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'

To the Editor

We appreciate the comments provided by Hafer and Johnson¹ 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 manuscript² 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)₂₄₋₇₂ 252.2 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 (AUC₀₋₇₂) 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 (AUC₂₄₋₇₂) 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 ₀₋₂₄ 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 ₂₄₋₇₂ 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.

Thomas Ottoboni,¹ Barry Quart,¹ Jayne Pawasauskas,² Joseph F Dasta,^{3,4} Richard A Pollak,⁵ Eugene R Viscusi⁶

¹Heron Therapeutics, Inc, San Diego, California, USA

²College of Pharmacy, University of Rhode Island, Kingston, Rhode Island, USA

³College of Pharmacy, Ohio State University, Columbus, Ohio, USA

⁴College of Pharmacy, University of Texas, Austin, Texas, USA

⁵Endeavor Clinical Trials, San Antonio, Texas, USA

⁶Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania, USA

Correspondence to Dr Thomas Ottoboni, Heron Therapeutics, 4242 Campus Point Ct #200, San Diego, CA 92121, USA; TOttoboni@herontx.com

Contributors TO and BQ drafted the initial version of this letter; all remaining authors (JP, JFD, RAP, ERV) reviewed, revised content, and approved the final version.

Funding This study was funded by Heron Therapeutics (NA).

Competing interests TO and BQ are employees of Heron Therapeutics and receive salary and stock options. JP received consulting fees from Heron Therapeutics, Acacia Pharma, and Mallinckrodt Pharmaceuticals and is on the speaker's bureau for Mallinckrodt Pharmaceuticals. JFD receives consulting fees from Heron Therapeutics, AcelRx Pharmaceuticals, Neumentum Pharmaceuticals, Aries Pharmaceuticals, and Pacira Pharmaceuticals. ERV receives consulting fees from AcelRx, Concentric, Heron Therapeutics, Innacoll, Merck, Neumentum, Pfizer, Recro, Salix, and Trevena.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

OPEN ACCESS

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative

works on different terms, provided the original work is properly cited, an indication of whether changes were made, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

© American Society of Regional Anesthesia & Pain Medicine 2020. Re-use permitted under CC BY-NC. No commercial re-use. Published by BMJ.

To cite Ottoboni T, Quart B, Pawasauskas J, et al. *Reg Anesth Pain Med* 2020;**45**:1031–1032.

Received 23 March 2020

Accepted 26 March 2020

Published Online First 2 June 2020

► <http://dx.doi.org/10.1136/rapm-2020-101430>

Reg Anesth Pain Med 2020;**45**:1031–1032.

doi:10.1136/rapm-2020-101488

ORCID iD

Eugene R Viscusi <http://orcid.org/0000-0003-0260-4396>

REFERENCES

- Hafer J, Johnson KB. Mechanism of action of HTX-011: a novel, extended-release, dual-acting local anesthetic formulation for postoperative pain. *Reg Anesth Pain Med* 2020;**45**:1030–1.
- Ottoboni T, Quart B, Pawasauskas J, et al. Mechanism of action of HTX-011: a novel, extended-release, dual-acting local anesthetic formulation for postoperative pain. *Reg Anesth Pain Med* 2020;**45**:117–23.
- Viscusi E, Gimbel JS, Pollack RA, et al. HTX-011 reduced pain intensity and opioid consumption versus bupivacaine HCl in bunionectomy: phase III results from the randomized epoch 1 study. *Reg Anesth Pain Med* 2019;**44**:700–6.
- Viscusi E, Minkowitz H, Winkle P, et al. HTX-011 reduced pain intensity and opioid consumption versus bupivacaine HCl in herniorrhaphy: results from the phase 3 epoch 2 study. *Hernia* 2019;**23**:1071–80.
- Heron Therapeutics, Inc. *Data on file*, 2019.
- Hargreaves KM, Keiser K. Local anesthetic failure in endodontics: mechanisms and management. *Endod Topics* 2002;**1**:26–39.
- Ueno T, Tsuchiya H, Mizogami M, et al. Local anesthetic failure associated with inflammation: verification of the acidosis mechanism and the hypothetical participation of inflammatory peroxynitrite. *J Inflamm Res* 2008;**1**:41–8.