No Evidence of Bone-Healing Impairment or NSAID-Related Toxicity With (ZYNRELEF) HTX-011

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I (and/or my coauthors) have something to disclose along with a referral for more detailed disclosure information on the EOA App or via the Disclosure Program on the AAOS website.

Purpose

- There are questions about the risk of impaired bone healing from NSAID administration after arthroplasty or osteotomy
- ZYNRELEF is a dual-acting local anesthetic comprising bupivacaine and low-dose meloxicam in an extended-release polymer
- The low dose of meloxicam reduces inflammation thereby normalizing local pH which allows enhanced bupivacaine penetration across nerve cell membrane
- ZYNRELEF was superior to bupivacaine solution in reducing postoperative pain and opioid use over 72 hours in multiple surgical procedures
- Purpose of this review was to assess potential impact of low dose of meloxicam in ZYNRELEF on bone healing and NSAID-related toxicity in preclinical and clinical studies

Materials and Methods

Studies and Assessments

Study Description	Treatment Regimens	Safety Assessments
Preclinical Studies		
Rat surgical bone defect model (2 studies)	• ZYNRELEF 14.6 mg /0.44 mg (n=8) • Saline placebo (n=8)	• CT post-surgery days 1, 6, 13, 20, 34 (1 study) • Radiography post-surgery days 1, 14, 28, 35 (1 study) • Microscopic evaluation of tissue sections
Clinical Studies		
Phase 2 bunionectomy (dose-finding)	• ZYNRELEF 30 mg/0.9 mg up to 200 mg/6 mg (n=174) • Bupivacaine HCl 50 mg (n=25) • Saline placebo (n=104)	• Radiography between post-surgery days 28 and 42 (1 x-ray)
Phase 3 bunionectomy (EPOCH-1)	• ZYNRELEF 60 mg/1.8 mg (n=157) • Bupivacaine HCl 50 mg (n=154) • Saline placebo (n=101)	• Radiography post-surgery days 28, 42 • Assessment of potential NSAID-related AEs*
Phase 2 open-label bunionectomy (EPOCH-1 follow-on study)	• ZYNRELEF $\leq$ 60 mg/1.8 mg + scheduled MMA (n=31)	• Assessment of potential NSAID-related AEs*

ZYNRELEF doses listed as bupivacaine/meloxicam; AE= adverse event; CT, computer tomography; MMA= multimodal analgesia; NSAID, nonsteroidal anti-inflammatory drug

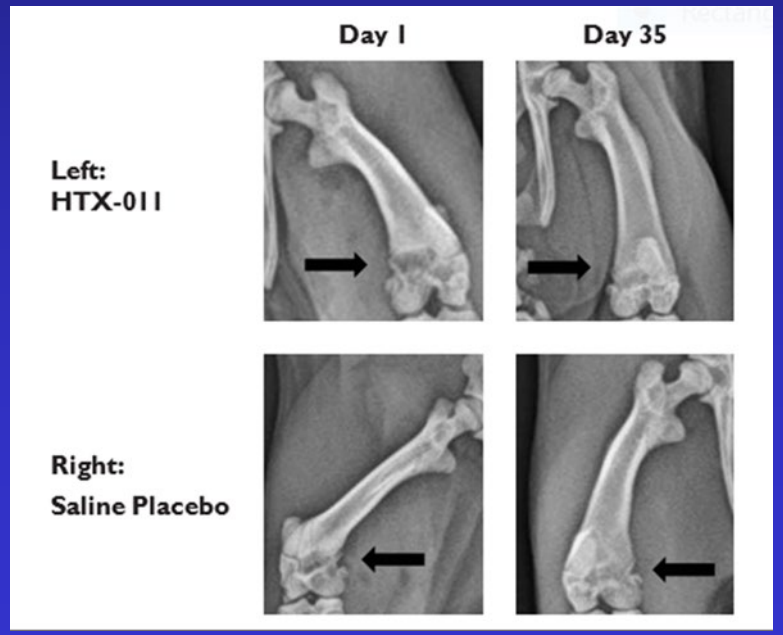
MMA consisted of oral ibuprofen 600 mg q6h + oral acetaminophen 1000 mg q6h

*Based on customized list of preferred terms. Essex MN et al. *Expert Opin Drug Safety*. 2013;12:465-477.

Results
Normal Bone Healing

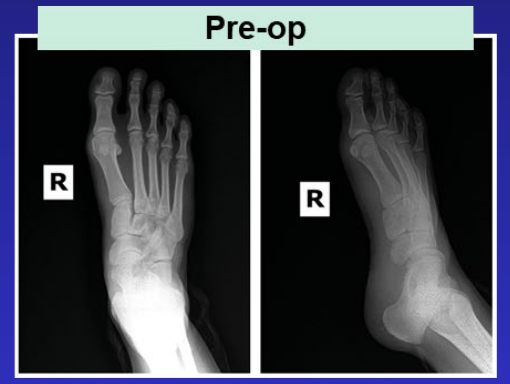
Preclinical Studies

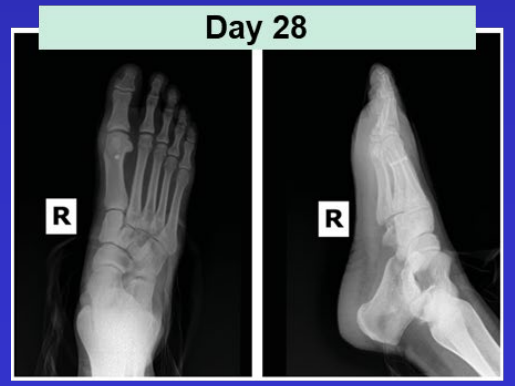
- No differences in bone in-growth or regeneration of adipose and hematopoietic tissue observed

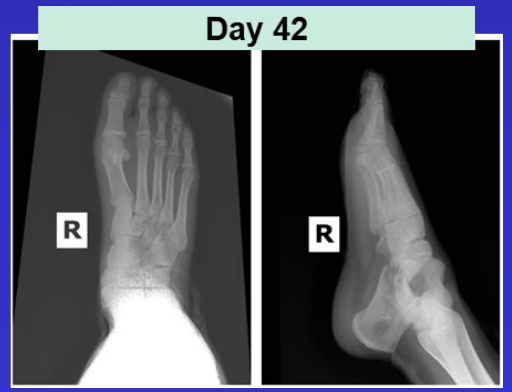


Clinical Studies

Normal healing	HTX-011		Bupivacaine HCl		Placebo	
Phase 2 Study N (%)	N=168		N=24		N=98	
	168 (100)		24 (100)		98 (100)	
EPOCH-1 Study N (%)	Day 28 N=144	Day 42 N=153	Day 28 N=148	Day 42 N=149	Day 28 N=99	Day 42 N=100
	143 (99)	152 (99)	147 (99)	148 (99)	99 (100)	99 (99)







Results

Incidence of Potential NSAID-related AEs Similar to Saline and Bupivacaine Controls

n, (%)	EPOCH-1 (Phase 3 Pivotal Trial)			EPOCH-1 Follow-On
	Saline Placebo (n=101)	Bupivacaine HCl 50 mg (n=154)	ZYNRELEF 60 mg/1.8 mg (n=157)	ZYNRELEF <60 mg/1.8 mg + MMA (n=31)
Patients reporting ≥1 NSAID-related AE	29 (28.7)	38 (24.7)	41 (26.1)	2 (6.5)
Potential NSAID-related AEs ≥3%				
Pruritis	6 (5.9)	1 (0.6)	8 (5.1)	1 (3.2)
Pruritis generalized	4 (4.0)	8 (5.2)	4 (2.5)	0
Pyrexia	3 (3.0)	1 (0.6)	2 (1.3)	0
Hypertension	2 (2.0)	1 (0.6)	0	1 (3.2)
Hypotension	2 (2.0)	7 (4.5)	7 (4.5)	0
Alanine aminotransferase ↑	1 (1.0)	5 (3.2)	3 (1.9)	0
Gamma-glutamyltransferase ↑	1 (1.0)	5 (3.2)	5 (3.2)	0
Drug hypersensitivity	0	1 (0.6)	0	1 (3.3)
Rash	0	1 (0.6)	0	1 (3.3)

MMA consisted of oral ibuprofen 600 mg q6h + oral acetaminophen 1000 mg q6h

Essex MN et al. *Expert Opin Drug Safety*. 2013;12:465-477.

Conclusions

- ZYNRELEF did not impair bone healing in a surgical rat bone defect model or in studies of patients undergoing bunionectomy with osteotomy
- ZYNRELEF did not increase the incidence of NSAID-related AEs compared to saline or bupivacaine and was well tolerated when used as the foundation of non-opioid postoperative MMA that included 72 hours of scheduled ibuprofen