Safety, Pharmacokinetics, and Analgesia of HTX-011 in Total Shoulder Arthroplasty

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I and/or my coauthors have something to disclose.
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Purpose/Hypothesis

- Phase 4, randomized, controlled study conducted to support broadening indication for HTX-011 (ZYNRELEF®), an extended-release bupivacaine/meloxicam solution, to all orthopedic procedures

Methods

- Adults undergoing unilateral reverse or traditional TSA under general anesthesia (without regional blocks) randomized to receive ZYNRELEF 400 mg/12 mg (14 mL) via instillation or bupivacaine HCl 100 mg via injection during surgery
- Scheduled non-opioid MMA regimen for 7 days: PO acetaminophen 1 g q8h alternating with PO ibuprofen 400 mg q8h, so that an analgesic medication was taken q4h
- Rescue medication during first 72 hours (in-house):
  - PO ibuprofen 400 mg and PO acetaminophen 500 mg together, at most once q12h, in addition to scheduled MMA regimen
  - If additional rescue medication requested: PO immediate-release oxycodone (≤10 mg per 4h period) OR IV morphine (≤5 mg per 4h period)

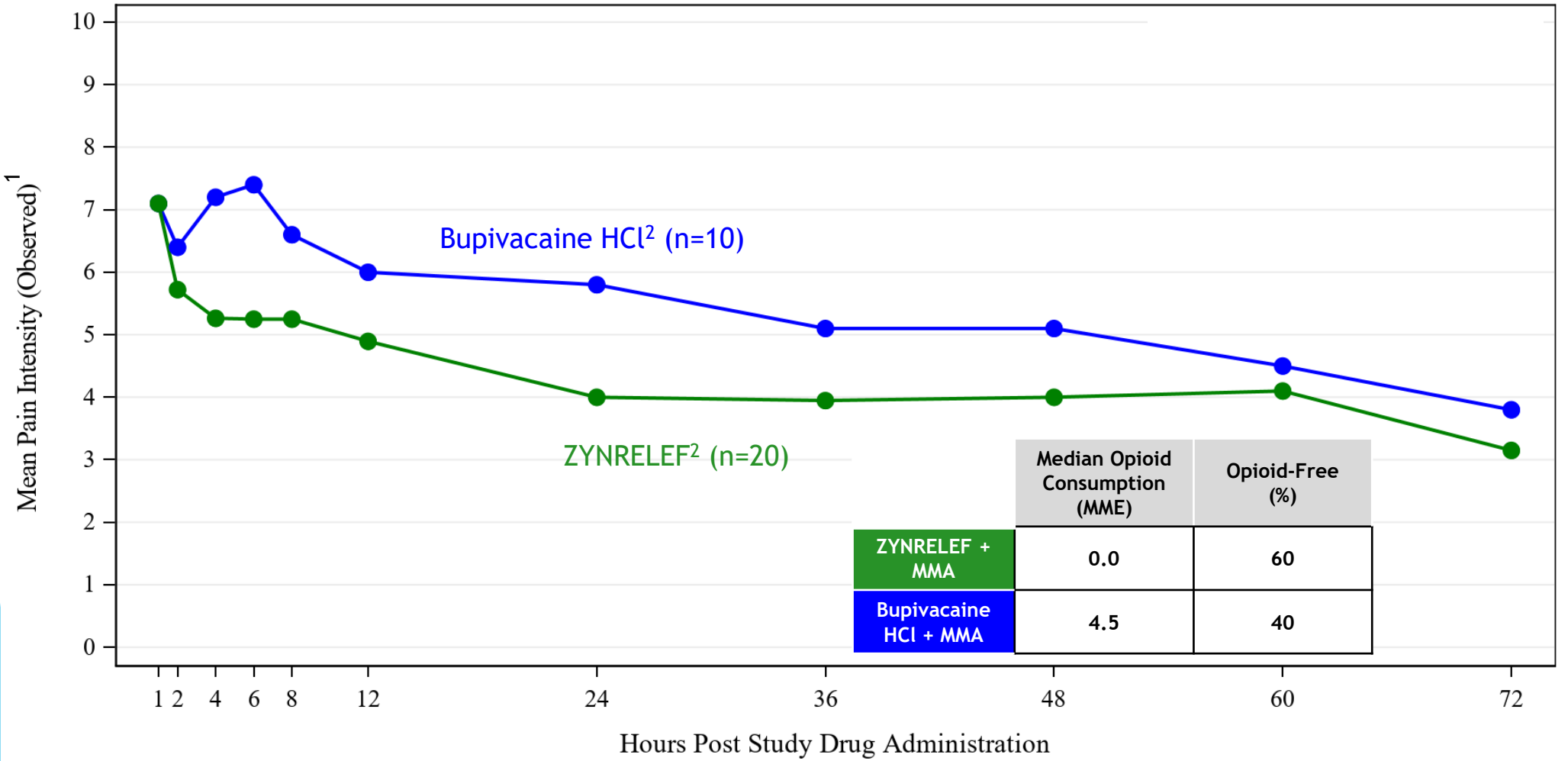
Results

- ZYNRELEF well tolerated:
  - Most AEs mild or moderate in severity; no SAEs
  - Most common AEs: constipation (30%), dizziness (25%), nausea (15%)
  - No surgical wound healing-related AEs
  - No LAST observed
  - No notable differences vs bupivacaine HCl other than a higher incidence of constipation (30% vs 0%)
- Bupivacaine PK exposure well below levels associated with risk for LAST[1]

	ZYNRELEF 400 mg/12 mg	Bupivacaine HCl 100 mg
Mean bupivacaine C_{max}	372 ng/mL	398 ng/mL
Highest individual bupivacaine C_{max}	775 ng/mL	1070 ng/mL
Mean meloxicam C_{max}	248 ng/mL	NA

1. C_{max} 2000 ng/mL and 4000 ng/mL, respectively, for CNS and CV toxicity. References: Bardsley H et al., *Br J Clin Pharmacol* 1998;46(3):245-249; Jorfeldt L et al., *Acta Anaesthesiol Scand* 1968;12(4):153-169; Kastrissios H et al. *Eur J Clin Pharmacol* 1993;44(6):555-557.

TSA: Less Pain and Less Opioid Consumption with ZYNRELEF vs Bupivacaine HCl



	Median Opioid Consumption (MME)	Opioid-Free (%)
ZYNRELEF + MMA	0.0	60
Bupivacaine HCl + MMA	4.5	40

1. Unadjusted pain scores with activity as reported by subject
2. All subjects received background scheduled non-opioid MMA

Conclusions

- ZYNRELEF (HTX-011) as part of a scheduled, non-opioid MMA regimen was well tolerated in patients undergoing TSA
- There was no increase in potential NSAID-related AEs vs bupivacaine HCl and no wound healing AEs
- There was no evidence of LAST, and mean bupivacaine plasma levels were well below levels associated with LAST
- ZYNRELEF showed promising analgesic activity in TSA with less pain and less opioid use