Postoperative Pain Management of Total Knee Arthroplasty Using HTX-011 With Multimodal Analgesia: Results From a Phase 3b Open-Label Study

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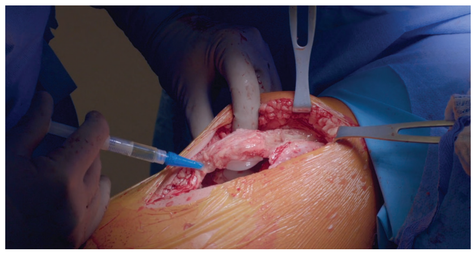
INTRODUCTION

- Opioids are commonly prescribed for pain relief following orthopedic surgery but come with the potential for misuse and dependence[1-2]
  - A mean of 90 opioid pills are prescribed at discharge following total knee arthroplasty (TKA)[3]
- Although local anesthetics are commonly used for surgical pain, they are limited by their duration of action (6-12 hours)[4]; currently approved extended-release (ER) anesthetics provide pain relief for up to 24 hours[5]
- HTX-011 is an investigational, ER, dual-acting local anesthetic (DALA) with a unique, synergistic mechanism of action[6] containing a combination of bupivacaine and low-dose meloxicam in a proprietary Biochronomer® polymer, which allows for the controlled diffusion of active ingredients over 72 hours
  - HTX-011 is administered via needle-free application to the surgical site prior to wound closure using a syringe and a Luer lock applicator (**Figure 1**)
- In a prior Phase 2b study of patients undergoing TKA, HTX-011 400 mg/12 mg (bupivacaine/meloxicam) significantly reduced pain over 48 hours and 72 hours, decreased opioid use, and reduced time to discharge readiness compared with saline placebo and bupivacaine hydrochloride (HCl), despite the absence of a scheduled multimodal analgesic (MMA) regimen

Figure 1. HTX-011 Application[a] During TKA



[a]HTX-011, a viscous solution, is applied to the surgical site and surrounding pain-generating tissues prior to would closure.

OBJECTIVE

- To assess pain control, opioid use, safety, and tolerability of HTX-011 when used as the foundation of a scheduled non-opioid MMA regimen in patients undergoing TKA

METHODS

Study Design and Patients

- This phase 3b, open-label study enrolled patients undergoing primary unilateral TKA who met study criteria (**Table 1**)
  - Results presented are an interim analysis prior to database lock

Table 1. Key Inclusion and Exclusion Criteria

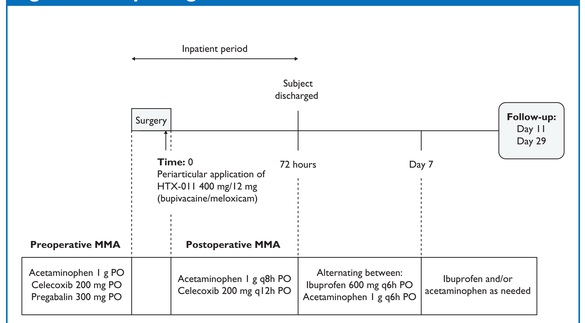
Key Inclusion Criteria	Key Exclusion Criteria
Adult males and females who are not pregnant or lactating	Pre-existing acute or chronic painful/ restrictive condition that may require analgesia during the postoperative period
Scheduled to undergo primary unilateral TKA under spinal anesthesia	Use of the following within a defined period prior to surgery: • NSAIDs within 10 days[a] • Bupivacaine within 5 days • Long-acting opioids within 3 days • Any local anesthetic within 72 hours • Any opioid within 24 hours
ASA Physical Status Classification System category 1-3	BMI >40 kg/m^2
Able to walk at least 20 feet	Planned concurrent surgical procedure

ASA, American Society of Anesthesiologists; BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drug; TKA, total knee arthroplasty.

[a]Unless low-dose (≤100 mg) daily acetylsalicylic acid for cardioprotection.

- All patients received a single, intraoperative dose of HTX-011 400 mg/12 mg (bupivacaine/meloxicam) via needle-free periarticular application into the surgical site prior to wound closure (**Figure 1**)
- All patients also received a scheduled, non-opioid MMA regimen (**Figure 2**)
- Patients were discharged 72 hours following surgery

Figure 2. Study Design



MMA, multimodal analgesia; PO, oral; q6h, every 6 hours; q8h, every 8 hours; q12h, every 12 hours.

- During the 72-hour inpatient period, opioid rescue medication (oral immediate-release oxycodone, intravenous [IV] morphine, and/or IV hydromorphone) was administered only upon subject request for pain control
- At discharge, patients were only eligible to receive a prescription for opioids if they had received ≥10 mg of oxycodone within the prior 12 hours
- Patients returned for follow-up assessments on Day 11 and Day 29 (study end)
- The primary endpoint was mean area under the curve (AUC) of visual analog scale (VAS) scores from 12-48 hours (AUC_{12-48})

Assessments

- Pain was assessed using a VAS and numeric rating scale (NRS) at scheduled timepoints following surgery
- Use of opioid rescue medication was recorded through the Day 11 visit
- Discharge readiness was assessed using a validated Modified Postanesthetic Discharge Scoring System (MPADSS)
- Safety assessments included adverse events (AEs), hematology and serum chemistry, vital signs, physical examinations, and wound healing assessments

Statistical analyses

- The population for analysis included all patients who received study drug
- VAS results were divided by 10 for analysis and presentation
- "Opioid-free" was defined as not using an opioid rescue medication during the time period of interest
- To adjust for the analgesic effect of opioid rescue medication, pain intensity scores during periods of rescue medication administration were replaced by the highest observed score before rescue medication use

RESULTS

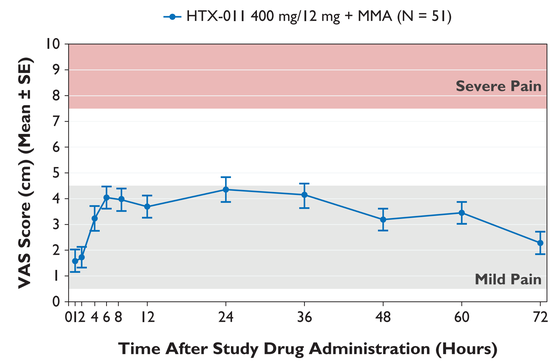
Disposition and Baseline Characteristics

- 51 patients received HTX-011
- 61% of patients were female; 92% were white; mean age was 65 years

Pain Intensity

- The mean (SD) AUC_{12-48} of the VAS was 143.2 (93.5) in patients treated with HTX-011 + MMA
- Mean pain intensity, measured by VAS, remained in the mild range (VAS 5-44 mm)[7] throughout the 72-hour postoperative period (**Figure 3**)
- 37% of patients did not experience severe pain at any time during the 72-hour inpatient period

Figure 3. Mean Pain Intensity Through 72 Hours as Measured by Visual Analog Scale

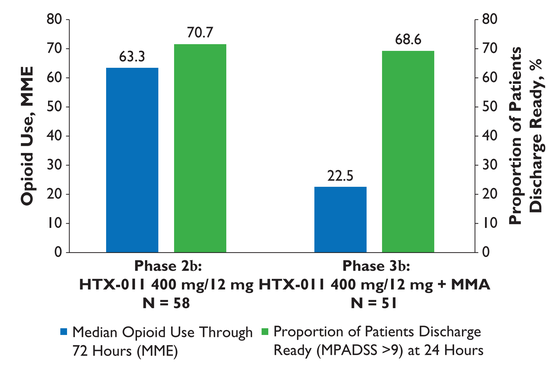


MMA, multimodal analgesia; SE, standard error; VAS, visual analog scale.

Opioid Use and Discharge Readiness

- Six patients (11.8%) remained opioid-free through the 72-hour inpatient period
- Median opioid consumption was 22.5 mg morphine milligram equivalents (MME; 4-5 oxycodone pills) per patient throughout 72 hours, approximately one-third the amount consumed by patients that received HTX-011 in the prior phase 2b study (**Figure 4**)
  - Geometric mean (SE) of opioid use through 72 hours was 3.7 (2.5) mg
- 68.6% of patients (35/51) were deemed ready for discharge within 24 hours using MPADSS, a proportion similar to that observed for HTX-011 in the prior phase 2b study (**Figure 4**)
- Most patients (74.5%) were discharged without an opioid prescription

Figure 4. Median Opioid Use and Discharge Readiness



MMA, multimodal analgesia; MME, morphine milligram equivalents; MPADSS, Modified Postanesthetic Discharge Scoring System.

Safety and Tolerability

- AEs were reported by approximately 75% of patients, were generally mild-to-moderate in severity, and most were considered related to opioid use (**Table 3**)
- The most common AEs were nausea, vomiting, and constipation
- There were no deaths or serious adverse events, and no patients discontinued the study due to AEs
- No NSAID-related toxicity was reported

Table 3. Summary of AEs

	HTX-011 + MMA (N = 51)
AEs, n (%)	38 (74.5)
Possibly related to study drug, n (%)	6 (11.8)
Opioid-related[a]	31 (60.8)
Leading to study withdrawal	0
Most common AEs, n (%)	
Nausea	28 (54.9)
Vomiting	14 (27.5)
Constipation	10 (19.6)
Bradycardia	3 (5.9)
Urinary retention	3 (5.9)
Dizziness	3 (5.9)

AE, adverse event; MMA, multimodal analgesia.

[a]Opioid-related AEs included those with sponsor pre-specified preferred terms of nausea, vomiting, constipation, pruritis, pruritis generalized, somnolence, respiratory depression, and urinary retention.

DISCUSSION/CONCLUSIONS

- HTX-011, as the foundation of a scheduled, non-opioid MMA regimen, effectively managed postoperative pain relief, maintained mean pain scores in the mild range through 72 hours, and minimized the need for opioid discharge prescriptions following TKA
- HTX-011, with a scheduled non-opioid MMA regimen, was well-tolerated in patients undergoing TKA
- In a recent study examining the use of liposomal bupivacaine + bupivacaine HCl + MMA in TKA[8]:
  - Mean AUC_{12-48} of the VAS was 180.8
  - Geometric mean of opioid use through 72 hours was 20.9 mg
- In this study, HTX-011 + MMA reduced pain and opioid use
  - Mean AUC_{12-48} of the VAS was 143.2
  - Geometric mean of opioid use through 72 hours was 3.7 mg
  - 74.5% of patients were discharged without an opioid prescription
- Using HTX-011 as the foundation of an MMA regimen has the potential to dramatically reduce the number of opioids sent home with patients following TKA (**Table 4**)

Table 4. Potential Impact of Study[3,9]

	Pills Prescribed
Current practice estimates[a]	93,870,000
Study estimates[b]	23,936,850
Potential reduction with HTX-011 + MMA	69,933,150 ↓

MMA, multimodal analgesia; TKA, total knee arthroplasty.

[a]Estimated number of pills extrapolated by multiplying 1,043,000 annual TKA surgeries with mean of 90 pills provided at discharge.

[b]Estimated number of pills extrapolated by dividing 93,870,000 by the proportion of patients discharged with an opioid prescription in this study (25.5%).

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