Local Administration of HTX-011, a Long-Acting Biochronomer®-Based Bupivacaine/Meloxicam Combination, in Hernia Repair: Preliminary Results of an Interim Analysis

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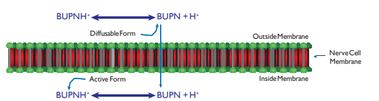
BACKGROUND

- 80% of patients experience moderate to severe pain after surgery that lasts for up to 3 days[1,2]
- Local anesthetics only effectively address postoperative pain for 8-12 hours[3]
- Opioids are often used to cover the multiple days of postoperative pain, but are associated with negative health consequences[4-7]
  - Short-term opioid use can result in side effects
  - Short-term opioid use can also lead to long-term opioid dependency[4,6]
- There is a need for effective, non-opioid postoperative therapeutic options that provide effective pain relief through 72 hours after surgery
- HTX-011 is a novel, extended-release, fixed-dose combination product that contains a local anesthetic (bupivacaine) and a nonsteroidal anti-inflammatory drug (meloxicam); this unique dual mechanism allows the product to target both pain and inflammation
- Inflammation produces an acidic environment that shifts the balance to the ionized form of bupivacaine (unable to penetrate nerve cell membrane); an anti-inflammatory drug should result in a less acidic environment and therefore more bupivacaine entering the cell[8-10] (**Figure 1**)

Figure 1. HTX-011:A Novel, Extended-Release Polymer Formulation of Bupivacaine and Low-Dose Meloxicam Using Biochronomer® Technology



Local anesthetic nerve-penetration model adapted from Becker and Reed, *Anesth Prog* 53:98–109 2006

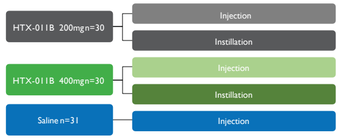
- Initial results of an ongoing Phase 2 trial investigating HTX-011 in patients undergoing hernia repair are presented

METHODS

Study Design

- This is an ongoing Phase 2, randomized, placebo-controlled, multicenter study in subjects undergoing open inguinal hernia repair
  - After a 28-day screening period, the study followed subjects for their pain and opioid use over 4 days, and then had a 28-day post-op visit
  - Three formulations of HTX-011 were evaluated. Results of Part B of the study, which compared use of the planned, Phase 3 formulation of HTX-011 (HTX-011B) at 200 mg and 400 mg to saline placebo administered via injection or instillation, are shown (**Figure 2**)

Figure 2. Study Design: Part B



Subjects

- Key inclusion criteria
  - Adults (aged ≥18 years or older) scheduled to undergo an elective unilateral open inguinal hernia repair
- Key exclusion criteria
  - American Society of Anesthesiologists Physical Status classification system category of ≥IV
  - Clinically significant renal or hepatic abnormalities (AST or ALT >3x ULN, creatinine >2x ULN)
  - 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. Opioid rescue medication for pain control was allowed after surgery as needed

Assessments

Efficacy

- Following the administration of HTX-011B at the end of surgery, pain scores (using the 11-point numerical pain rating scale [NPRS]) and opioid usage were recorded through the first 96 hours
- The primary efficacy endpoint was the magnitude and duration of pain control following study drug administration, as assessed by comparison of the summed pain intensity through 24 hours (SPI_{0-24}) between active arms and saline placebo
- Secondary endpoints and ad hoc analyses included, among others
  - The mean area under the curve of the NPRS score through 24 and 72 hours (AUC_{0-24},AUC_{0-72})
  - The summed pain intensity at additional time points SPI_{0-48} SPI_{0-72} and SPI_{0-96}
  - The proportion of opioid-free patients
  - Total opioid consumption (24, 48, 72, 96 hours posttreatment)

Pharmacokinetics

- Plasma samples for PK analysis were drawn prior to administration of the study treatment, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 30, 36, 48, 60, 72, 96, and 120 hours posttreatment
- Maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the curve to infinity (AUC_{inf}), area under the curve to last measured point (AUC_{last}), and half-life were assessed

Safety

- Safety and tolerability were evaluated by:
  - Treatment-emergent adverse events (TEAEs)
  - Wound assessment findings
  - Vital signs
  - Clinical laboratory tests
  - Electrocardiogram findings

Statistical Analysis

- Efficacy endpoints were analyzed using ANOVA, chi-square tests, and log-rank tests, as appropriate
  - Last Observation Carried Forward (LOCF) was used for any time points where the PI scores are missing
- PK parameters for bupivacaine and meloxicam were calculated using non-compartmental analysis of the plasma concentration-time profiles

RESULTS

Subjects and Disposition

- The current interim analysis included a total of 91 patients comprising 30, 30, and 31 patients who received HTX-011B 200mg, HTX-011B 400 mg, and saline placebo, respectively
- Baseline demographics were similar across all treatment arms (**Table 1**)

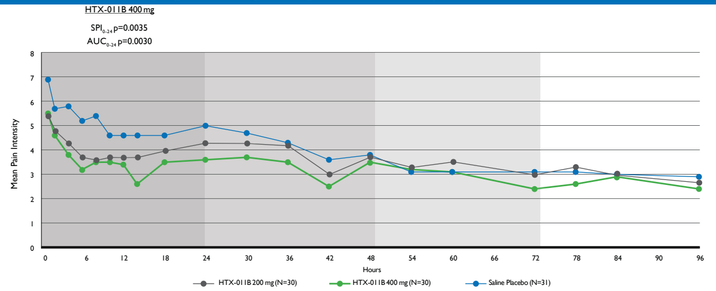
Table 1. Baseline Demographics

Characteristic	Parameter	HTX-011B 200 mg N =31	HTX-011B 400 mg N =30	Saline Placebo N =31
Age, years	Mean	45.2	44.3	44.8
	Minimum	24	19	21
	Maximum	67	79	62
Sex, n (%)	Male	31 (100)	29 (97)	30 (97)
	Female	0 (0)	1 (3)	1 (3)
Race, n (%)	Caucasian	29 (94)	25 (83)	24 (77)
	African American	2 (6)	2 (7)	7 (23)
	Other	0	3 (10)	0
Ethnicity, n (%)	Hispanic	13 (42)	12 (40)	12 (39)
	Not Hispanic	18 (58)	18 (60)	19 (61)

EFFICACY OF HTX-011

- Duration of analgesia, as assessed by mean SPI_{0-24} and AUC_{0-24}, was significantly improved with 400 mg HTX-011B versus saline placebo
  - Mean (standard deviation [SD]) SPI_{0-24} was significantly lower for HTX-011B versus saline placebo (85.7 [41.681] vs. 121.6 [50.00]; p=0.0035) (**Figure 3, Table 2**)
  - Mean [SD] AUC_{0-24} scores were significantly lower for HTX-011B versus saline placebo (80.8 [39.907] vs. 115.1 [46.368]; p=0.0030) (**Figure 3**)

Figure 3. Mean Pain Intensity Scores Following Surgery for the 200 mg and 400 mg Doses of HTX-011B (not adjusted for opioid use)*



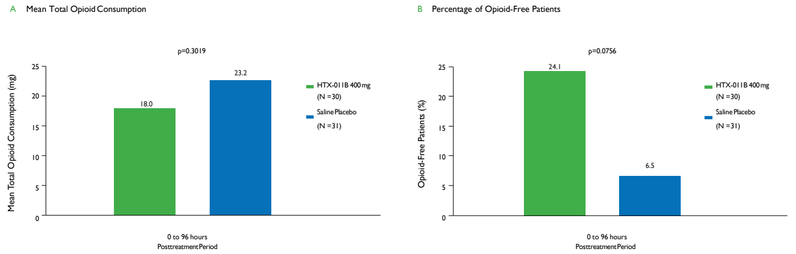
*Imputation method = last observation carried forward

Table 2: Summed Pain Intensity Through 24 Hours, 48 Hours, 72 Hours, and 96 Hours

	Saline Placebo (N=31)	HTX-011B 200mg (N=30)		HTX-011B 400mg (N=30)	
	Mean (SD)	Mean (SD)	P-Value	Mean (SD)	P-Value
SPI_{0-24}	121.6 (50.0)	97.8 (49.9)	0.0673	85.7 (41.7)	0.0035
SPI_{0-48}	220.4 (104.9)	188.6 (103.0)	0.2379	164.9 (81.7)	0.0250
SPI_{0-72}	294.5 (155.8)	266.0 (148.0)	0.4645	231.1 (121.2)	0.0818
SPI_{0-96}	366.5 (205.7)	336.6 (187.9)	0.5562	292.7 (154.7)	0.1195

- The use of opioid rescue medication for breakthrough pain was reduced with HTX-011B 400 mg
  - Mean total opioid consumption decreased by 23% with HTX-011B versus saline placebo through 96 hours of the posttreatment period (**Figure 4A**)
  - The percentage of patients who were opioid-free through 96 hours of the posttreatment period was substantially higher with HTX-011B versus saline placebo (24.1% vs. 6.5%; p=0.0756) (**Figure 4B**)

Figure 4.Assessment of Opioid Usage in Patients Receiving HTX-011B 400 mg: A) Mean Total Opioid Consumption; B) Percentage of Opioid-Free Patients



PHARMACOKINETICS OF HTX-011B

Figure 5. HTX-011B Bupivacaine Plasma Concentration Over Time

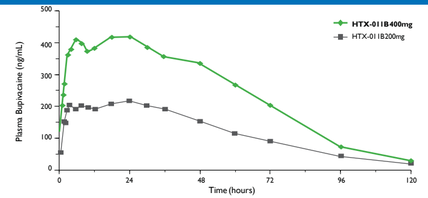


Table 3. 400 mg HTX-011B Pharmacokinetic Profiles

Bupivacaine PK Parameter	Mean	SD
AUC_{inf} (ng*hr/mL)	26,166.71	10,404.95
AUC_{last} (ng*hr/mL)	24,918.52	10,548.78
C_{max} (ng/mL)	562.23	180.59
Half-life (hr)	14.01	4.39
T_{max} (hr)	21.69	13.87

SAFETY OF HTX-011B

- HTX-011B was generally well tolerated
  - ≥1 TEAE was reported in 38.7%, 33.3%, and 51.6% of patients receiving HTX-011B 200mg, HTX-011B 400mg, and saline placebo, respectively
  - The most common TEAEs were nausea, headache, and constipation (**Table 4**)
  - No deaths, treatment-related serious AEs, or AEs leading to early termination were reported

Table 4. Summary of Treatment-Emergent Adverse Events (TEAEs)

Preferred Term	HTX-011B 200 mg (N=31)	HTX-011B 400 mg (N=30)	Saline Placebo (N=31)
Any TEAE	12 (38.7%)	10 (33.3%)	16 (51.6%)
>1 TEAE in any treatment arm			
Nausea	2 (6.5%)	5 (16.7%)	4 (12.9%)
Headache	3 (9.7%)	3 (10.0%)	0
Constipation	3 (9.7%)	1 (3.3%)	5 (16.1%)
Hypersensitivity	0	0	2 (6.5%)

CONCLUSIONS

- This interim analysis demonstrated that a single dose of 400 mg HTX-011B significantly decreased pain intensity and substantially reduced the proportion of patients requiring opiates after undergoing open inguinal hernia repair compared to saline placebo
- HTX-011B was well tolerated in this study; bupivacaine C_{max} values were well below the central nervous system and cardiac toxicity thresholds reported in the literature
- The results of the interim analysis of this study highlight the potential of HTX-011B to provide postoperative pain relief and reduce opioid use

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DISCLOSURES

Erol Onel, Guy Boccia, Alice Chu, Neil J. Clendeninn, Mary Rose Keller, Thomas Ottoboni, Sanjay S. Patel, and Barry Quart are employees of Heron Therapeutics, Inc.
Harold Minkowitz is a consultant for and has received research funds from Heron Therapeutics, Inc.
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