Local Administration of HTX-011, a Long-Acting Biochronomer®-Based Bupivacaine/Meloxicam Combination, in Hernia Repair Provides Similar Initial Results Whether Injected or Instilled

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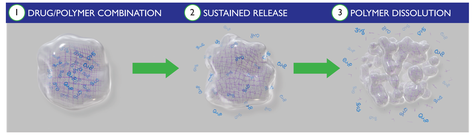
BACKGROUND

- 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 pain relief through 72 hours and are easy to administer
- HTX-011 is a novel, investigational, extended-release product comprising fixed-dose bupivacaine/meloxicam in a Biochronomer®-based delivery system[8] (**Figure 1**)

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



- The mode of local analgesic administration can be an important factor in providing optimal postoperative pain management
  - Administration by instillation is more convenient, less invasive, and potentially reduces the risk of procedural complications, such as venous puncture
  - Instillation works better with an agent less likely to be washed away by irrigation or routine manipulation during wound closure
- This analysis examines differences in pain control and safety that may be related to differences in administration technique

METHODS

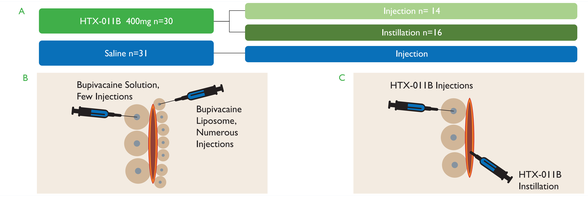
Study Design

- 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 our planned, Phase 3 formulation of HTX-011 (HTX-011B) to placebo administered via injection or installation are shown for the 400 mg dose, which was statistically different from placebo (see poster #144, Winkle et al.) (**Figure 2**)

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

Figure 2. A) Part B Study Design. B) Administration Techniques into the Incision Site Following Surgery With Currently Available Options. C) Administration Techniques into the Incision Site Following Surgery During this Study



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 ($SPI_{0\text{-}24}$) between active arms and saline placebo
- Secondary endpoints included
  - Total opioid consumption
  - The percentage of opioid-free patients
- Additional endpoints included
  - Duration of analgesia as assessed by mean area under the curve of the NPRS score through 24 hours ($AUC_{0\text{-}24}$)

Safety

- Safety and tolerability was evaluated by:
  - Treatment-emergent adverse events (TEAEs)
  - Wound assessment findings
  - Vital signs
  - Clinical laboratory tests, including routine blood chemistry and hematology
  - Electrocardiogram (ECG) findings

Statistical Analysis

- Efficacy endpoints were analyzed using ANOVA, chi-square tests, and log-rank tests, as appropriate

RESULTS

Subjects and Disposition

- The current interim analysis included a total of 61 patients comprising 30 and 31 patients who received HTX-011B 400 mg, and saline placebo, respectively
- Baseline demographics were similar across all treatment arms (**Table 1**)

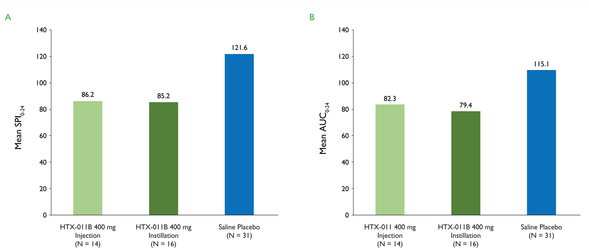
Table 1. Baseline Demographics

Characteristic	Parameter	HTX-011B 400 mg Injection N = 14	HTX-011B 400 mg Instillation N = 16	Saline Placebo N = 31
Age, years	Mean	43.6	44.9	44.8
	Minimum	19	22	21
	Maximum	79	65	62
Sex, n (%)	Male	13 (93)	16 (100)	30 (97)
	Female	1 (7)	0 (0)	1 (3)
Race, n (%)	Caucasian	11 (79)	14 (88)	24 (77)
	African American	1 (7)	1 (6)	7 (23)
	Other	2 (14)	1 (6)	0
Ethnicity, n (%)	Hispanic	6 (43)	6 (37)	12 (39)
	Not Hispanic	8 (57)	10(63)	19 (61)

EFFICACY OF HTX-011B BY ADMINISTRATION TECHNIQUE

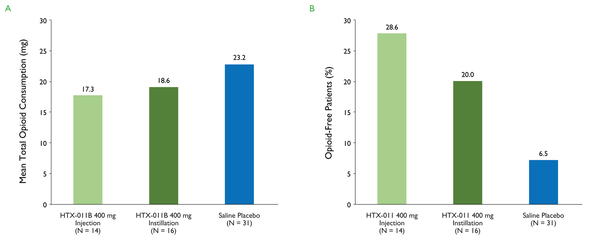
- HTX-011B 400 mg by injection, and HTX-011B 400 mg by instillation were associated with similar mean $SPI_{0\text{-}24}$ scores (86.2 and 85.2, respectively) and $AUC_{0\text{-}24}$ (82.3 and 79.4, respectively); the two routes were not significantly different (**Figure 3A and 3B**)

Figure 3. A) Mean Summed Pain Intensity Scores Through 24 Hours ($SPI_{0\text{-}24}$) Following Surgery. B) Mean Area Under the Curve Through 24 Hours ($AUC_{0\text{-}24}$) Following Surgery



- Similarly, outcomes related to the use of opioid rescue medication for breakthrough pain were similar between the modes of administration
  - Mean total opioid consumption through 96 hours was similar between the two HTX-011B arms (**Figure 4A**)
  - No significant differences were identified in the percentage of patients who were opioid-free through 96 hours of the posttreatment period between HTX-011B 400 mg by injection, and HTX-011B 400mg by instillation. (**Figure 4B**)

Figure 4. Assessment of Opioid Usage in Patients Receiving HTX-011B 400 mg by Administration Technique: A) Mean Total Opioid Consumption Through 96 Hours; B) Percentage of Opioid-Free Patients Through 96 Hours



SAFETY OF HTX-011B BY ADMINISTRATION TECHNIQUE

- HTX-011B was generally well tolerated in this study and TEAEs were similar among modes of administration
  - Following administration of study treatments, ≥1 TEAE was reported in 42.9%, 25.0%, and 51.6% of patients receiving HTX-011B 400 mg by injection, HTX-011B 400 mg by instillation, and saline placebo, respectively. (**Table 2**)
  - The most common TEAEs were nausea, headache, and constipation
  - No deaths, treatment-related serious AEs, or AEs leading to early termination from the study were reported
  - No clinically meaningful differences were observed in vital signs, laboratory tests, ECG findings, or wound assessment

Table 2. Summary of Treatment Emergent Adverse Events (TEAEs)

Preferred Term	HTX-011B 400 mg Injection N = 14	HTX-011B 400 mg Instillation N = 16	Saline Placebo N = 31
Any TEAE	6 (42.9%)	4 (25.0%)	16 (51.6%)
>1 TEAE in any treatment arm			
Nausea	3 (21.4%)	2 (12.5%)	4 (12.9%)
Headache	1 (7.1%)	2 (12.5%)	0
Constipation	1 (7.1%)	0	5 (16.1%)
Hypersensitivity	0	0	2 (6.5%)

CONCLUSIONS

- This interim analysis demonstrated that single 400-mg doses of HTX-011B administered by injection or instillation to the surgical wound were similarly effective at providing postoperative pain relief in patients who underwent open inguinal hernia repair
- The administration of HTX-011B by injection or instillation was associated with similar pain scores and opioid use outcomes
- Furthermore, treatment in both HTX-011B administration arms was similarly well tolerated
- These findings indicate that following open inguinal hernia repair, different modes of HTX-011B administration did not demonstrate meaningful differences in safety or efficacy. Therefore, the potential benefits regarding safety and convenience will likely make instillation a preferred method of administration

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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.
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