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HTX-011: No Evidence of Local Anesthetic Systemic Toxicity

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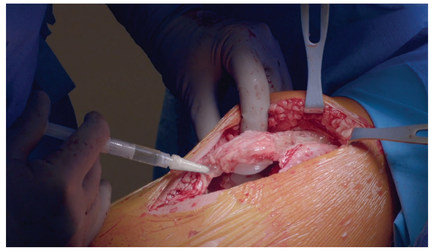
INTRODUCTION

- HTX-011 is an investigational dual-acting local anesthetic formulation comprising bupivacaine and meloxicam in an extended-release polymer
  - HTX-011 has demonstrated superiority over bupivacaine hydrochloride (HCl) for managing postoperative pain over 72 hours in multiple surgical procedures, including bunionectomy, herniorrhaphy, and total knee arthroplasty (TKA)[1-3]
  - Meloxicam, a non-steroidal anti-inflammatory drug, normalizes the local pH at the site of HTX-011 administration, enhancing the penetration of bupivacaine into pain-transmitting neurons and generating a synergistic analgesic effect[4]
- Local anesthetic systemic toxicity (LAST) is a rare but potentially life-threatening adverse event (AE) associated with high plasma levels of local anesthetics[5,6]
  - The most common features of LAST are central nervous system (CNS) toxicity (eg, the potential for seizures, loss of consciousness, and respiratory arrest) and cardiac symptoms (eg, conduction disturbances and myocardial dysfunction)
  - The risk of LAST is increased following inadvertent intravascular injection, and when local anesthetics are administered to highly vascularized areas and therefore absorbed into the plasma quickly, resulting in higher systemic plasma concentrations
- For bupivacaine, development of LAST is generally associated with plasma concentrations above 2000 ng/mL (CNS symptoms) and 4000 ng/mL (cardiac symptoms)[7]
- Here we present:
  - Potential LAST-related AEs
  - A non-validated questionnaire looking at potential LAST symptoms in patients who received HTX-011, bupivacaine HCl, or placebo
  - Bupivacaine plasma concentrations across several different surgical models of varying vascularity

METHODS

- Potential LAST-related AEs were assessed in two phase 2b (N = 298) and two phase 3 (N = 830) placebo- and active-controlled studies
- In all studies, a single intraoperative dose of HTX-011 was administered without a needle to the surgical site and surrounding tissues prior to closure (**Figure 1**)
  - Doses of HTX-011 studied were:
    - 60 mg bupivacaine/1.8 mg meloxicam (bunionectomy)
    - 300 mg bupivacaine/9 mg meloxicam (herniorrhaphy)
    - 400 mg bupivacaine/12 mg meloxicam (mammoplasty and TKA)
  - Bupivacaine HCl was administered via injection at doses that ranged from 50 mg to 125 mg

Figure 1. HTX-011 is Administered Without a Needle into the Surgical Site



- LAST-related AEs were identified using a prespecified list of preferred terms as outlined in **Table 2**
- The two phase 3 studies also included a questionnaire designed to monitor for early CNS and cardiac symptoms potentially associated with LAST
  - The LAST questionnaire was given at 30 minutes and 1, 2, 4, 18, 24, and 72 hours after medication administration to encompass the T_{max} determined in prior studies
    - Additional safety assessments were performed, including a comprehensive evaluation of 12-lead electrocardiograms/Holter monitoring, vital signs, and bupivacaine concentrations

RESULTS

Potential LAST-Related AEs

- No significant difference was observed in the incidence of potential LAST-related AEs between patients who did not receive any bupivacaine products (ie, received saline placebo only) and those who received HTX-011 in any study (**Table 1**)
  - The incidence of potential LAST-related AEs did not increase with increasing doses of HTX-011
  - Potential LAST-related AEs occurred with greater frequency in patients receiving bupivacaine HCl than those receiving either HTX-011 or saline placebo in the phase 3 studies

Table 1. Incidence of Potential LAST-Related Adverse Events Across Studies, N (%)

Phase 2b Studies			
Augmentation Mammoplasty (NCT03011333)			
	HTX-011 400 mg/12 mg (n = 50)	Bupivacaine HCl 50 mg NB (n = 41)	Saline placebo (n = 41)
Potential LAST-Related AE	13 (26.0)	10 (24.4)	9 (22.0)
Total Knee Arthroplasty (NCT03015532)			
	HTX-011 400 mg/12 mg (n = 58)	Bupivacaine HCl 125 mg (n = 55)	Saline placebo (n = 53)
Potential LAST-Related AE	15 (25.9)	11 (20.0)	14 (26.4)
Phase 3 Studies			
Bunionectomy (NCT03295721)			
	HTX-011 60 mg/1.8 mg (n = 157)	Bupivacaine HCl 50 mg (n = 154)	Saline placebo (n = 101)
Potential LAST-Related AE	55 (35.0)	64 (41.6)	34 (33.7)
Herniorrhaphy (NCT03237481)			
	HTX-011 300 mg/9 mg (n = 163)	Bupivacaine HCl 75 mg (n = 173)	Saline placebo (n = 82)
Potential LAST-Related AE	54 (33.1)	71 (41.0)	28 (34.1)

AE, adverse event; HCl, hydrochloride; LAST, local anesthetic systemic toxicity; NB, nerve block.

- Most potential LAST-related AEs were mild or moderate in severity; no severe potential LAST-related AEs occurred with the 400 mg/12 mg dose of HTX-011
- In the phase 3 studies, the most common potential LAST-related AEs in the HTX-011 groups were dizziness and bradycardia, occurring at rates similar to placebo (**Table 2**)
- A solicited LAST questionnaire showed roughly equal responses from patients receiving HTX-011 and those not receiving any bupivacaine (data on file)

Table 2. Incidence of Potential LAST-Related Adverse Events in Phase 3 Studies, N (%)

Herniorrhaphy (NCT03237481)			
	HTX-011 300 mg/9 mg (n = 163)	Bupivacaine HCl 75 mg (n = 173)	Saline placebo (n = 82)
Any potential LAST-related AE	54 (33.1)	71 (41.0)	28 (34.1)
Dizziness	24 (14.7)	42 (24.3)	13 (15.9)
Bradycardia	15 (9.2)	16 (9.2)	6 (7.3)
Dysgeusia	15 (9.2)	21 (12.1)	3 (3.7)
Hypotension	7 (4.3)	7 (4.0)	3 (3.7)
Tremor	7 (4.3)	12 (6.9)	8 (9.8)
Muscle twitching	6 (3.7)	6 (3.5)	4 (4.9)
Paresthesia oral	4 (2.5)	3 (1.7)	0
Visual impairment	3 (1.8)	5 (2.9)	2 (2.4)
Sinus arrhythmia	3 (1.8)	3 (1.7)	0
Tinnitus	3 (1.8)	6 (3.5)	5 (6.1)
Paresthesia	1 (0.6)	1 (0.6)	0
Sinus bradycardia	1 (0.6)	0	0
Vision blurred	1 (0.6)	1 (0.6)	0
Bunionectomy (NCT03295721)			
	HTX-011 60 mg/1.8 mg (n = 157)	Bupivacaine HCl 50 mg (n = 154)	Saline placebo (n = 101)
Any potential LAST-related AE	55 (35.0)	64 (41.6)	34 (33.7)
Dizziness	34 (21.7)	36 (23.4)	18 (17.8)
Bradycardia	12 (7.6)	12 (7.8)	6 (5.9)
Muscle twitching	9 (5.7)	8 (5.2)	5 (5.0)
Hypotension	7 (4.5)	7 (4.5)	2 (2.0)
Sinus arrhythmia	6 (3.8)	10 (6.5)	6 (5.9)
Dysgeusia	4 (2.5)	6 (3.9)	6 (5.9)
Paresthesia	3 (1.9)	0	2 (2.0)
Tinnitus	2 (1.3)	8 (5.2)	2 (2.0)
Paresthesia oral	2 (1.3)	0	0
Tremor	0	2 (1.3)	2 (2.0)
Arrhythmia supraventricular	0	1 (0.6)	0
Sinus bradycardia	0	3 (1.9)	0
Vision blurred	0	1 (0.6)	0
Visual impairment	0	1 (0.6)	0

AE, adverse event; HCl, hydrochloride; LAST, local anesthetic systemic toxicity.

Bupivacaine Plasma Concentrations

- At the highest recommended dose of HTX-011 (400 mg bupivacaine/12 mg meloxicam) mean maximum bupivacaine plasma concentrations (C_{max}) were 710 ng/mL and 695 ng/mL in the mammoplasty and TKA studies, respectively (**Table 3**)

Table 3. Mean Maximum Plasma Concentration (C_{max}) Across Studies (ng/mL)

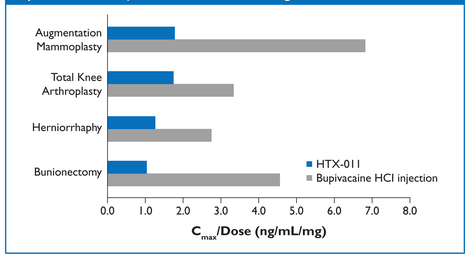
	Augmentation Mammoplasty	TKA	Herniorrhaphy	Bunionectomy
Bupivacaine HCl				
N	41	55	32[a]	25[a]
Dose	50 mg NB	125 mg	75 mg	50 mg
C_{max}, mean (SD)	341 (136)	416 (172)	206 (90.1)[a]	228 (89.3)[a]
HTX-011				
N	49	53	161	157
Dose	400 mg/12 mg	400 mg/12 mg	300 mg/9 mg	60 mg/1.8 mg
Bupivacaine C_{max}, mean (SD)	710 (246)	695 (411)	381 (172)	62.4 (37.3)
Meloxicam C_{max}, mean (SD)	527 (149)	274 (133)	196 (60.8)	33.2 (17.7)

[a]Data from precedent phase 2 study.

HCl, hydrochloride; NB, nerve block; SD, standard deviation; TKA, total knee arthroplasty.

- When bupivacaine C_{max} was normalized by HTX-011 dose (C_{max} [ng/mL]/dose [mg]), patients treated with HTX-011 demonstrated a narrow range of values (1.04-1.78) which did not appear to be affected by site vascularity (**Figure 2**)
- In contrast, dose-normalized bupivacaine C_{max} varied considerably (2.75-6.82) between surgeries in patients treated with bupivacaine HCl

Figure 2. Dose-Normalized C_{max} Following HTX-011 Application and Bupivacaine HCl Injection Across Various Surgical Procedures



HCl, hydrochloride.

DISCUSSION/CONCLUSIONS

- No evidence of LAST was observed with HTX-011 in any study, even at the highest dose of 400 mg bupivacaine/12 mg meloxicam
  - HTX-011 administration without a needle further reduces the risk of inadvertent intravascular injection
- In contrast to bupivacaine HCl, bupivacaine released from the HTX-011 extended-release formulation exhibited consistent dose-normalized C_{max} independent of site vascularity
  - For a detailed analysis of release rates of bupivacaine and meloxicam in HTX-011, please see ePoster A4283 (Luke C, et al.)
- Taken together, these data suggest that the unique formulation of HTX-011 may reduce the risk of LAST and minimize the effect of vascularity on systemic bupivacaine concentrations compared with bupivacaine HCl

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HERON THERAPEUTICS

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