Safety of HTX-011 in Patients ≥65 Years Old as Part of a Postoperative Multimodal Analgesia Regimen

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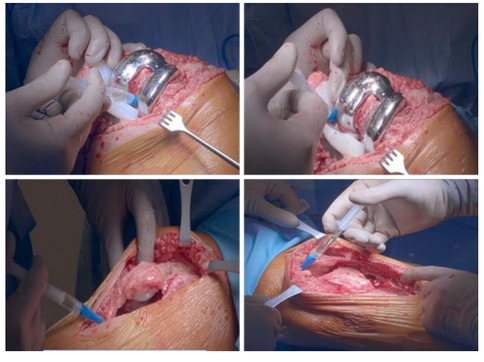
INTRODUCTION

- Elderly adults (≥65 years old) undergo surgery more frequently than any other age group and management of postoperative pain in this population can be challenging[1]
  - Elderly adults are at a higher risk of adverse effects including opioid-related adverse events (ORAEs) and complications from nonsteroidal anti-inflammatory drugs (NSAIDs)[1,2]
- HTX-011 is a dual-acting local anesthetic formulation comprising bupivacaine and low-dose meloxicam in an extended-release polymer that allows for simultaneous diffusion of active ingredients over 72 hours[3,4]
- Administration during total knee arthroplasty (TKA) is depicted in **Figure 1**
  - Meloxicam reduces surgery-related inflammation, thereby normalizing the local pH and resulting in enhanced penetration of bupivacaine into the nerve[5]
  - As HTX-011 is applied directly to the surgical site, the low dose of meloxicam is not expected to increase NSAID-related adverse events
- HTX-011 demonstrated superior postoperative pain management, reduced opioid use, and had a safety profile comparable to saline placebo and bupivacaine hydrochloride (HCl) in randomized, controlled Phase 3 and Phase 2b studies in patients undergoing bunionectomy, herniorrhaphy, and TKA[3,4,6]
- HTX-011 has also demonstrated effective pain management and limited opioid use as the foundation of a scheduled, NSAID-containing non-opioid multimodal analgesia (MMA) regimen[3,4,7,8]

OBJECTIVE

- The objective was to evaluate the safety of HTX-011, with or without an NSAID-containing non-opioid MMA regimen, in elderly patients ≥65 years of age undergoing bunionectomy, herniorrhaphy, or TKA

Figure 1. Needle-free HTX-011 Administered Using a Luer Lock Applicator During Total Knee Arthroplasty. Top pictures illustrate administration to posterior capsule, Bottom pictures illustrate administration to anterior capsule.



METHODS

- Data for this analysis was obtained from 3 randomized, placebo- and active-controlled studies of HTX-011 alone[3,4,6] and 4 single-arm follow-on studies of HTX-011 as the foundation of a scheduled NSAID-containing non-opioid MMA regimen[7,8]
  - Patients ≥65 years old were included in this subpopulation analysis
- Patients underwent primary unilateral metatarsal bunionectomy with osteotomy, open inguinal herniorrhaphy with mesh placement, or primary unilateral TKA
  - Patients with a known or suspected history of drug abuse or daily use of opioids for ≥7 consecutive days within the previous 6 months were excluded
- In all studies, a single dose of HTX-011 was administered via needle-free application into the surgical site prior to wound closure; postoperative MMA varied across studies (**Table 1**)

Table 1. HTX-011 and MMA Regimens in Single-Arm Follow-On Studies

	Bunionectomy	Herniorrhaphy	TKA
HTX-011 Dose	≤60 mg/1.8 mg	300 mg/9 mg	400 mg/12 mg
Registry Number(s)	NCT03718039	NCT03695367, NCT03907176	NCT03974932
Scheduled Preoperative MMA		• PO APAP 1000 mg[1] • PO ibuprofen 400 mg[a]	• PO APAP 1000 mg, PO celecoxib 200 mg, PO pregabalin 300 mg
Scheduled Postoperative MMA	• PO ibuprofen 600 mg every 6 hours through 72 hours • PO APAP 1000 mg every 6 hours through 72 hours	• PO ibuprofen 600 mg every 6 hours through 72 hours or 5 days – A cohort of patients also received one intraoperative dose of IV ketorolac 30 mg[b] • PO APAP 1000 mg every 6 hours through 72 hours or 5 days	• PO celecoxib 200 mg every 12 hours through 72 hours, followed by PO ibuprofen 600 mg every 6 hours for the next 4 days • PO APAP 1000 mg every 8 hours through 72 hours, followed by PO APAP 1000 mg every 6 hours for the next 4 days • PO acetylsalicylic acid 325 mg twice a day through 72 hours (for DVT prophylaxis)

APAP, acetaminophen; DVT, deep vein thrombosis; IV, intravenous; PO, orally administered;TKA, total knee arthroplasty.
[a]Ibuprofen included in NCT03907176 only.
[b]15 mg for patients aged ≥65 years, serum creatinine >1.5, and/or weight <50 kg.

- Safety analyses included adverse events, vital signs, laboratory parameters, physical examinations, wound healing assessment, and assessment for potential local anesthetic systemic toxicity (LAST) events
  - Symptoms that could be attributed to LAST, ORAEs, or NSAIDs were assessed based on prespecified adverse event preferred terms

RESULTS

- A total of 166 HTX-011-treated patients ≥65 years of age were included in this analysis; 88 received HTX-011 alone and 78 received HTX-011 as the foundation of a NSAID-containing non-opioid MMA regimen
- Baseline characteristics were similar between studies (**Table 2**)

Table 2. Baseline Characteristics

	Randomized Controlled Studies HTX-011				Single-Arm Follow-on Studies HTX-011 + MMA			
	HTX-011 60 mg/1.8 mg N = 24	HTX-011 300 mg/9 mg N = 15	HTX-011 400 mg/12 mg N = 49	HTX-011 Pooled N = 88	HTX-011 ≤60 mg/1.8 mg N = 2	HTX-011 300 mg/9 mg N = 33	HTX-011 400 mg/12 mg N = 43	HTX-011 + MMA Pooled N = 78
Age, mean (SD)	68.8 (3.59)	72.8 (5.39)	71.5 (5.08)	71.0 (4.94)	68.0 (2.83)	69.9 (4.61)	72.8 (5.36)	71.5 (5.20)
Sex								
Female, n (%)	19 (79.2)	2 (13.3)	21 (42.9)	42 (47.7)	2 (100)	12 (36.4)	25 (58.1)	39 (50.0)
Male, n (%)	5 (20.8)	13 (86.7)	28 (57.1)	46 (52.3)	0	21 (63.6)	18 (41.9)	39 (50.0)
Race, n (%)								
Asian	2 (8.3)	0	0	2 (2.3)	0	0	0	0
Black or African American	0	0	2 (4.1)	2 (2.3)	0	6 (18.2)	6 (14.0)	12 (15.4)
White	22 (91.7)	15 (100)	47 (95.9)	84 (95.5)	2 (100)	27 (81.8)	37 (86.0)	66 (84.6)
BMI (kg/m^2), mean (SD)	28.3 (4.82)	26.3 (4.95)	30.6 (4.90)	29.2 (5.12)	27.3 (8.35)	29.4 (5.07)	29.9 (3.69)	29.6 (4.38)

BMI, body mass index; MMA, multimodal analgesia; SD, standard deviation.

HTX-011 Was Well Tolerated With or Without an NSAID-Containing Non-opioid MMA Regimen

- Overall, patients receiving HTX-011 with a scheduled MMA regimen did not experience an increase in adverse events compared with patients receiving HTX-011 alone (**Table 3**)
- Acetaminophen 1000 mg every 6 hours was well tolerated in this population
- Review of vital signs, laboratory parameters, and physical examinations did not reveal any safety concerns

Table 3. Summary of Adverse Events in Patients ≥65 Years Old

	Randomized Controlled Studies HTX-011				Single-Arm Follow-on Studies HTX-011 + MMA			
Adverse events, n (%)	HTX-011 60 mg/1.8 mg N = 24	HTX-011 300 mg/9 mg N = 15	HTX-011 400 mg/12 mg N = 49	HTX-011 Pooled N = 88	HTX-011 ≤60 mg/1.8 mg N = 2	HTX-011 300 mg/9 mg N = 33	HTX-011 400 mg/12 mg N = 43	HTX-011 + MMA Pooled N = 78
Any AE	21 (87.5)	15 (100)	46 (93.9)	82 (93.2)	0 (0)	24 (72.7)	33 (76.7)	57 (73.1)
Severe AE	0 (0)	1 (6.7)	3 (6.1)	4 (4.5)	0 (0)	2 (6.1)	0 (0)	2 (2.6)
Serious AE	1 (4.2)	1 (6.7)	3 (6.1)	5 (5.7)	0	0	2 (4.7)	2 (2.6)
AEs leading to study withdrawal	0	0	2 (4.1)	2 (2.3)	0	0	0	0
Opioid-related AE[a]	10 (41.7)	3 (20.0)	36 (73.5)	49 (55.7)	0 (0)	19 (57.6)	22 (51.2)	41 (52.6)
Local inflammatory AE	8 (33.3)	2 (13.3)	4 (8.2)	14 (15.9)	0 (0)	6 (18.2)	1 (2.3)	7 (9.0)
Potential LAST-related AE[b]	8 (3.33)	3 (20.0)	11 (22.4)	22 (25.0)	0 (0)	3 (9.1)	9 (20.9)	12 (15.4)

AE, adverse event; MMA, multimodal analgesia; LAST, local anesthetic systemic toxicity.
[a]Opioid-related AEs were prespecified as nausea, vomiting, constipation, pruritus, pruritus generalized, somnolence, respiratory depression, and urinary retention.
[b]Potential LAST-related AEs were identified using a custom list of preferred terms relating to abnormal cardiac or neurologic signs and symptoms potentially associated with LAST.

HTX-011 With NSAID-Containing MMA Did Not Increase NSAID-Related Toxicity

- The addition of a scheduled, postoperative NSAID-containing non-opioid MMA regimen did not increase NSAID-related adverse events (Table 4)
- The most common NSAID-related adverse events were hypertension, pyrexia, and peripheral edema

Table 4. Incidence of NSAID-Related Adverse Events (>5% in Any Treatment Group)

	Randomized Controlled Studies HTX-011				Single-Arm Follow-on Studies HTX-011 + MMA			
NSAID-related AE, n (%)[a]	HTX-011 60 mg/1.8 mg N = 24	HTX-011 300 mg/9 mg N = 15	HTX-011 400 mg/12 mg N = 49	HTX-011 Pooled N = 88	HTX-011 ≤60 mg/1.8 mg N = 2	HTX-011 300 mg/9 mg N = 33	HTX-011 400 mg/12 mg N = 43	HTX-011 + MMA Pooled N = 78
Any NSAID-related AE	5 (20.8)	1 (6.7)	26 (53.1)	32 (36.4)	0	8 (24.2)	8 (18.6)	16 (20.5)
Edema peripheral	1 (4.2)	0	0	1 (1.1)	0	4 (12.1)	0	4 (5.1)
Erythema	2 (8.3)	0	2 (4.1)	4 (4.5)	0	1 (3.0)	0	1 (1.3)
Hepatic enzyme increased	0	1 (6.7)	0	1 (1.1)	0	0	0	0
Hypertension	0	0	6 (12.2)	6 (6.8)	0	0	3 (7.0)	3 (3.8)
Hypotension	0	0	4 (8.2)	4 (4.5)	0	2 (6.1)	0	2 (2.6)
Pruritis	1 (4.2)	0	3 (6.1)	4 (4.5)	0	0	0	0
Pruritis generalized	0	0	3 (6.1)	3 (3.4)	0	0	0	0
Pyrexia	0	0	5 (10.2)	5 (5.7)	0	0	0	0

AE, adverse event; NSAID, nonsteroidal anti-inflammatory drug; SMQ, standardized MedDRA query.
[a]NSAID-related AEs were identified using a customized NSAID-related SMQ list based on Essex MN, et al.[9]

HTX-011 Did Not Impair Wound Healing in Elderly Patients

- More than 95% of patients ≥65 years old had normal wound healing across treatment groups in herniorrhaphy and TKA studies, as assessed via the Southampton Wound Scoring System
- In bunionectomy studies, incidence of any abnormal wound healing was 5/8 (62.5%) with saline placebo, 9/24 (37.5%) with HTX-011, and 4/16 (25%) with bupivacaine HCl in the randomized controlled studies and 0/2 (0%) in the HTX-011+MMA follow on study, as assessed using a custom list of preferred terms (**Table 5**)

Table 5. Wound Healing in Patients ≥65 Years Old in Bunionectomy Studies

	Randomized Controlled Bunionectomy Study			Single-Arm Follow-on Bunionectomy Study
Wound Healing at Day 42, n (%)[a]	HTX-011 60 mg/1.8 mg n = 24	Saline placebo n = 8	Bupivacaine HCl 50 mL n = 16	HTX-011 + MMA ≤60 mg/1.8 mg n = 2
Any abnormal healing	9 (37.5)	5 (62.5)	4 (25.0)	0
Bruising	1 (4.2)	0	0	0
Erythema	4 (16.7)	2 (25.0)	1 (6.3)	0
Edema	8 (33.3)	5 (62.5)	4 (25.0)	0
Heat	2 (8.3)	0	0	0
Drainage	0	0	0	0
Cellulitis	0	0	0	0
Delayed healing	2 (8.3)[b]	0	0	0
Dehiscence	0	0	0	0

HCl, hydrochloride; MMA, multimodal analgesia.
[a]Wound healing was assessed according to a custom list of preferred terms.
[b]Both cases of delayed healing were mild/moderate and considered unlikely to be related to study drug.

DISCUSSION AND CONCLUSIONS

- HTX-011 was well tolerated in the elderly, either used alone or as the foundation of a scheduled NSAID-containing non-opioid MMA regimen
- In the elderly, the incidence of adverse events, including NSAID-related adverse events, was not increased when HTX-011 was used in combination with NSAID-containing MMA compared to patients receiving HTX-011 alone
- These data support the safety of HTX-011 in combination with NSAID-containing non-opioid MMA in the elderly population

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