Overall Safety Of HTX-011 When Used With Scheduled Non-Opioid NSAID-containing Multimodal Analgesia (MMA)

Harold Minkowitz[1], Charles Luke[2], David Hardman[3], Jia Hu[4]

[1]HD Research Group, Houston, TX, USA; [2]UPMC Passavant, Pittsburgh, PA; Philadelphia, PA, USA; [3]University of North Carolina, Chapel Hill, NC, USA; [4]Heron Therapeutics, San Diego, CA, USA

INTRODUCTION

- HTX-011 (ZYNRELEF™) is a dual-acting local anesthetic formulation comprising bupivacaine and low-dose meloxicam in an extended-release polymer that controls the release of active ingredients over 72 hours, which results in enhanced and sustained analgesia.[1-4] HTX-011 is approved for use in the United States and European Union.[5-6]
  - Meloxicam reduces surgery-related inflammation, thereby normalizing the local pH, resulting in enhanced penetration of bupivacaine into the nerves[1]
- HTX-011 is administered via needle-free application into the surgical site and surrounding tissues prior to wound closure **(Figure 1)**
- In registrational trials, HTX-011 demonstrated superior postoperative pain management over 72 hours, reduced opioid use, and had a safety profile comparable to saline placebo and bupivacaine hydrochloride (HCl)[2-4]
- Multimodal analgesia (MMA) is recommended throughout various treatment guidelines. HTX-011 as the foundation of a scheduled non-opioid MMA regimen was investigated in 4 single-arm studies where it demonstrated effective pain management with minimal or no opioid use[7-10]

OBJECTIVE

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

METHODS

- Data were obtained from 4 randomized, placebo- and active-controlled studies of HTX-011 alone and 4 single-arm follow-on studies of HTX-011 with an NSAID-containing non-opioid MMA regimen
  - Studies of HTX-011 alone included primary unilateral metatarsal bunionectomy with osteotomy, open inguinal herniorrhaphy with mesh, primary unilateral total knee arthroplasty (TKA), and augmentation mammoplasty
  - Studies of HTX-011 with non-opioid MMA included primary unilateral metatarsal bunionectomy with osteotomy, open inguinal herniorrhaphy with mesh, and primary unilateral TKA
- In all studies, a single dose of HTX-011 was administered via needle-free application into the surgical site; postoperative non-opioid MMA varied across studies **(Table 1)**
- Safety analyses included adverse events (AEs), vital signs, laboratory parameters, physical examinations, wound healing assessments, and assessment for prespecified NSAID-related and opioid-related AEs

Figure 1. HTX-011 Administered without Needle

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 • 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

APAP, acetaminophen; DVT, deep vein thrombosis; IV, intravenous; PO, orally administered; TKA, total knee arthroplasty.
In the TKA study, patients received PO acetylsalicylic acid 325 mg twice a day through 72 hours for DVT prophylaxis
[a]Ibuprofen included in NCT03907176 only.
[b]15 mg for patients aged ≥65 years, serum creatinine >1.5, and/or weight <50 kg.

RESULTS

- A total of 856 HTX-011-treated patients were included in this analysis; 504 received HTX-011 alone and 352 received HTX-011 as the foundation of an NSAID-containing non-opioid MMA regimen
- Baseline characteristics by dose/surgery were similar between randomized and single-arm follow-on studies **(Table 2)**

Presented at the American Society of Anesthesiologists Annual Meeting, Oct 9-12, 2021; San Diego, CA, USA

RESULTS

Table 2. Baseline Characteristics

	Randomized Controlled Studies HTX-011						Single-Arm Follow-on Studies HTX-011 + MMA			
	Placebo Pooled N= 247	Bupivacaine HCl Pooled N= 392	HTX-011 60 mg/1.8 mg N = 157	HTX-011 300 mg/9 mg N = 163	HTX-011 400 mg/12 mg N = 164	HTX-011 Pooled N = 504	HTX-011 ≤60 mg/1.8 mg N = 31	HTX-011 300 mg/9 mg N = 251	HTX-011 400 mg/12 mg N = 70	HTX-011+MMA Pooled N = 352
Age, mean (SD)	51.3 (13.9)	50.0 (13.8)	48.0 (14.5)	48.8 (13.3)	53.4 (16.8)	50.6 (15.0)	49.1 (12.7)	53.5 (14.2)	62.0 (12.5)	54.8 (14.2)
Sex										
Female, n (%)	122 (49.4)	179 (45.7)	138 (87.9)	12 (7.4)	103 (62.8)	266 (52.8)	29 (93.5)	23 (9.2)	41 (58.6)	93 (26.4)
Male, n (%)	125 (50.6)	213 (54.3)	19 (12.1)	151 (92.6)	61 (37.2)	238 (47.2)	2 (6.5)	228 (90.8)	29 (41.4)	259 (73.6)
Race, n (%)										
Asian	3 (1.2)	4 (1.0)	8 (5.1)	2 (1.2)	3 (1.8)	13 (2.6)	0	2 (0.8)	0	2 (0.6)
Black or African American	25 (10.1)	49 (12.5)	24 (15.3)	16 (9.8)	22 (13.4)	67 (13.3)	4 (12.9)	23 (9.2)	8 (11.4)	35 (9.9)
White	219 (88.7)	334 (85.2)	123 (78.3)	139 (85.3)	137 (83.5)	414 (82.1)	27 (87.1)	222 (88.4)	61 (87.1)	310 (88.1)
BMI (kg/m^2), mean (SD)	29.0 (4.8)	27.9 (4.5)	27.3 (4.8)	27.1 (4.4)	29.2 (5.5)	28.0 (5.0)	28.1 (3.8)	28.0 (4.2)	31.6 (4.9)	28.7 (4.5)

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 non-opioid MMA regimen experienced a lower incidence of adverse events compared to HTX-011 alone, which correlates with a lower incidence of opioid-related AEs **(Table 3)**
- HTX-011 had a similar adverse event profile compared to saline placebo and bupivacaine HCl
- Review of vital signs, laboratory parameters, and physical examinations did not reveal any safety concerns

Table 3. Summary of Adverse Events

	Randomized Controlled Studies HTX-011						Single-Arm Follow-on Studies HTX-011 + MMA			
Adverse events, n (%)	Placebo Pooled N= 247	Bupivacaine HCl Pooled N= 392	HTX-011 60 mg/1.8 mg N = 157	HTX-011 300 mg/9 mg N = 163	HTX-011 400 mg/12 mg N = 164	HTX-011 Pooled N = 504	HTX-011 ≤60 mg/1.8 mg N = 31	HTX-011 300 mg/9 mg N = 251	HTX-011 400 mg/12 mg N = 70	HTX-011+MMA Pooled N = 352
Any AE	201 (81.4)	319 (81.4)	131 (83.4)	119 (73.0)	155 (94.5)	424 (84.1)	20 (64.5)	97 (38.6)	58 (82.9)	175 (49.7)
Severe AE	8 (3.2)	10 (2.6)	5 (3.2)	3 (1.8)	4 (2.4)	12 (2.4)	0	4 (1.6)	3 (4.3)	7 (2.0)
Serious AE	5 (2.0)	7 (1.8)	3 (1.9)	2 (1.2)	6 (3.7)	11 (2.2)	0	1 (0.4)	3 (4.3)	4 (1.1)
AEs leading to study withdrawal	1 (0.4)	0	1 (0.6)	0	2 (1.2)	3 (0.6)	0	0	0	0
Opioid-related AE[a]	137 (55.5)	198 (50.5)	69 (43.9)	53 (32.5)	128 (78.0)	266 (52.8)	9 (29.0)	49 (19.5)	40 (57.1)	98 (27.8)

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.

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 AEs **(Table 4)**
- The most common NSAID-related AEs were pyrexia, hypotension, and hypertension

Table 4. Incidence of NSAID-Related Adverse Events (≥3% in Any Treatment Group)

	Randomized Controlled Studies HTX-011						Single-Arm Follow-on Studies HTX-011 + MMA			
NSAID-related AE, n (%)	Placebo Pooled N= 247	Bupivacaine HCl Pooled N= 392	HTX-011 60 mg/1.8 mg N = 157	HTX-011 300 mg/9 mg N = 163	HTX-011 400 mg/12 mg N = 164	HTX-011 Pooled N = 504	HTX-011 ≤60 mg/1.8 mg N = 31	HTX-011 300 mg/9 mg N = 251	HTX-011 400 mg/12 mg N = 70	HTX-011+MMA Pooled N = 352
Any NSAID-related AE	82 (33.2)	99 (25.3)	41 (26.1)	25 (15.3)	88 (53.7)	164 (32.5)	2 (6.5)	27 (10.8)	26 (37.1)	55 (15.6)
Anemia	1 (0.4)	0	0	1 (0.6)	4 (2.4)	5 (1.0)	0	0	4 (5.7)	4 (1.1)
Leukocytosis	2 (0.8)	5 (1.3)	1 (0.6)	0	11 (6.7)	13 (2.6)	0	0	0	0
Hypotension	8 (3.2)	15 (3.8)	7 (4.5)	7 (4.3)	11 (6.7)	25 (5.0)	0	5 (2.0)	2 (2.9)	7 (2.0)
Hypertension	15 (6.1)	14 (3.6)	0	2 (1.2)	19 (11.6)	23 (4.6)	1 (3.2)	1 (0.4)	3 (4.3)	5 (1.4)
Pruritis	7 (2.8)	9 (2.3)	8 (5.1)	0	12 (7.3)	22 (4.4)	1 (3.2)	3 (1.2)	7 (10.0)	11 (3.1)
Rash	3 (1.2)	5 (1.3)	0	2 (1.2)	5 (3.0)	7 (1.4)	0	1 (0.4)	0	1 (0.3)
Pruritis generalized	11 (4.5)	11 (2.8)	4 (2.5)	2 (1.2)	8 (4.9)	16 (3.2)	0	0	0	0
Pyrexia	8 (3.2)	14 (3.6)	2 (1.3)	5 (3.1)	22 (13.4)	30 (6.0)	0	0	3 (4.3)	3 (0.9)
Hyperthermia	2 (0.8)	0	0	0	5 (3.0)	5 (1.0)	0	0	0	0
GGT ↑	8 (3.2)	10 (2.6)	5 (3.2)	2 (1.2)	2 (1.2)	9 (1.8)	0	0	0	0
Anemia postoperative	7 (2.8)	2 (0.5)	0	0	2 (1.2)	6 (1.2)	0	0	9 (12.9)	9 (2.6)

AE, adverse event; NSAID, nonsteroidal anti-inflammatory drug; SMQ, standardized MedDRA query; GGT, gamma-glutamyltransferase.
[a]NSAID-related AEs were identified using a customized list of NSAID toxicity-related preferred terms (>1,800) derived from Essex MN, et al.[11]

RESULTS

Addition of MMA to HTX-011 Did Not Impair Wound Healing

- 98% of patients 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 35% with saline placebo, 37.7% with HTX-011, and 39.3% with bupivacaine HCl in the randomized controlled studies and 35.5% in the HTX-011+MMA follow on study, as assessed using a custom list of preferred terms **(Table 5)**

Table 5. Wound Healing 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 = 151	Saline placebo n = 100	Bupivacaine HCl 50 mL n = 150	HTX-011 + MMA ≤60 mg/1.8 mg n = 31
Any abnormal healing	57 (37.7)	35 (35.0)	59 (39.3)	11 (35.5)
Bruising	5 (3.3)	5 (5.0)	6 (4.0)	2 (6.5)
Erythema	12 (7.9)	11 (11.0)	13 (8.7)	1 (3.2)
Edema	45 (29.8)	33 (33.0)	55 (36.7)	9 (29)
Heat	1 (0.7)	0	0	0
Drainage	2 (1.3)	2 (2.0)	4 (2.7)	3 (9.7)
Cellulitis	3 (2.0)	0	0	0
Delayed healing	6 (4.0)	1 (1.0)	5 (3.3)	0
Dehiscence	5 (3.3)	2 (2.0)	2 (1.3)	1 (3.2)

HCl, hydrochloride; MMA, multimodal analgesia.
[a]Wound healing was assessed according to a custom list of preferred terms as displayed in Table 5.

SUMMARY AND CONCLUSIONS

- HTX-011 was well tolerated, either used alone or as the foundation of a scheduled NSAID-containing non-opioid MMA regimen
- The incidence of AEs, including opioid-related and NSAID-related AEs, was lower 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

REFERENCES

1. Ottoboni T et al. Reg Anesth Pain Med. 201945:117-123.
2. Viscusi E et al. Reg Anesth Pain Med. 2019;44:700-706.
3. Viscusi E et al. Hernia. 2019;23:1071-1080.
4. Lachiewicz PF et al. J Arthroplasty. 2020;35:2843-2851.
5. ZYNRELEF (bupivacaine and meloxicam) Extended-Release Solution [Full Prescribing Information].
6. Zynrelef (bupivacaine/meloxicam) Prolonged-release wound solution. EMEA/H/C/005205.
7. Pollak R et al. J Am Podiatr Med Assoc. 2021;20-204.
8. Singla N et al. Surgery. 2020;168:915-920.
9. Minkowitz H et al. Pain Ther. 2021 Jul 27.
10. Hacker S. Presented at Orthopedics Today Hawaii, 2020, Kauai, HI.
11. Essex MN et al. Expert Opin Drug Saf. 2013;12:465-477.

ACKNOWLEDGMENTS

Funding for this research was provided by Heron Therapeutics, Inc. (San Diego, CA, USA).

HERON THERAPEUTICS