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Response to the letter to the editor by Hafer and Johnson concerning 'Mechanism of action of HTX-011: a novel, extended-release, dual-acting local anesthetic formulation for postoperative pain'.

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To the Editor

We appreciate the comments provided by Hafer and Johnson[1] regarding our recent manuscript.[2] Their primary concern appears to be the clinical evidence supporting the analgesic properties of HTX-011 beyond 24 hours.

HTX-011 is a dual-acting local anesthetic consisting of bupivacaine and low-dose meloxicam in an extended-release polymer. Preclinical data demonstrated that meloxicam normalized the local pH at the surgical site and synergistically potentiated the magnitude and duration of analgesic activity of bupivacaine in a pig postoperative pain model through 72 hours. The early proof-of-concept phase II bunionectomy study presented in our manuscript[2] confirmed the preclinical findings and demonstrated that HTX-011 resulted in greater pain reduction than either extended-release bupivacaine or extended-release meloxicam through 72 hours following surgery. Moreover, HTX-011 significantly reduced mean pain intensity 24 to 72 hours post surgery when compared with extended-release bupivacaine (area under the concentration time curve $(AUC)_{24\text{-}72}$, 252.2 vs 312.3, p=0.0156), validating that meloxicam does indeed potentiate the effect of bupivacaine in HTX-011 beyond the first 24 hours.

Drs. Hafer and Johnson suggest that further investigation is needed to validate the clinical efficacy of HTX-011 beyond 24 hours.[1] Two published phase III studies (EPOCH-1 (bunionectomy) and EPOCH-2 (herniorrhaphy))[3 4] provide such evidence. In EPOCH-1, HTX-011 demonstrated a significant reduction in mean pain intensity over 72 hours ($AUC_{0\text{-}72}$) compared with saline placebo (p<0.0001) and bupivacaine HCl (p=0.0002).[3] Importantly, the analgesic benefit continued beyond 24 hours as HTX-011 demonstrated significantly lower mean pain scores from 24 to 72 hours ($AUC_{24\text{-}72}$) compared with saline placebo (p<0.0001) and bupivacaine HCl (p=0.0072)[3] (table 1), confirming that the efficacy observed through 72 hours was not merely a carry-over from the efficacy observed in the first 24 hours. Similar results were observed in EPOCH-2, with HTX-011 providing superior pain reduction compared with saline placebo and bupivacaine HCl through 72 hours (both p<0.001) and specifically from 24 to 72 hours (p=0.0264 and p=0.0007, respectively), again confirming that HTX-011 continues to provide sustained

Table 1 Select efficacy results from HTX-011 phase III studies, EPOCH-1 (bunionectomy) and EPOCH-2 (herniorrhaphy)[3–5]

	EPOCH-1			EPOCH-2		
	Saline placebo (n=100)	Bupivacaine HCl 50 mg (n=155)	HTX-011 60 mg/1.8 mg (n=157)	Saline placebo (n=82)	Bupivacaine HCl 75 mg (n=172)	HTX-011 300 mg/9 mg (n=164)
Pain intensity						
$AUC_{0\text{-}24}$ of the NRS pain intensity scores						
Mean (SD)	155.8 (48.49)	131.4 (48.86)	98.7 (59.55)	143.8 (54.94)	126.7 (52.68)	97.7 (60.31)
P value vs saline placebo		0.0004	<0.0001		0.0238	<0.0001
P value vs bupivacaine HCl			<0.0001			<0.0001
$AUC_{24\text{-}72}$ of the NRS pain intensity scores						
Mean (SD)	289.6 (115.64)	262.1 (117.25)	224.6 (131.28)	207.1 (122.32)	215.2 (111.97)	171.7 (120.40)
P value vs saline placebo		0.0806	<0.0001		0.6041	0.0264
P value vs bupivacaine HCl			0.0072			0.0007
Opioid use						
Opioid consumption from 0 to 24 hours (MME)						
Mean (SD)	14.1 (8.58)	11.8 (9.39)	7.4 (7.82)	11.7 (10.82)	7.3 (8.61)	5.2 (7.86)
Median (min, max)	14.0 (0.0 to 45.0)	10.0 (0.0 to 44.0)	5.0 (0.0 to 29.0)	9.8 (0.0 to 37.0)	5.0 (0.0 to 37.0)	0.0 (0.0 to 35.0)
P value vs saline placebo			<0.0001			<0.0001
P value vs bupivacaine HCl			<0.0001			0.0073
Opioid consumption from 24 to 72 hours (MME)						
Mean (SD)	15.9 (14.77)	13.3 (14.56)	11.4 (13.64)	5.9 (9.30)	7.2 (11.10)	5.62 (11.09)
Median (min, max)	12.5 (0.0 to 60.0)	8.0 (0.0 to 57.0)	5.0 (0.0 to 54.0)	0.0 (0.0 to 37.0)	0.0 (0.0 to 69.0)	0.0 (0.0 to 68.0)
P value vs saline placebo			0.0024			0.2532
P value vs bupivacaine HCl			0.1585			0.0161
Opioid-free						
% patients opioid-free through 72 hours	2%	11%	29%	22%	40%	51%
P value vs saline placebo			<0.0001			<0.0001
P value vs bupivacaine HCl			0.0001			0.0486

AUC, area under the concentration time curve; MME, morphine milligram equivalents; NRS, numeric rating scale.

and superior analgesia beyond the first 24 hours.[4]

The beneficial effects of HTX-011 on opioid reduction were also confirmed to persist beyond 24 hours in the phase III studies. In both studies, HTX-011 significantly reduced opioid consumption and enabled significantly more patients to recover without requiring any opioids (opioid-free) throughout the 72 hours postoperative period compared with both saline placebo and bupivacaine HCl (p values ranging from $p<0.001$ to $p<0.05$).[3 4] In EPOCH-1, HTX-011 treatment reduced opioid consumption by 48% versus saline placebo and by 37% versus bupivacaine HCl over the first 24 hours following surgery (both $p<0.0001$; table 1).[5] Efficacy extended beyond 24 hours as HTX-011 significantly reduced opioid use between 24 and 72 hours versus saline placebo ($p=0.0024$), and decreased opioid use versus bupivacaine HCl.[5] In EPOCH-2, HTX-011 significantly reduced opioid use during the first 24 hours ($p<0.0001$ vs saline placebo, $p=0.0073$ vs bupivacaine HCl), with continued reduction between 24 and 72 hours versus bupivacaine HCl ($p=0.0161$).[5]

These phase III studies confirm that HTX-011 provides sustained and superior analgesic efficacy throughout the 72 hour postoperative period with significantly lower pain scores, reduced opioid consumption, and more opioid-free patients compared to placebo and bupivacaine HCl. Together, the preclinical and clinical data support the mechanism of action (MOA) put forth in our publication.[2] In addition, our proposed MOA is consistent with the established phenomenon of acidic pH limiting the duration of action of local anesthetics.[6 7] We hope the consistent clinical efficacy observed across several studies, including in the 24 to 72 hours window, reassures Drs. Hafer and Johnson, along with their colleagues, of the 72 hours duration of action of HTX-011.

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