity (NRS). Severe pain was defined as an NRS-R score of ≥7. All opiate dosages and formulations had the IV morphine milligram equivalents (MME) calculated.

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ANALGESIC RESULTS (cont.)

- Additional analgesic activity assessments also favored HTX-011 (**Table 4**).
  - Median duration in the postanesthesia care unit (PACU) was shorter for HTX-011 than bupivacaine HCl.
  - Median time to first ambulation was shorter for HTX-011 than bupivacaine HCl.
  - Patients administered HTX-011 completed a 20-meter walk test earlier than bupivacaine HCl.
  - Readiness for discharge was assessed using the Modified Postanaesthetic Discharge Scoring System (MPADSS). MPADSS considers vital signs, ambulation, nausea/vomiting, pain, and surgical bleeding using a 0-10 scale and a score of ≥9 is considered ready for discharge. Patients administered HTX-011 were ready for discharge earlier than bupivacaine HCl.

Table 4. Summary of Additional Analgesic Assessments

	Cohort 1 Bupivacaine HCl 100 mg (N=6)	Cohort 2 HTX-011 up to 200 mg/6 mg (N=13)	Cohort 3 HTX-011 up to 200 mg/6 mg (N=13)
Median duration in PACU (min)	101	81	75
Median time to first ambulation (hours)	24.21	4.83	16.77
Patients who completed 20-meter walk test by 4 hours, n (%)	1 (16.7%)	7 (53.8%)	4 (30.8%)
Patients who were discharge ready by 12 hours, n (%)[a]	1 (16.7%)	11 (84.6%)	6 (46.2%)

[a] Discharge readiness was defined as a Modified Postanaesthetic Discharge Scoring System (MPADSS) score ≥9.

CONCLUSIONS

- A single individualized dose of HTX-011 up to 200 mg/6 mg was well tolerated and had a safety profile that was generally similar to bupivacaine HCl in patients undergoing open lumbar spinal decompression surgery.
- The safety, PK, and analgesic activity with HTX-011 were similar for single-level versus multi-level spinal decompression surgery.
- There were no AEs of bleeding or local inflammatory AEs.
- There was no evidence of prolonged motor or sensory block with HTX-011.
- PK analysis demonstrated dose-proportional PK with systemic bupivacaine concentrations well below levels associated with risk of LAST.
- Analgesic activity analyses favoring HTX-011 compared with bupivacaine HCl included
  - Lower pain scores and fewer patients experiencing severe pain.
  - Fewer missed rehabilitation sessions due to pain.
  - Lower opioid consumption.
  - Shorter PACU duration.
  - Earlier ambulation and earlier completion of a 20-meter walk test.
  - Earlier discharge readiness.

REFERENCES

1. ZYNRELEF™ USPI. Heron Therapeutics, Inc. December 2022.
2. Ottoboni T el al. Reg Anesth Pain Med. 2019; 45:117-123.

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