Total Knee Arthroplasty Pain Management With HTX-011 as the Foundation of a Multimodal Analgesic Regimen Results in Low Incidence of Severe Pain

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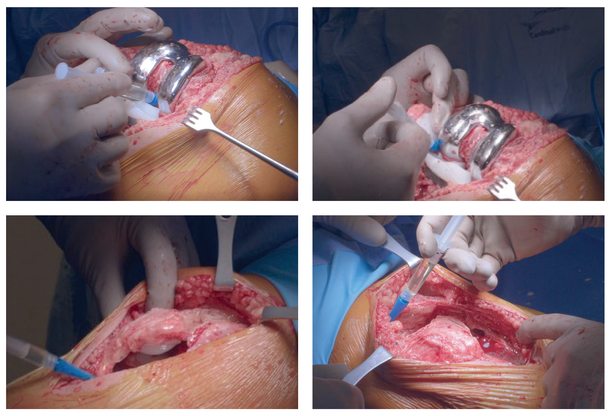
INTRODUCTION

- Severe postoperative pain and resultant opioid use are common after total knee arthroplasty (TKA)[1,2]
- ZYNRELEF (HTX-011) is an extended-release, dual-acting local anesthetic (DALA) formulation comprising bupivacaine and low-dose meloxicam in a controlled-diffusion polymer that allows for controlled delivery of active ingredients over 72 hours[3,4]
  - HTX-011 was approved in the European Union on September 24, 2020, and was approved in the United States on May 12, 2021
  - The NSAID meloxicam in HTX-011 reduces surgery-related inflammation, thereby normalizing the local pH, which enhances penetration of bupivacaine into the nerve cell and potentiates its analgesic effect[5]
  - Neither the low dose of meloxicam contained in HTX-011 nor the addition of NSAID-containing multimodal analgesia (MMA) have been shown to increase NSAID-related adverse events[6-8]
- HTX-011 has demonstrated superior postoperative pain management and limited opioid use compared with the standard of care local anesthetic bupivacaine hydrochloride (HCl) and saline placebo in randomized, controlled registration studies of patients undergoing bunionectomy, herniorrhaphy, and TKA[3,4,9]
- Administration of HTX-011 during TKA is depicted in **Figure 1**

Figure 1. HTX-011 Is Administered Needle-free Using a Luer Lock Applicator. Top pictures illustrate administration to posterior capsule; bottom pictures illustrate administration to anterior capsule.



HTX-011 was applied during surgery after cementation of components, placement of the tibial liner, and completion of irrigation and suction.

OBJECTIVES

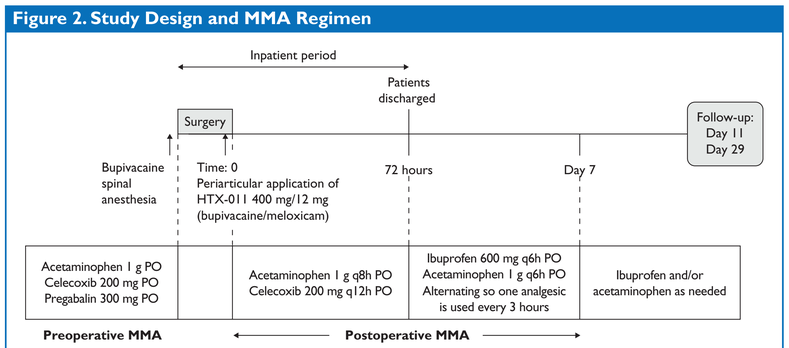
- The objective of this study was to examine the efficacy and safety of HTX-011 as the foundation of a perioperative scheduled non-opioid MMA regimen after TKA
- In this analysis, we examined the effect of HTX-011 + MMA on severe pain following TKA

METHODS

Study Design and Patients

- This open-label, single-arm study enrolled patients undergoing primary unilateral TKA under bupivacaine spinal anesthesia (NCT03974932)
  - Patients were included if they had an American Society of Anesthesiologists Physical Status of I, II, or III and were able to walk ≥20 feet
  - Patients were excluded if they had used:
    - NSAIDs within 10 days (unless ≤100 mg daily acetylsalicylic acid for cardioprotection)
    - Bupivacaine within 5 days or any local anesthetic within 72 hours
    - Long-acting opioids within 3 days or any opioid within 24 hours
- All patients received a single, intraoperative dose of HTX-011 (400 mg bupivacaine/12 mg meloxicam) via needle-free periarticular application into the surgical site prior to wound closure
- All patients received a perioperative scheduled, NSAID-containing, non-opioid MMA regimen (**Figure 2**)
  - During the 72-hour inpatient period, opioid rescue medication was available upon patient request (oral oxycodone, intravenous [IV] morphine, or IV hydromorphone)

Figure 2. Study Design and MMA Regimen



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

Assessments and Endpoints

- The primary endpoint was the area under the curve of visual analog scale of pain intensity (VAS) scores from 12-48 hours (AUC_{12-48}), adjusted for opioid use
  - In the 10 cm VAS, a pain score of <4.4 cm was considered "mild" and a score of ≥7.5 cm was considered "severe"
- Additional pain endpoints included:
  - Pain control over the preceding 24 hours, evaluated using a 4-point Patient Global Assessment (PGA) scale in which 0 represents "poor" and 3 represents "excellent"[10]
  - Ability to participate in scheduled rehabilitation sessions
- Discharge readiness was assessed using the Modified Postanesthetic Discharge Scoring System (MPADSS) criteria, which consider vital signs, ambulation, nausea/vomiting, pain, and surgical bleeding[11]
  - Patients were deemed "ready for discharge" if they had a MPADSS of ≥9
- Mean postoperative opioid consumption was measured in IV morphine milligram equivalents (MME) through 72 hours
- Safety endpoints included the incidence of adverse events and serious adverse events

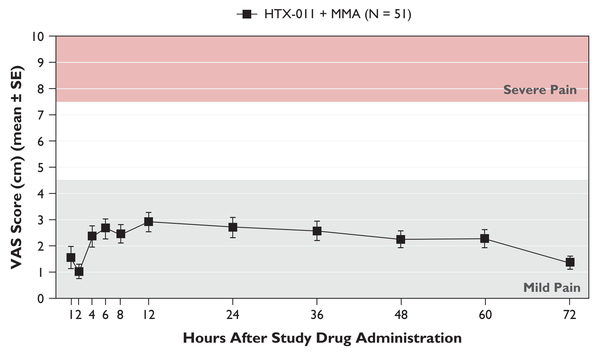
RESULTS

- Fifty-one patients were included and received HTX-011
- Mean patient age was 65.4 years, and mean body mass index was 30.97 kg/m^2
- Most patients were female (60.8%) and white (92.2%)

Pain Intensity

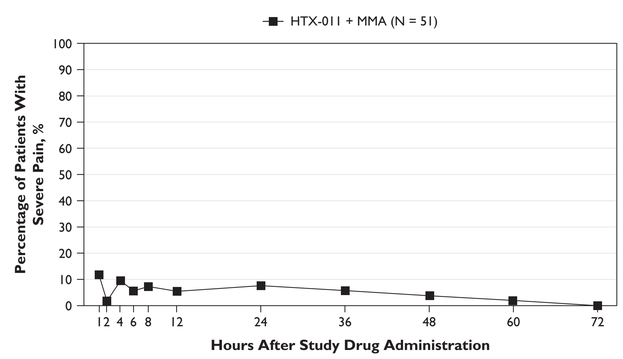
- Mean pain scores remained in the mild range (VAS <4.4 cm) throughout the 72-hour postoperative period (**Figure 3**)
  - Mean (standard error [SE]) VAS AUC_{12-48} was 145.4 (13.00)
- Most patients (≥88%) did not experience severe pain (VAS ≥7.5 cm) at any individual time point (**Figure 4**)
- On Day 2 (1 day after surgery), 88% of patients rated their pain control as "good" to "excellent;" this increased to 100% of patients by Day 4 (3 days after surgery) (**Figure 5**)
- No patients missed rehabilitation sessions because of pain on Day 2, and only 2 patients (3.9%) missed a rehabilitation session because of pain on Day 3 (**Table 1**)

Figure 3. Mean Pain Intensity Scores Through 72 Hours



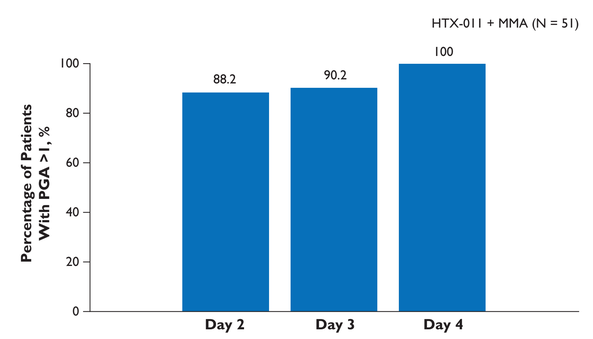
MMA, multimodal analgesia; SE, standard error; VAS, visual analog scale of pain intensity.

Figure 4. Percentage of Patients With Severe Pain[a] Through 72 Hours



MMA, multimodal analgesia;
[a]Defined as VAS of pain intensity ≥7.5 cm.

Figure 5. Percentage of Patients Rating Pain Control as "Good" or "Excellent"[a]



PGA, patient global assessment; MMA, multimodal analgesia.
[a]Good or excellent rating based on patient-reported PGA score of >1.

Table 1. Proportion of Patients Unable to Participate in Rehabilitation Sessions Due to Pain[a]

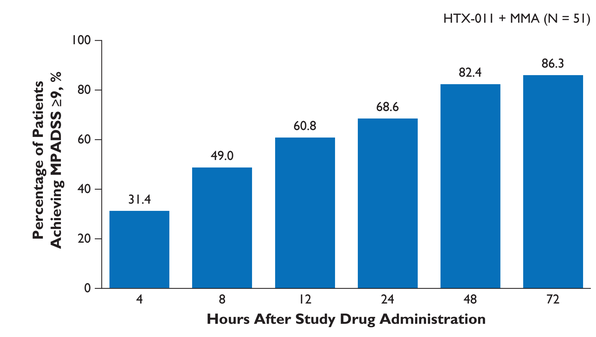
Timepoint N (%)	HTX-011 + MMA (N = 51)
Day 1	
Session 1	7 (13.7)
Day 2	
Session 1	0 (0)
Session 2	0 (0)
Day 3	
Session 1	1 (2.0)
Session 2	1 (2.0)

[a]Patients who were unable to participate in rehabilitation sessions more than once per day were only counted once.

Discharge Readiness

- Using MPADSS criteria, approximately half of patients were deemed ready for discharge by 8 hours after surgery, and >60% were ready for discharge by 12 hours after surgery (**Figure 6**)

Figure 6. Percentage of Patients Designated Ready for Discharge[a]



MMA, multimodal analgesia; MPADSS, Modified Postanesthetic Discharge Scoring System.
[a]MPADSS score ≥9.

Opioid Use

- Mean total opioid consumption was 24.8 MME within the 72-hour postoperative period (<2 10 mg oxycodone tablets/day) (**Table 2**)
- 22% of patients did not require opioids (ie, they remained opioid-free) through 24 hours after surgery; 12% remained opioid-free throughout the 72-hour postoperative period
- 39% of TKA patients treated with HTX-011 plus a scheduled non-opioid MMA regimen were discharged without an opioid prescription and did not call the study site for additional pain medication through Day 11
  - Only patients who received ≥10 mg of oxycodone within 12 hours before discharge were eligible to receive a discharge prescription for opioids

Table 2. Total Opioid Consumption (MME)

	HTX-011 + MMA (N = 51)
0-24 hours	
Mean (SE)	10.6 (1.30)
Median (range)	7.5 (0.0-35.0)
0-48 hours	
Mean (SE)	19.4 (2.46)
Median (range)	15.8 (0.0-93.3)
0-72 hours	
Mean (SE)	24.8 (3.18)
Median (range)	21.7 (0.0-118.3)

MMA, multimodal analgesia; MME, morphine milligram equivalents; SE, standard error.

Safety and Tolerability

- HTX-011 was well-tolerated; most adverse events were rated mild or moderate (**Table 3**)
- No serious adverse events were reported
- There was no evidence of NSAID-related toxicity

Table 3. Adverse Events

N (%)	HTX-011 + MMA (N = 51)
≥1 AE	42 (82.4)
Mild	17 (33.3)
Moderate	24 (47.1)
Severe[a]	1 (2.0)
AE possibly related to study drug[b]	7 (13.7)
AEs leading to study withdrawal	0
SAE	0

AE, adverse event; MMA, multimodal analgesia; SAE, serious adverse event.
[a]Severe postoperative pain in left knee.
[b]AEs reported by the investigator as possibly related to study drug were nausea (5 patients), vomiting (3 patients), dizziness (1 patient), and intermittent elevated blood pressure (1 patient).

CONCLUSIONS

- HTX-011, as the foundation of a perioperative scheduled non-opioid MMA regimen, has the potential to keep most patients out of severe pain, maintain mean pain in the mild range, minimize opioid consumption, provide high patient satisfaction, and allow most patients to be discharged within 12 hours following TKA

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