ZYNRELEF®
(bupivacaine and meloxicam)
extended-release solution
29.25 mg/mL and 0.88 mg/mL

ZYNRELEF®

(bupivacaine and meloxicam) extended-release solution

a dual-acting local anesthetic (DALA)

Clinical, Administration, and Pricing Overview

Table of Contents

Indication

ZYNRELEF is indicated in adults for soft tissue or periarticular instillation to produce postsurgical analgesia for up to 72 hours after foot and ankle, small-to-medium open abdominal, and lower extremity total joint arthroplasty surgical procedures.

Limitations of Use: Safety and efficacy have not been established in highly vascular surgeries, such as intrathoracic, large multilevel spinal, and head and neck procedures.

Important Safety Information

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use.**
- **ZYNRELEF is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.**
- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.**

Please see **IMPORTANT SAFETY INFORMATION** on pages 64 to 68 and full Prescribing Information, including **Boxed Warning**.

ZYNRELEF Overview

- ZYNRELEF is the first and only extended-release dual-acting local anesthetic (DALA)[1-4]
- It is also the only local anesthetic considered by FDA to be extended-release, based on superiority to bupivacaine through 72 hours[1]
- ZYNRELEF is a fixed-dose combination of the local anesthetic bupivacaine and a low dose of the nonsteroidal anti-inflammatory drug meloxicam in the proprietary Biochronomer® polymer[1-4]
- ZYNRELEF is a clear, pale yellow to yellow, viscous liquid; it is administered as a single dose and **applied without a needle** into the surgical site following final irrigation and suction and prior to suturing[1]

References: 1. ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **2.** Viscusi E, Gimbel JS, Pollack RA, et al. *Reg Anesth Pain Med*. 2019;44(7):700-706. **3.** Viscusi E, Minkowitz H, Winkle P, et al. *Hernia*. 2019;23(6):1071-1080. **4.** Lachiewicz PF, Lee G-C, Pollak R, et al. *J Arthroplasty*. 2020;35(10):2843-2851.

Please see **IMPORTANT SAFETY INFORMATION** on pages 64 to 68 and full Prescribing Information, including **Boxed Warning**.

ZYNRELEF Overview (cont)

- ZYNRELEF has been clinically proven to manage postoperative pain better than standard-of-care bupivacaine HCl solution through 72 hours, including fewer patients with severe pain, and to reduce or even eliminate opioid utilization following surgery[1-3]
- ZYNRELEF has demonstrated superior efficacy against standard-of-care bupivacaine HCl solution and placebo across multiple and varied surgical models, including both orthopedic and soft tissue models, making it the only local anesthetic to demonstrate superiority to bupivacaine HCl solution in Phase 3 trials[1-3]
- ZYNRELEF was approved by the FDA on May 12, 2021; it is the only pain drug to have been granted Fast Track, Breakthrough Therapy, and Priority Review designations by the FDA[4]
- With the recent approval of the sNDA in December 2021, ZYNRELEF's indication has significantly expanded
  - ZYNRELEF is now indicated for foot and ankle, small-to-medium open abdominal, and lower extremity total joint arthroplasty surgical procedures.
  - The sNDA was approved just 7 months after the initial approval of ZYNRELEF and just 2 months after sNDA submission
  - No new studies were needed for the approval of the sNDA

References: 1. ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **2.** Viscusi E, Gimbel JS, Pollack RA, et al. *Reg Anesth Pain Med.* 2019;44(7):700-706. **3.** Viscusi E, Minkowitz H, Winkle P, et al. *Hernia.* 2019;23(6):1071-1080. **4.** Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review. https://www.fda.gov/ForPatients/Approvals/Fast/default.htm. Accessed March 31, 2021.

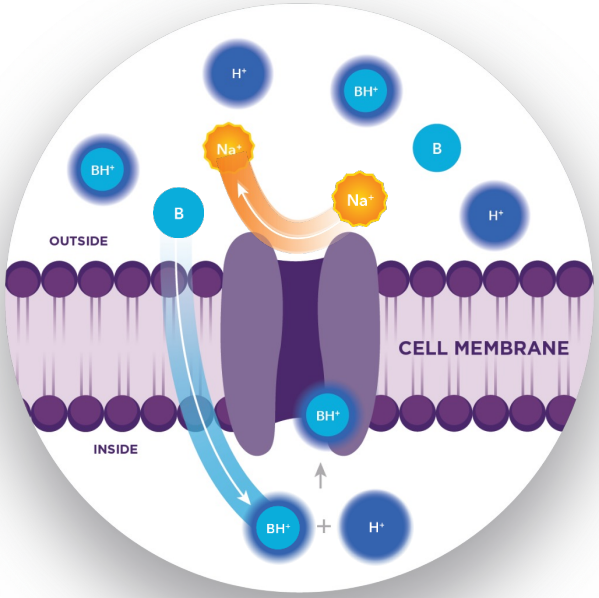
Inflammation and Postsurgical Pain

- Postsurgical pain is greatest during the first 72 hours after surgery[1]
- Most local anesthetics, including liposomal bupivacaine and formulations delivered via wound infiltration catheters or pumps, inconsistently provide pain relief beyond 12 to 24 hours after surgery[2-7]
- The primary reason most longer-acting local anesthetics are less effective beyond 12 to 24 hours may be inflammation at the wound site, which increases acidity. Acidity decreases the ability of local anesthetics to penetrate nerve cells and block pain signals.[2-7]
- ZYNRELEF is the first and only extended-release DALA, with a novel, synergistic mechanism of action designed to overcome the challenges of inflammation at the surgical site[8-11]

References: 1. Svensson I, Sjöström B, Haljamäe H. *J Pain Symptom Manage*. 2000;20(3):193-201. **2.** Ali A, Sundberg M, Hansson U, et al. *Acta Orthop*. 2015;86(3):373-377. **3.** Kim J, Burke SM, Kryzanski JT, et al. *World Neurosurg*. 2016;91:460-467. **4.** Data on file. DRG physician survey. San Diego, CA: Heron Therapeutics Inc; 2017. **5.** Becker DE, Reed KL. *Anesth Prog*. 2006;53(3):98-109. **6.** Exparel [package insert]. San Diego, CA: Pacira Pharmaceuticals Inc; 2021. **7.** Hargreaves KM, Keiser K. *Endod Topics*. 2002;1(1):26-39. **8.** ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **9.** Viscusi E, Gimbel JS, Pollack RA, et al. *Reg Anesth Pain Med*. 2019;44(7):700-706. **10.** Viscusi E, Minkowitz H, Winkle P, et al. *Hernia.* 2019;23(6):1071-1080. **11.** Lachiewicz PF, Lee G-C, Pollak R, et al. *J Arthroplasty*. 2020;35(10):2843-2851.

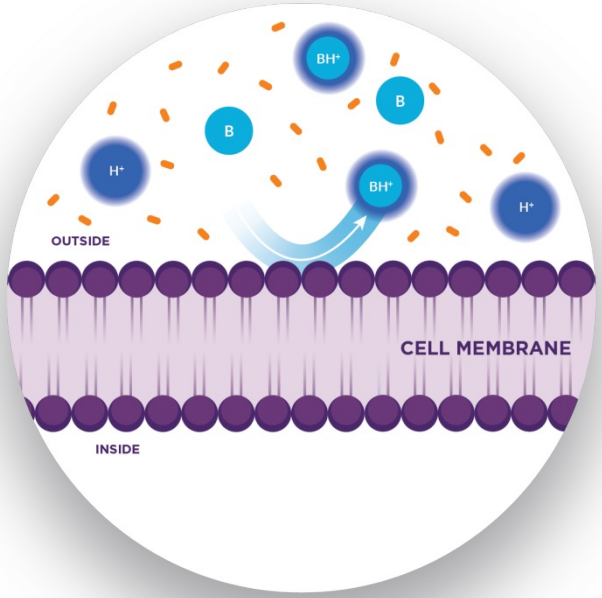
Inflammation Can Inhibit the Efficacy of Local Anesthetics Such as Bupivacaine[1-3]

Bupivacaine mechanism of action



To stop pain signals, bupivacaine **must diffuse through the nerve cell membrane** and bind to the voltage-gated sodium ion channels from inside the cell.[1-3]

Impact of inflammation



Inflammation causes the wound site to become more acidic, resulting in increased ionization of bupivacaine outside the cell.[2,3]

Ionized bupivacaine cannot penetrate the nerve cell membrane and therefore cannot block pain signals.[2,3]

B UN-IONIZED BUPIVACAINE

H+ POSITIVELY CHARGED HYDROGEN ION

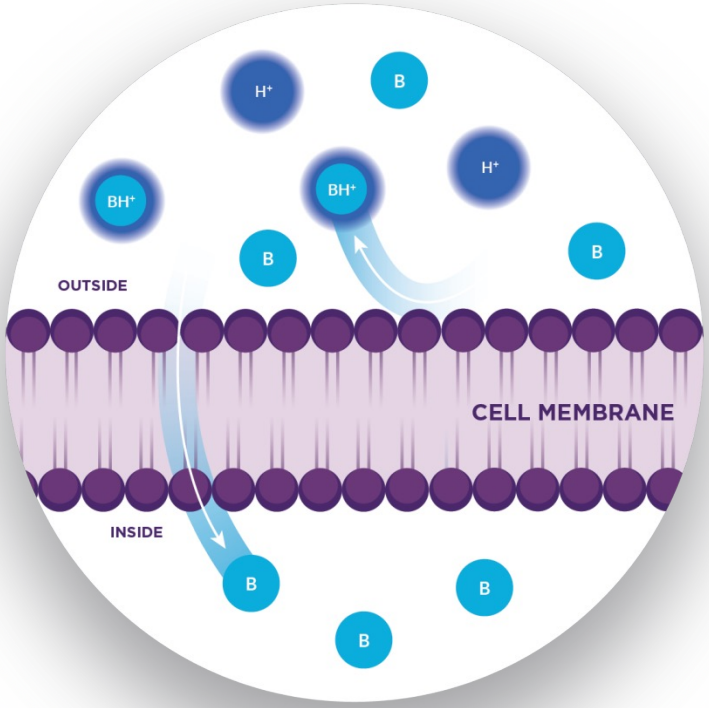
BH+ IONIZED BUPIVACAINE

ACIDIC METABOLITES

Na+ SODIUM ION

References: 1. Berde CB, Strichartz GR. In: Miller RD, Cohen NH, Eriksson LI, et al, eds. *Miller's Anesthesia*. Vol 1. 8th ed. Philadelphia, PA: Saunders; 2015:1028-1054.e4. **2.** Becker DE, Reed KL. *Anesth Prog*. 2006;53(3):98-109. **3.** Hargreaves KM, Keiser K. *Endod Topics*. 2002;1(1):26-39.

ZYNRELEF: Mechanism of Action



ZYNRELEF is designed to overcome the challenges associated with the local inflammatory process. Novel controlled-diffusion, polymer technology delivers both active ingredients simultaneously for 72 hours.[1,2]

It is thought that meloxicam in ZYNRELEF inhibits the acidotic effect of inflammation, and as a result reduces the concentration of hydrogen ions in the environment, normalizing the pH at the wound site and potentiating the effect of bupivacaine during the critical 72-hour window when pain is most severe.[2,3]

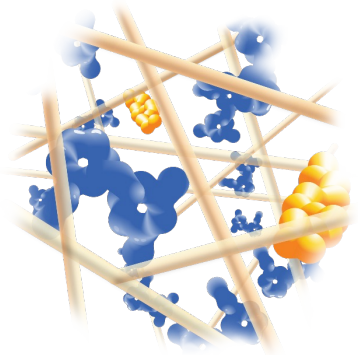
In animal studies, ZYNRELEF resulted in decreased tissue acidity (pH 6.87) versus the control group (pH 5.78), which resulted in considerably more un-ionized bupivacaine available to enter nerve cells.[2,4,a] The synergistic increase in analgesia through 72 hours was seen in a preclinical animal model and confirmed in human studies.[1,2,4-6]

[a]Measured at 48 hours post incision.

References: 1. ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **2.** Ottoboni T, Quart B, Pawasauskas J, et al. *Reg Anesth Pain Med*. 2020;45(2):117-123. **3.** Svensson I, Sjöström B, Haljamäe H. *J Pain Symptom Manage*. 2000;20(3):193-201. **4.** Data on file. Study 33-87. San Diego, CA: Heron Therapeutics Inc; 2018. **5.** Data on file. Study HTX-011-C2016-208. San Diego, CA: Heron Therapeutics Inc; 2017. **6.** Data on file. Study HTX-011-C2015-202. San Diego, CA: Heron Therapeutics Inc; 2018.

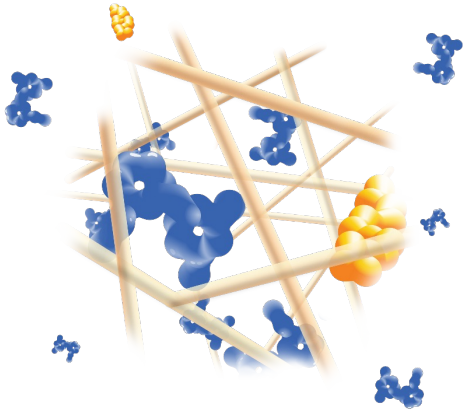
ZYNRELEF Is Formulated and Designed for 72-hour Postoperative Analgesia[1]

1. UNIQUE DRUG FORMULATION



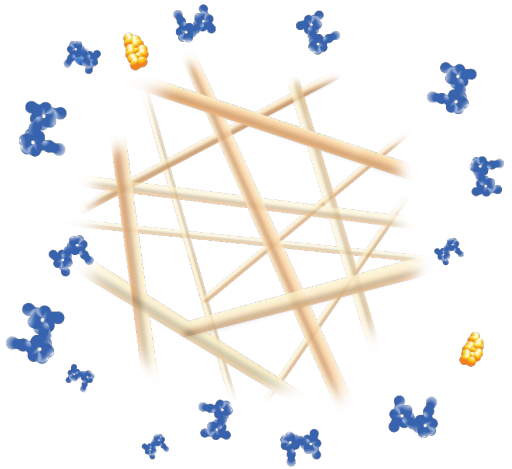
- Active ingredients are contained in a novel and proprietary controlled-diffusion polymer called Biochronomer[1,2]
- The ratio of bupivacaine to meloxicam is 33:1[1]

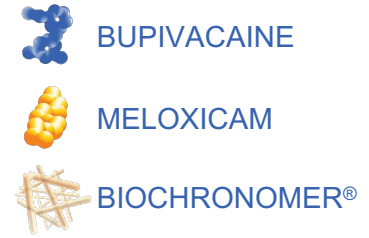
2. CONTROLLED DIFFUSION



- Biochronomer is designed for consistently regulated delivery of both active ingredients for 72 hours after surgery[1,2]
- 0 to 24 hours: 52% bupivacaine and 44% meloxicam released[3,a]
- 0 to 48 hours: 81% bupivacaine and 81% meloxicam released[3,a]
- 0 to 72 hours: 93% bupivacaine and 95% meloxicam released[3,a]

3. DISSOLUTION





- As the active components are released from the formulation, the polymer hydrolyzes into benign, water-soluble end products which are eliminated from the body via the kidneys[2]
- Biochronomer is in a product that has been used approximately 300,000 times[b] for CINV patients; it has been applied in over 1,500 patients during ZYNRELEF trials[1,4,5]

[a]Reflects in vitro release rates of active ingredients. [b]Based on units distributed.

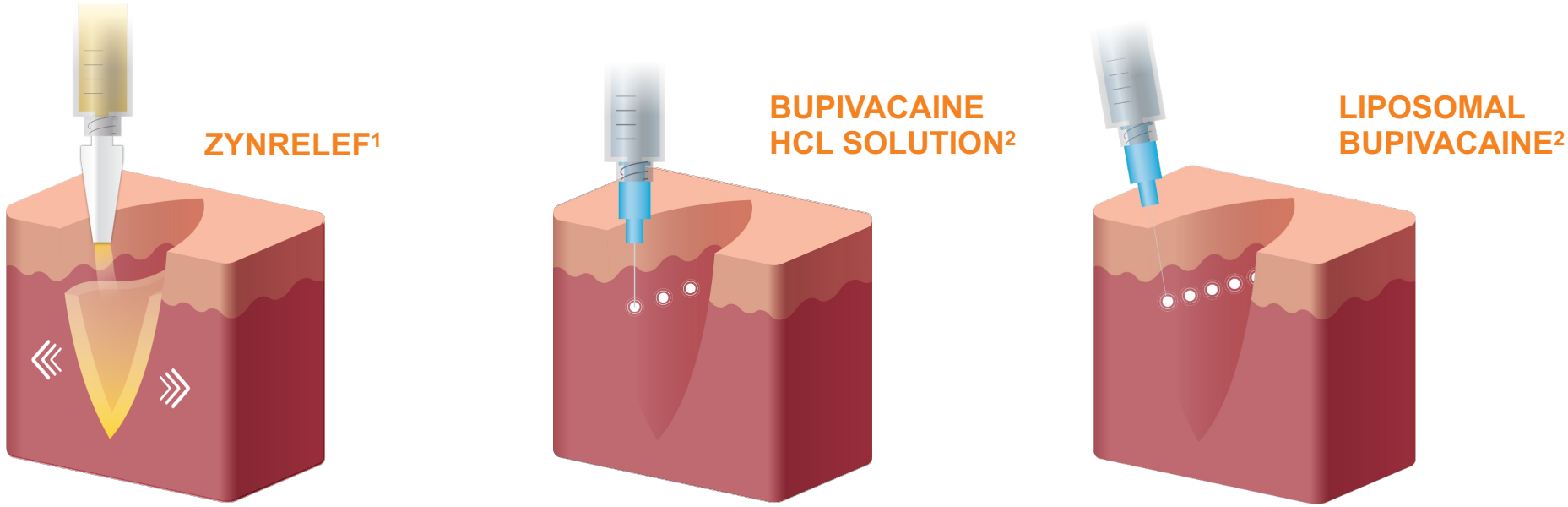
CINV: chemotherapy-induced nausea and vomiting.

References: 1. ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **2.** Ottoboni T, Quart B, Pawasauskas J, et al. *Reg Anesth Pain Med*. 2020;45(2):117-123. **3.** Data on file. Summary of biopharmaceutic studies and associated analytical methods. San Diego, CA: Heron Therapeutics Inc; 2018. **4.** Data on file. SUSTOL periodic safety update report 07. San Diego, CA: Heron Therapeutics Inc; 2020. **5.** Data on file. ZYNRELEF periodic safety update report 01. San Diego, CA: Heron Therapeutics Inc; 2021.

Please see **IMPORTANT SAFETY INFORMATION** on pages 64 to 68 and full Prescribing Information, including **Boxed Warning**.

ZYNRELEF Is Applied Without a Needle as a Single Dose[1]

- Applied via a needle-free syringe to directly coat the affected tissue within the surgical site, following irrigation and suction and prior to suturing; eliminates the need for up to 120 injections, as in total knee arthroplasty[1,2]
- **No mixing with bupivacaine is required to achieve efficacy[1]**
- Other local anesthetics can be administered before ZYNRELEF without causing release of the active ingredients all at once[1,3,4]

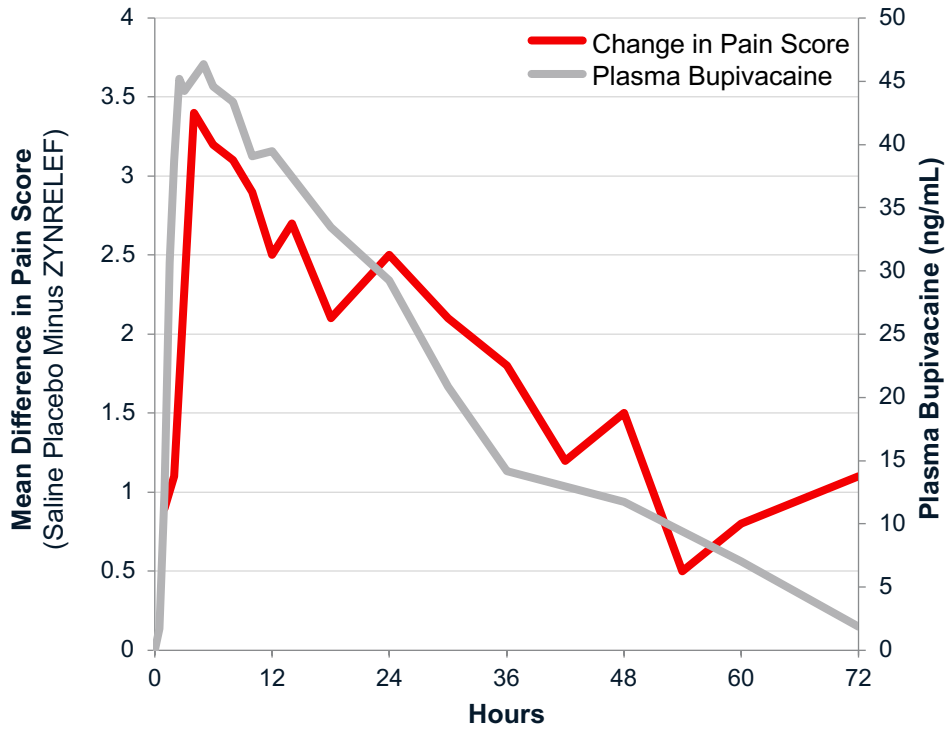


To see preparation and administration videos for ZYNRELEF, visit ZYNRELEF.com/admin.

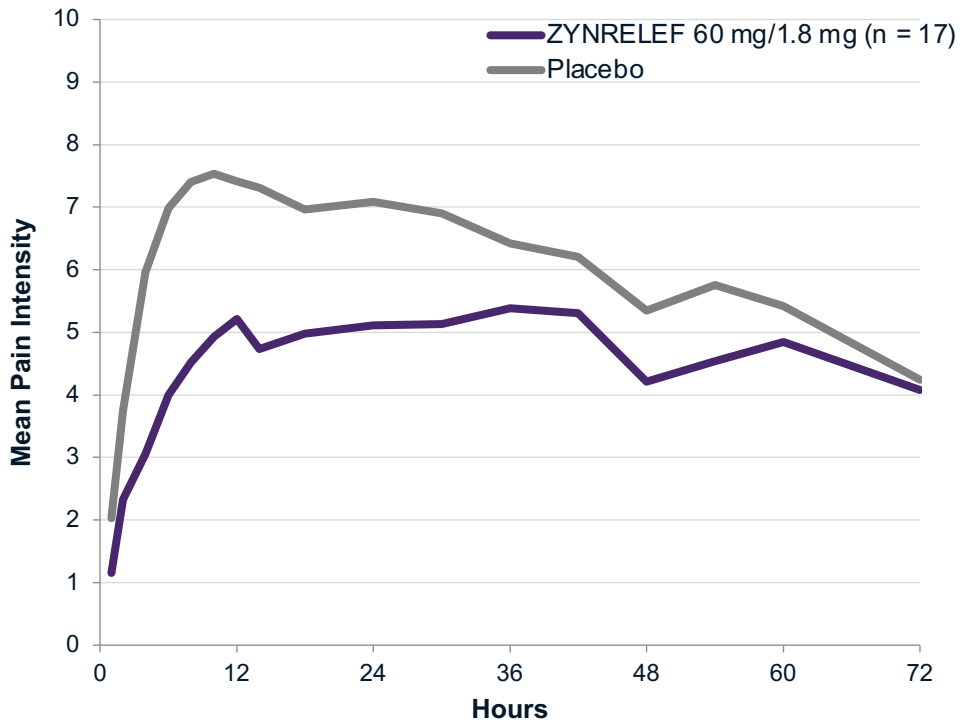
References: 1. ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **2.** Mont MA, Beaver WB, Dysart SH, et al. *J Arthroplasty*. 2018;33(1):90-96. **3.** Viscusi E, Gimbel JS, Pollack RA, et al. *Reg Anesth Pain Med*. 2019;44(7):700-706. **4.** Lachiewicz PF, Lee G-C, Pollak R, et al. *J Arthroplasty*. 2020;35(10):2843-2851.

ZYNRELEF Bupivacaine Plasma Levels and Efficacy Through 72 Hours in Phase 2 Bunionectomy Study[1]

PK/PD



Mean Pain Intensity Versus Time

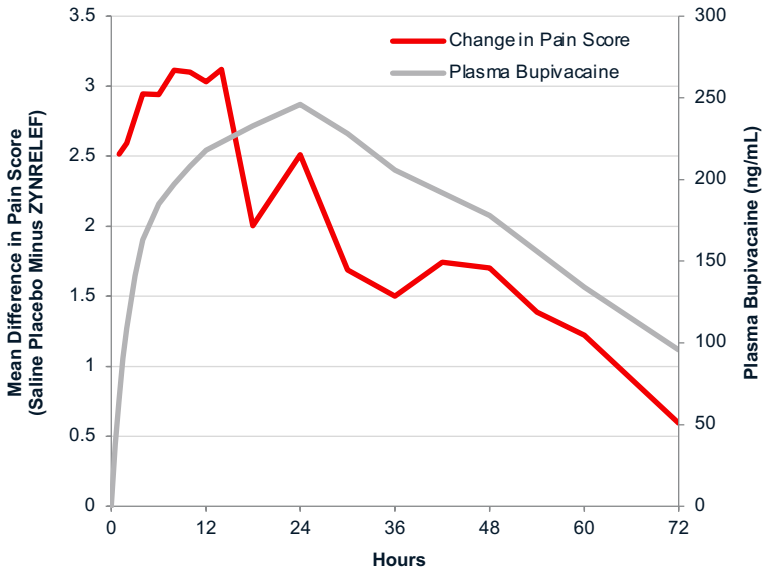


PK/PD: pharmacokinetic/pharmacodynamic.

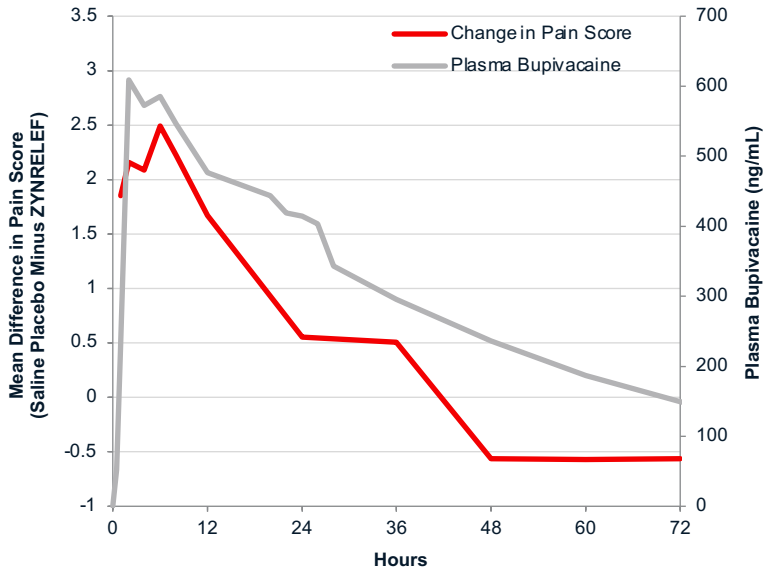
References: 1. Data on file. Study HTX-011-C2016-208. San Diego, CA: Heron Therapeutics Inc; 2017.

ZYNRELEF PK/PD Profiles Are Consistent Through 72 Hours Across Other Surgical Models

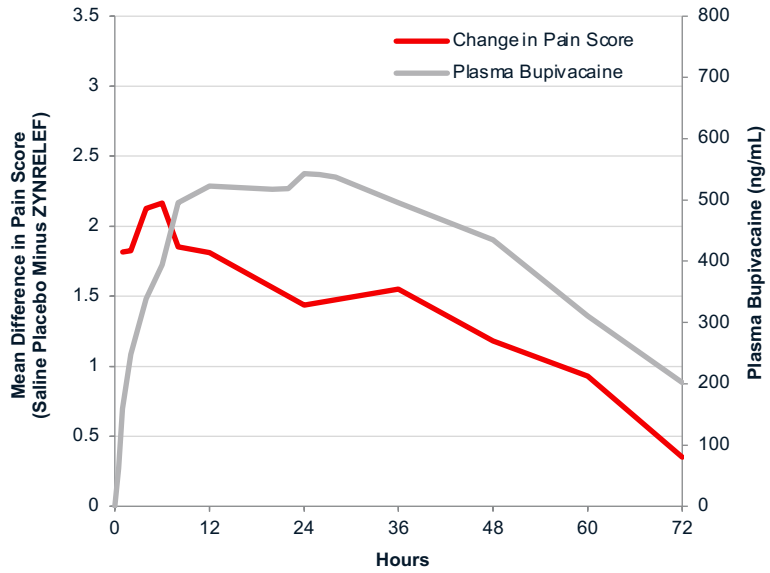
Herniorrhaphy[1]



Breast Augmentation[2]



Total Knee Arthroplasty[3]



ZYNRELEF is not indicated for use in breast augmentation surgery. Data shown here for comparison of PK/PD profiles across surgical models.

PK/PD: pharmacokinetic/pharmacodynamic.

References: 1. Data on file. Study HTX-011-C2015-202. San Diego, CA: Heron Therapeutics Inc; 2018. **2.** Data on file. Study HTX-011-211. San Diego, CA: Heron Therapeutics Inc; 2018. **3.** Data on file. Study HTX-011-209. San Diego, CA: Heron Therapeutics Inc; 2018.

Clinical Portfolio Development[1-11]

	Bunionectomy *With Osteotomy* (foot and ankle)	*Open Inguinal* **Herniorrhaphy** *With Mesh* (small-to-medium open abdominal)	**Total Knee Arthroplasty** (lower extremity total joint arthroplasty)
Phase 2a Studies Demonstrating Synergy	**Phase 2a** (Synergy vs ER bupivacaine and ER meloxicam alone) *Study 208*	**Phase 2a** (Synergy vs ER bupivacaine and ER meloxicam alone) *Study 202*	
RCT Studies Included in PI • *Did not include non-opioid MMA regimen* • *Included 72-hour in-hospital postoperative monitoring*	EPOCH 1 Evaluation of Pain Relief and Opioid Control **Phase 3** (vs placebo and bupivacaine) *Study 301*	EPOCH 2 Evaluation of Pain Relief and Opioid Control **Phase 3** (vs placebo and bupivacaine) *Study 302*	EPOCH TKA Evaluation of Pain Relief and Opioid Control **Phase 2b** (vs placebo and bupivacaine) *Study 209*
Follow-On Studies • *Open label, single-arm, uncontrolled* • *Included non-opioid MMA regimen* • *Included 72-hour in-hospital postoperative monitoring*	**EPOCH 1 Single-Arm Follow-On** *Study 218*	**EPOCH 2 Single-Arm Follow-On** *Study 215*	**EPOCH TKA Single-Arm Follow-On** *Study 306*
Real-World Setting • *Open label* • *Included non-opioid MMA regimen* • *Discharged per site practice (2.41 hours after surgery on average)*		HOPE **HOPE Hernia 1** *Study 304*	

Related Procedures

Based on similarities in surgical site characteristics, such as anatomic location, tissue type, length and depth of surgical area, and vascularity between:

- bunionectomy and other foot and ankle surgical procedures
- open inguinal herniorrhaphy and other small-to-medium open abdominal surgical procedures
- total knee arthroplasty and other lower extremity total joint arthroplasty surgical procedures

the pharmacokinetic profile and effectiveness of ZYNRELEF are not expected to be clinically significantly different when ZYNRELEF is administered at the same dose.[1]

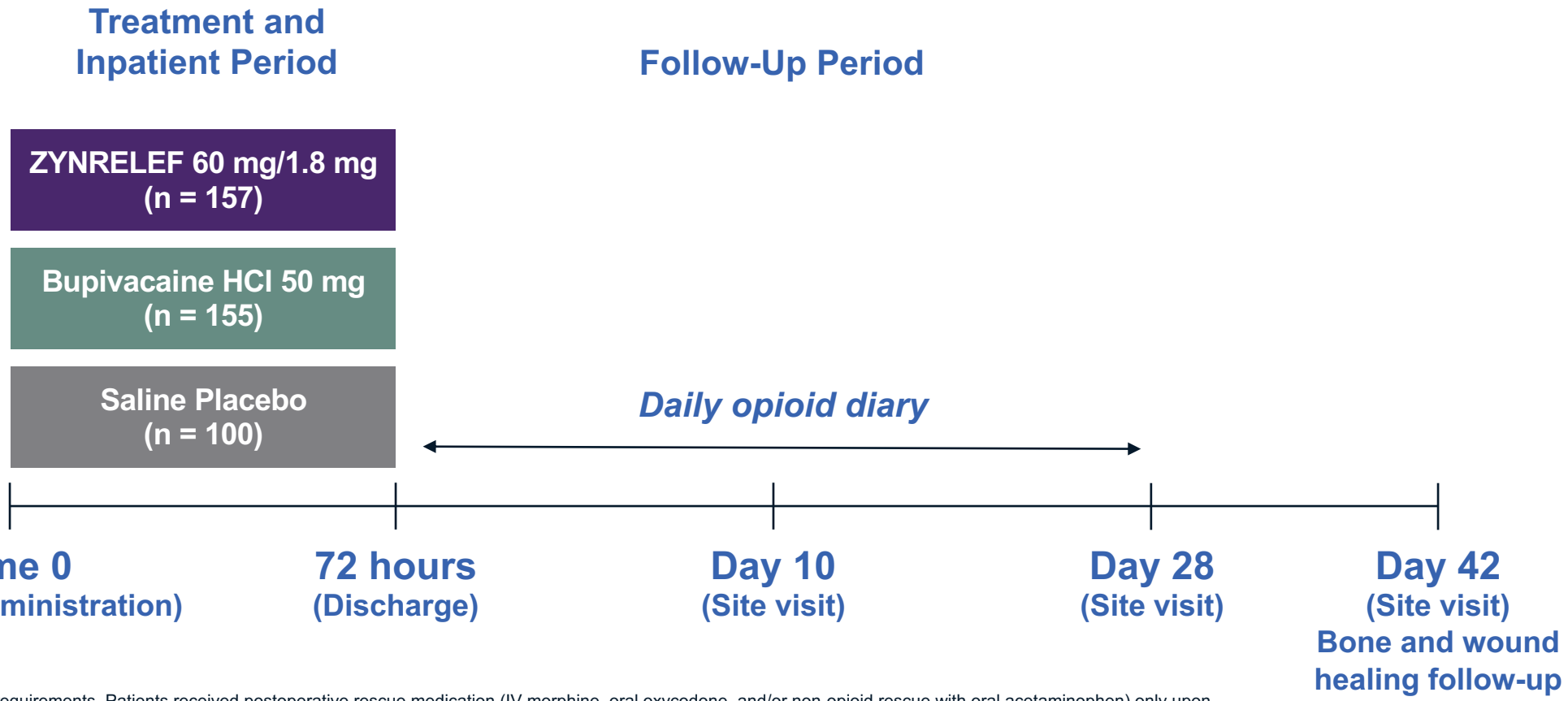
RCT: randomized controlled trials. **MMA:** multimodal analgesia.

References: 1. ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **2.** Data on file. Study HTX-011-C2016-208. San Diego, CA: Heron Therapeutics Inc; 2017. **3.** Data on file. Study HTX-011-C2015-202. San Diego, CA: Heron Therapeutics Inc; 2018. **4.** Viscusi E, Gimbel JS, Pollack RA, et al. *Reg Anesth Pain Med*. 2019;44(7):700-706. **5.** Viscusi E, Minkowitz H, Winkle P, et al. *Hernia*. 2019;23(6):1071-1080. **6.** Lachiewicz PF, Lee G-C, Pollak R, et al. *J Arthroplasty*. 2020;35(10):2843-2851. **7.** Pollak R, Cai D, Gan TJ. *J Am Podiatr Med Assoc*. 2021:20-204. doi:10.7547/20-204. **8.** Singla N, Winkle P, Bertoch T, et al. *Surgery*. 2020;168(5):915-920. **9.** Hacker S. Poster presented at: Orthopedics Today Hawaii 2020; January 12-16, 2020; Koloa, HI. **10.** Fanikos J, Minkowitz H, Reinhorn M, et al. Poster presented at: ASHP 2019 Midyear Clinical Meeting; December 9, 2019; Las Vegas, NV. **11.** Data on file. Study HTX-011-304. San Diego, CA: Heron Therapeutics Inc; 2020.

EPOCH 1 Bunionectomy: Phase 3 Study Design[1,2]

Bunionectomy With Osteotomy and Internal Fixation

- 13 sites in the United States
- N = 412
- **Protocol did not include a multimodal analgesic regimen (MMA)**



Note: This study was designed to meet regulatory requirements. Patients received postoperative rescue medication (IV morphine, oral oxycodone, and/or non-opioid rescue with oral acetaminophen) only upon request through 72 hours.

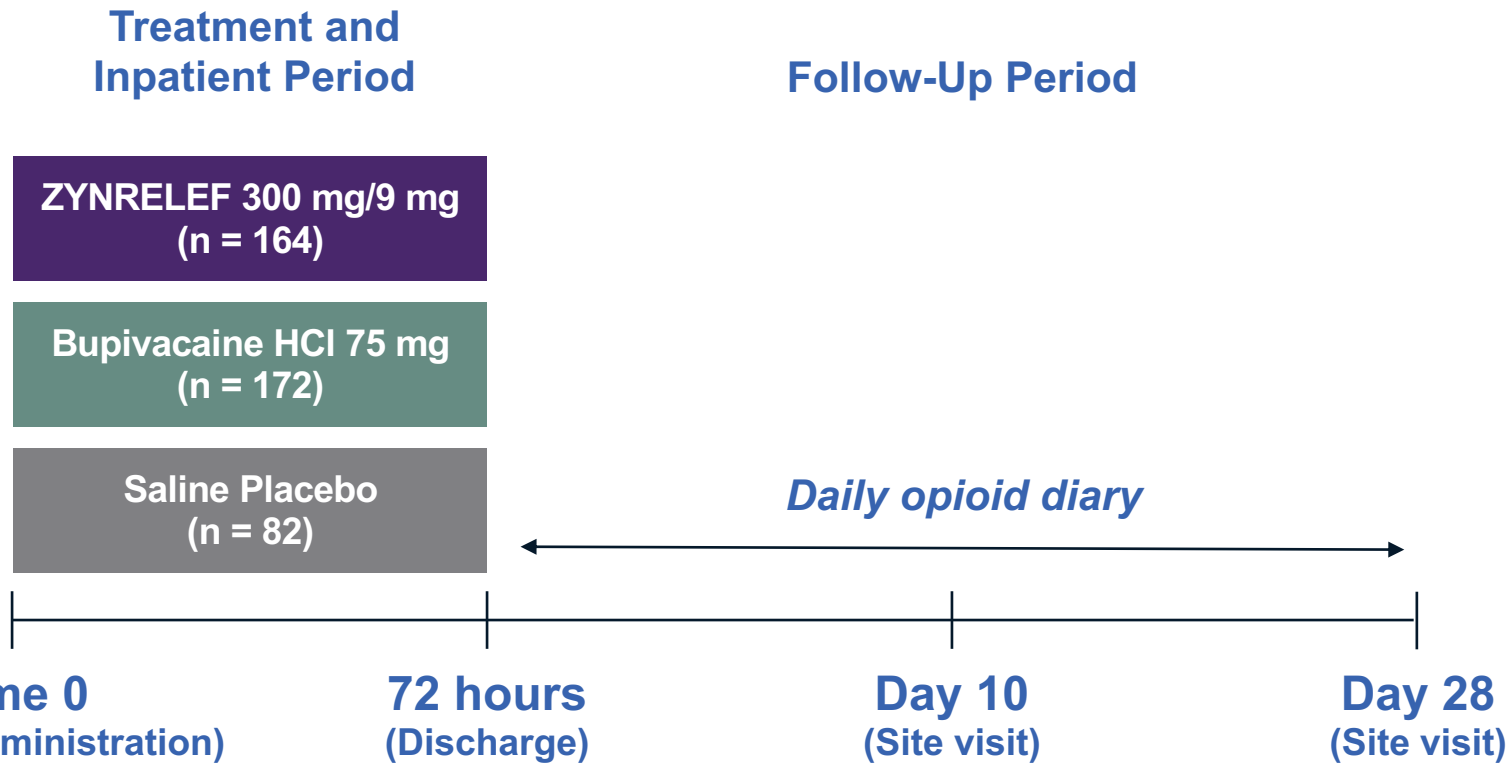
MMA: multimodal analgesia.

References: 1. Viscusi E, Gimbel JS, Pollack RA, et al. *Reg Anesth Pain Med*. 2019;44(7):700-706. **2.** ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021.

EPOCH 2 Herniorrhaphy: Phase 3 Study Design[1,2]

Open Inguinal Herniorrhaphy

- 16 sites in the United States, 1 site in the European Union
- N = 418
- **Protocol did not include a multimodal analgesic regimen (MMA)**



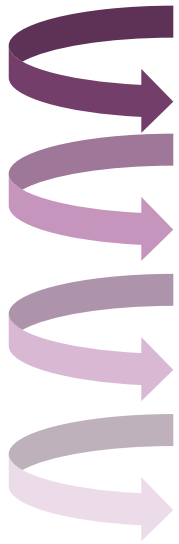
Note: This study was designed to meet regulatory requirements. Patients received postoperative rescue medication (IV morphine, oral oxycodone, and/or non-opioid rescue with oral acetaminophen) only upon request through 72 hours.

MMA: multimodal analgesia.

References: 1. Viscusi E, Minkowitz H, Winkle P, et al. *Hernia.* 2019;23(6):1071-1080. **2.** ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021.

ZYNRELEF Met All Primary and Key Secondary Endpoints in Both Phase 3 Trials (EPOCH 1 Bunionectomy and EPOCH 2 Herniorrhaphy)[1-3]

Hierarchical hypothesis testing ($P \leq .05$)



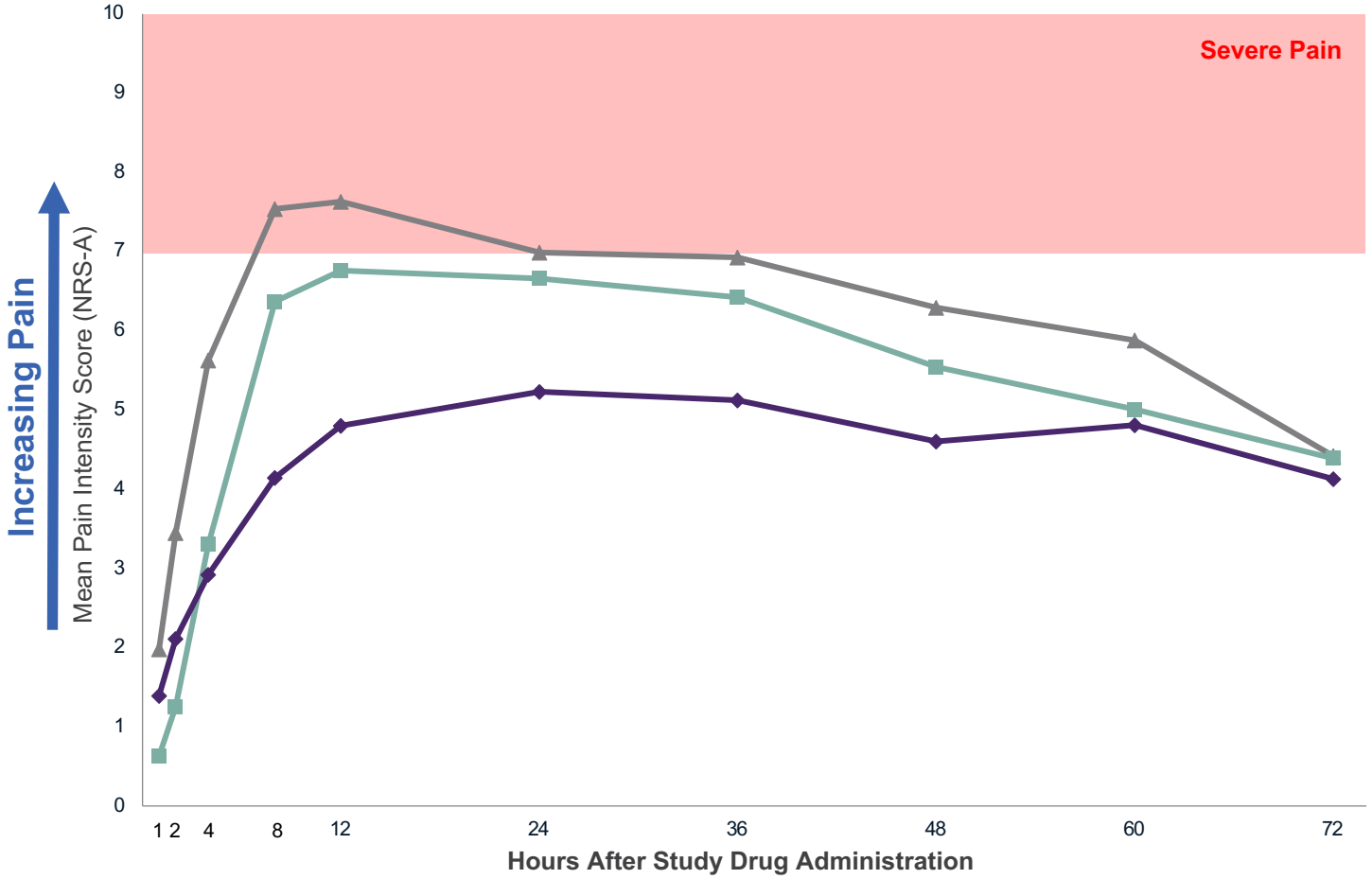
	Endpoint	EPOCH 1 Bunionectomy	EPOCH 2 Herniorrhaphy
Primary	Pain Intensity (AUC_{0-72}) vs Placebo	$P < .0001$	$P = .0004$
First Key Secondary	Pain Intensity (AUC_{0-72}) vs Bupivacaine	$P = .0002$	$P < .0001$
Second Key Secondary	Opioid Use (0-72 hours) vs Placebo	$P < .0001$	$P = .0001$
Third Key Secondary	Opioid-Free (0-72 hours) vs Bupivacaine	$P = .0001$	$P = .0486$
Fourth Key Secondary	Opioid Use (0-72 hours) vs Bupivacaine	$P = .0022$	$P = .0240$

Note: A strict testing hierarchy was applied on the primary and key secondary endpoints to control the study-wise alpha at the .05 level. This means the primary endpoint had to reach significance ($P \leq .05$) before the first key secondary endpoint was tested, continuing through each additional key secondary endpoint.

AUC: area under the curve.

References: 1. Viscusi E, Gimbel JS, Pollack RA, et al. *Reg Anesth Pain Med*. 2019;44(7):700-706. **2.** Viscusi E, Minkowitz H, Winkle P, et al. *Hernia.* 2019;23(6):1071-1080. **3.** ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021.

EPOCH 1 Bunionectomy: Superior Reduction in Pain Intensity Versus SOC Bupivacaine HCl Solution Through 72 Hours, the Time When Postsurgical Pain Is Most Intense[1-3]



AUC_{0-72} vs bupivacaine:

***P* = .0002**

AUC_{0-72} vs placebo:

***P* < .0001**

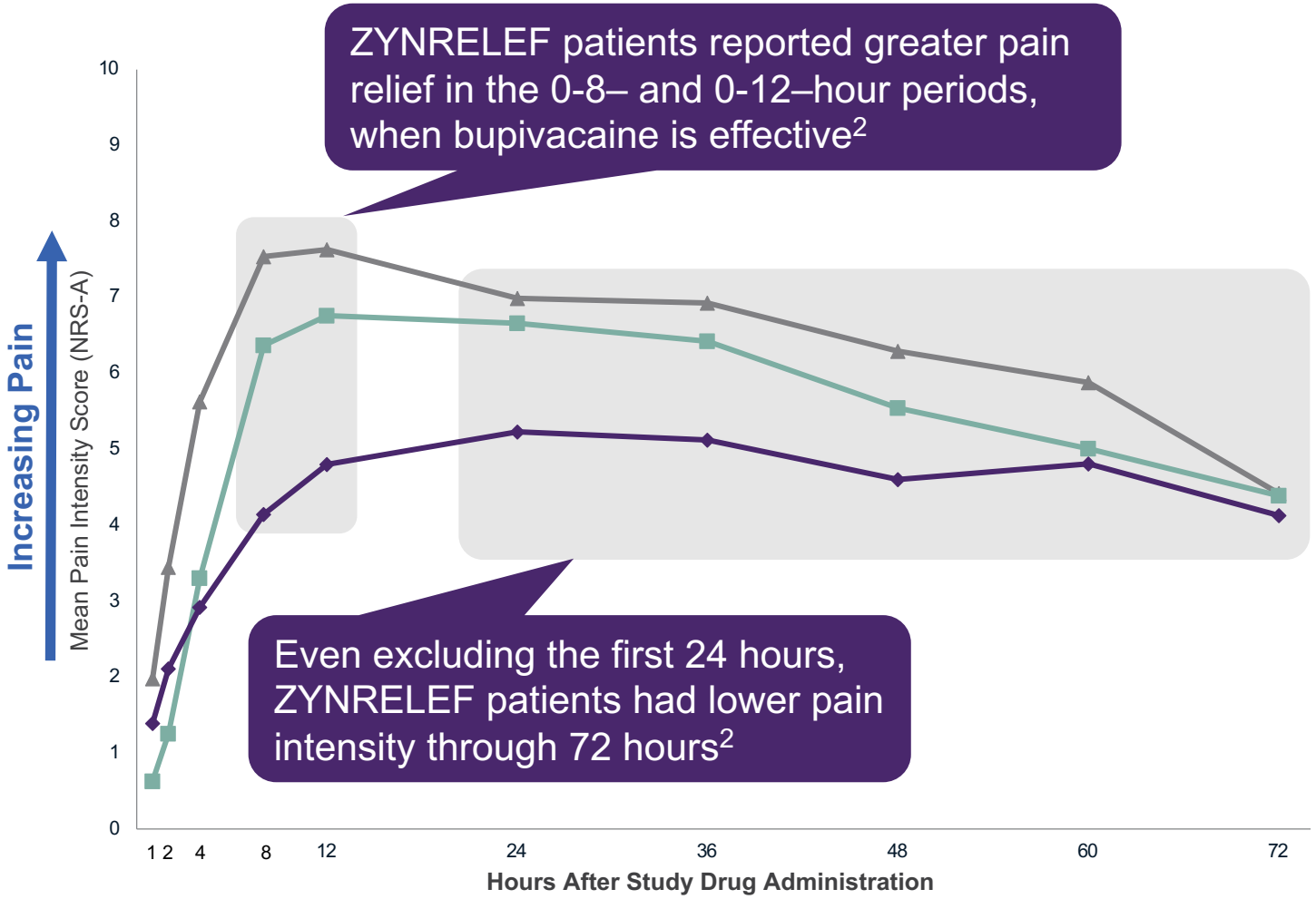
- **Saline Placebo (n = 100)**
- **Bupivacaine HCl Solution 50 mg (n = 155)**
- **ZYNRELEF 60 mg/1.8 mg (n = 157)**

Note: Pain scores were analyzed with adjustment for the analgesic duration of rescue medications.

SOC: standard-of-care. **NRS-A:** Numeric Rating Scale With Activity.
AUC: area under the curve.

References: 1. ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **2.** Viscusi E, Gimbel JS, Pollack RA, et al. *Reg Anesth Pain Med*. 2019;44(7):700-706. **3.** Svensson I, Sjöström B, Haljamäe H. *J Pain Symptom Manage*. 2000;20(3):193-201.

EPOCH 1 Bunionectomy: Greater Pain Relief Versus SOC Bupivacaine HCl Solution[1,2]



0-8 and 0-12 hours vs bupivacaine:

$AUC_{0\text{-}8}$: ***P* = .0477**[a]

$AUC_{0\text{-}12}$: ***P* < .0001**[b]

24-72 hours vs bupivacaine:

$AUC_{24\text{-}72}$: ***P* = .0072**[a]

Saline Placebo (n = 100)

Bupivacaine HCl Solution 50 mg (n = 155)

ZYNRELEF 60 mg/1.8 mg (n = 157)

[a]Analysis not prespecified; nominal *P* value not controlled for multiplicity.

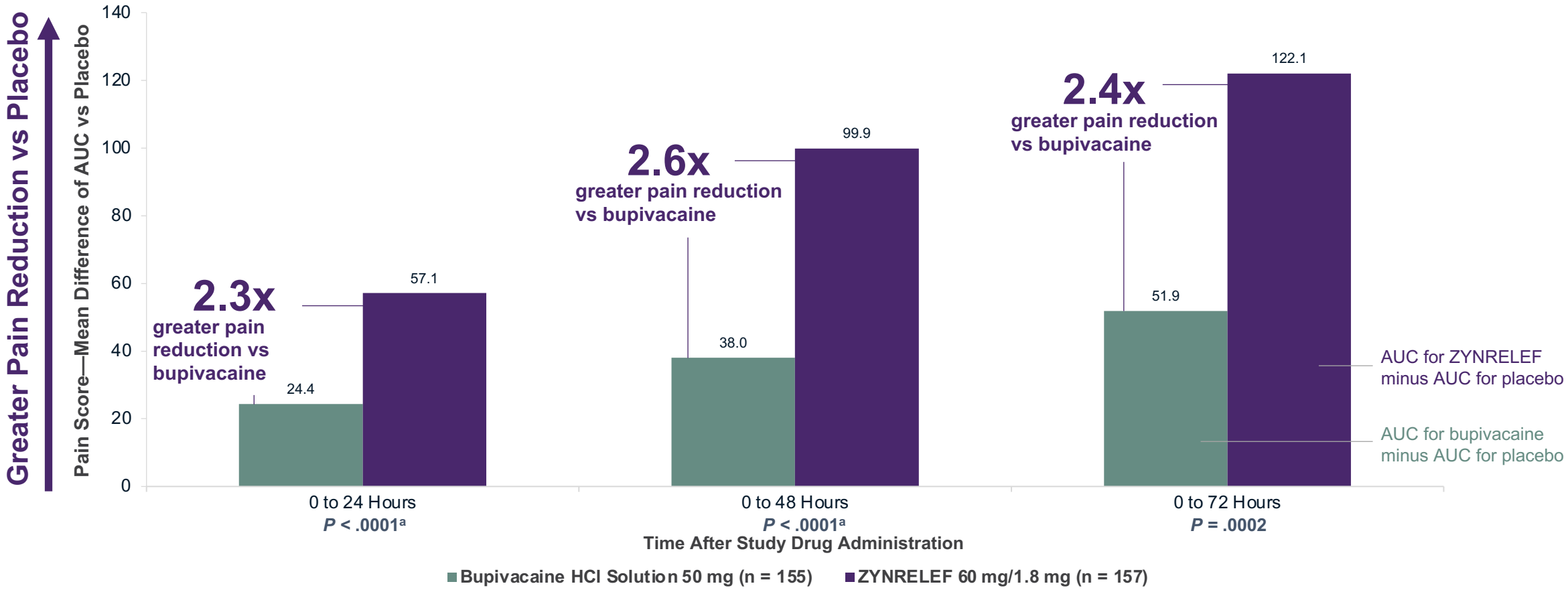
[b]Nominal *P* value not controlled for multiplicity.

Note: Pain scores were analyzed with adjustment for the analgesic duration of rescue medications.

SOC: standard-of-care. **NRS-A:** Numeric Rating Scale With Activity.
AUC: area under the curve.

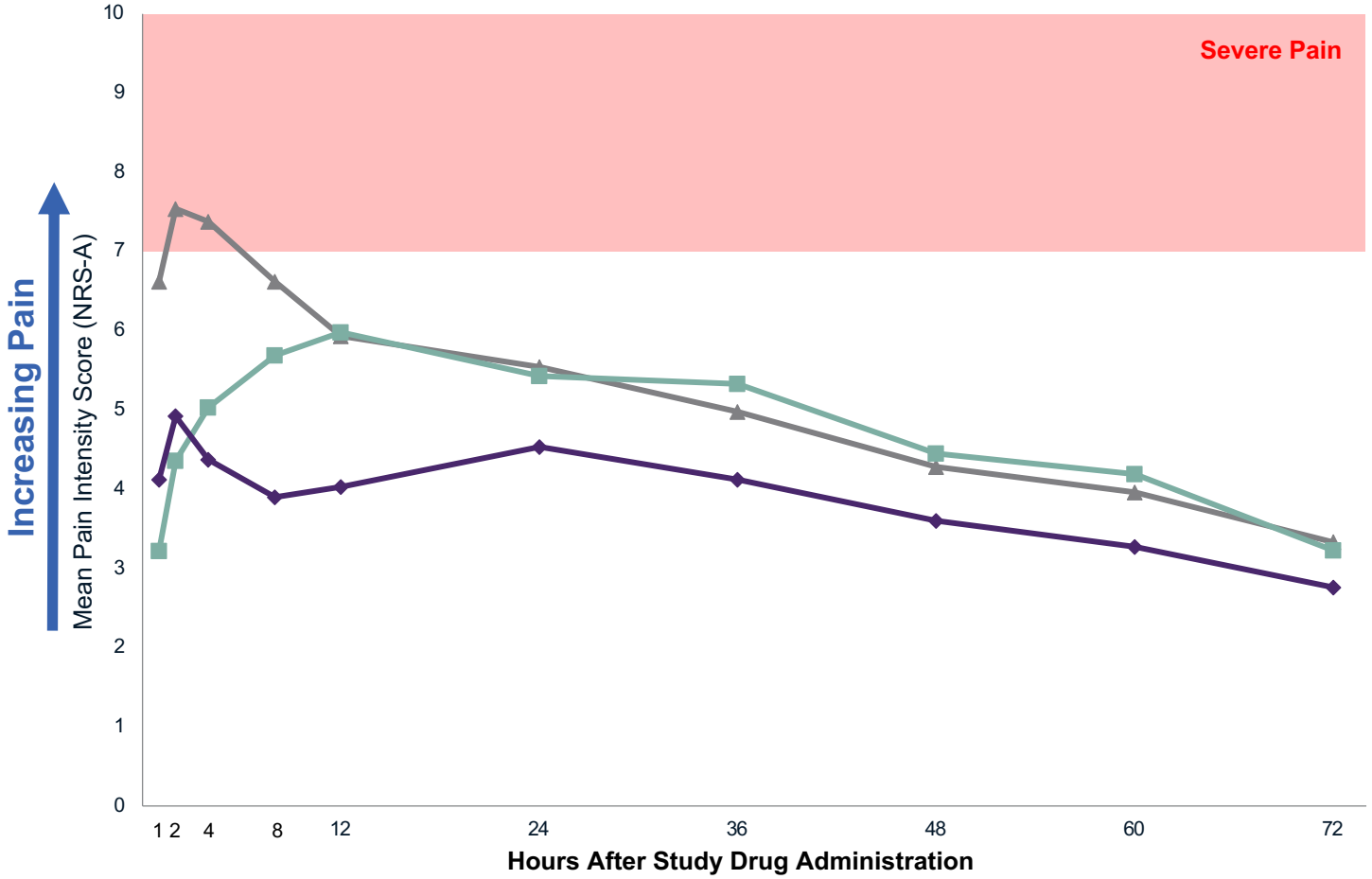
References: 1. ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **2.** Viscusi E, Gimbel JS, Pollack RA, et al. *Reg Anesth Pain Med*. 2019;44(7):700-706.

EPOCH 1 Bunionectomy: Reduction in Pain Intensity (AUC) Versus Placebo Greater Than That of Bupivacaine HCl Through 72 Hours[1-3]



[a]Nominal *P* value not controlled for multiplicity.
Note: Reduction in pain intensity: comparison of pain reduction vs placebo (LSMD of pain intensity score AUC) between groups, adjusting for the use of opioid rescue medication.
AUC: area under the curve. **LSMD:** least squares mean difference.
References: 1. Viscusi E, Gimbel JS, Pollack RA, et al. *Reg Anesth Pain Med*. 2019;44(7):700-706. **2.** ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **3.** Data on file. Study HTX-011-301. San Diego, CA: Heron Therapeutics Inc; 2018.

EPOCH 2 Herniorrhaphy: Superior Reduction in Pain Intensity Versus SOC Bupivacaine HCl Solution Through 72 Hours, the Time When Postsurgical Pain Is Most Intense[1-3]



AUC_{0-72} vs bupivacaine:

P < .0001

AUC_{0-72} vs placebo:

P = .0004

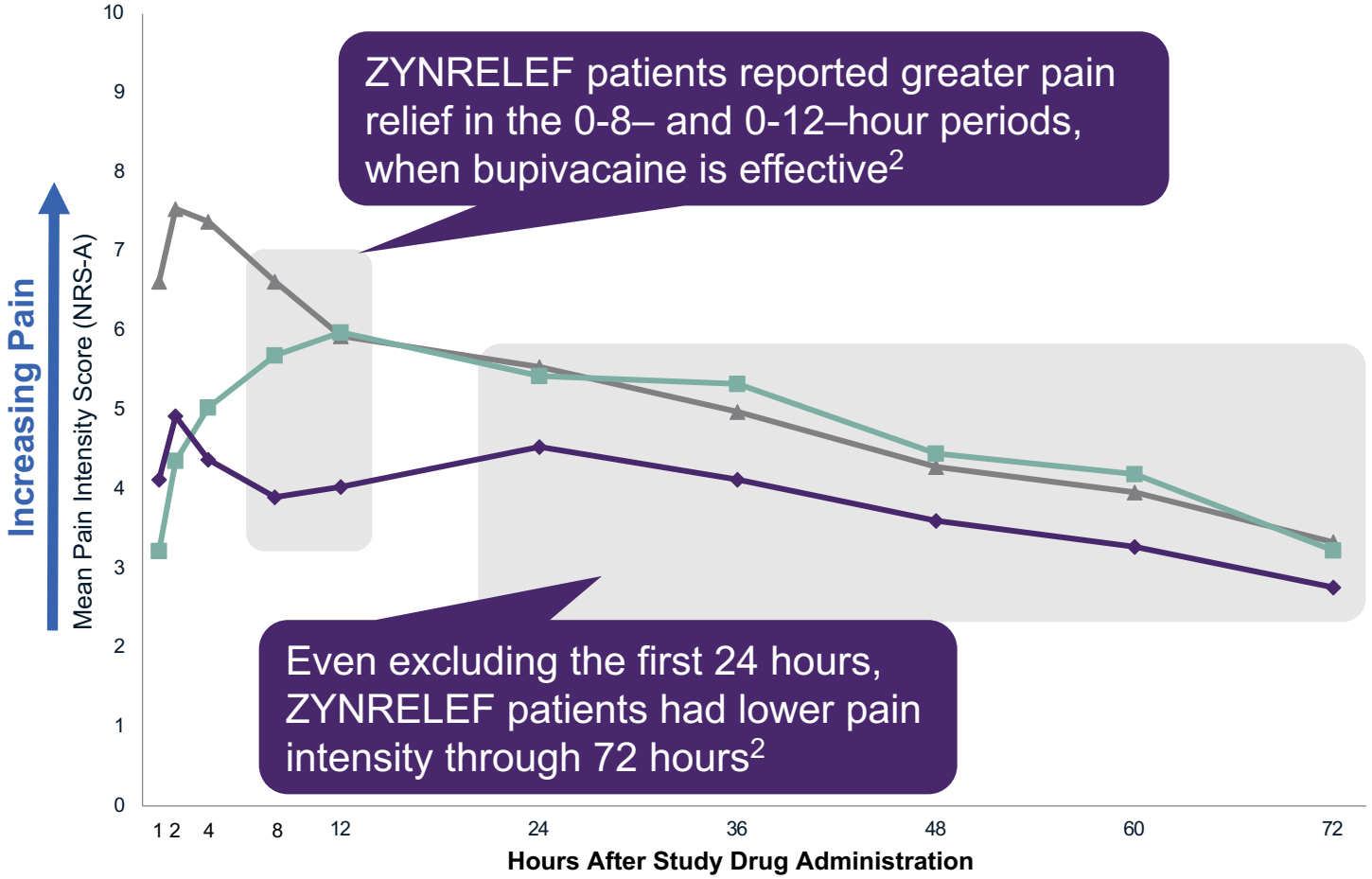
- **Saline Placebo (n = 82)**
- **Bupivacaine HCl Solution 75 mg (n = 172)**
- **ZYNRELEF 300 mg/9 mg (n = 164)**

Note: Pain scores were analyzed with adjustment for the analgesic duration of rescue medications.

SOC: standard-of-care. **NRS-A:** Numeric Rating Scale With Activity.
AUC: area under the curve.

References: 1. ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **2.** Viscusi E, Minkowitz H, Winkle P, et al. *Hernia*. 2019;23(6):1071-1080. **3.** Svensson I, Sjöström B, Haljamäe H. *J Pain Symptom Manage*. 2000;20(3):193-201.

EPOCH 2 Herniorrhaphy: Greater Pain Relief Versus SOC Bupivacaine HCl Solution[1,2]



0-8 and 0-12 hours vs bupivacaine:

$AUC_{0\text{-}8}$: ***P* = .0426**[a]

$AUC_{0\text{-}12}$: ***P* = .0001**[b]

24-72 hours vs bupivacaine:

$AUC_{24\text{-}72}$: ***P* = .0007**[a]

Saline Placebo (n = 82)

Bupivacaine HCl Solution 75 mg (n = 172)

ZYNRELEF 300 mg/9 mg (n = 164)

[a]Analysis not prespecified; nominal *P* value not controlled for multiplicity.

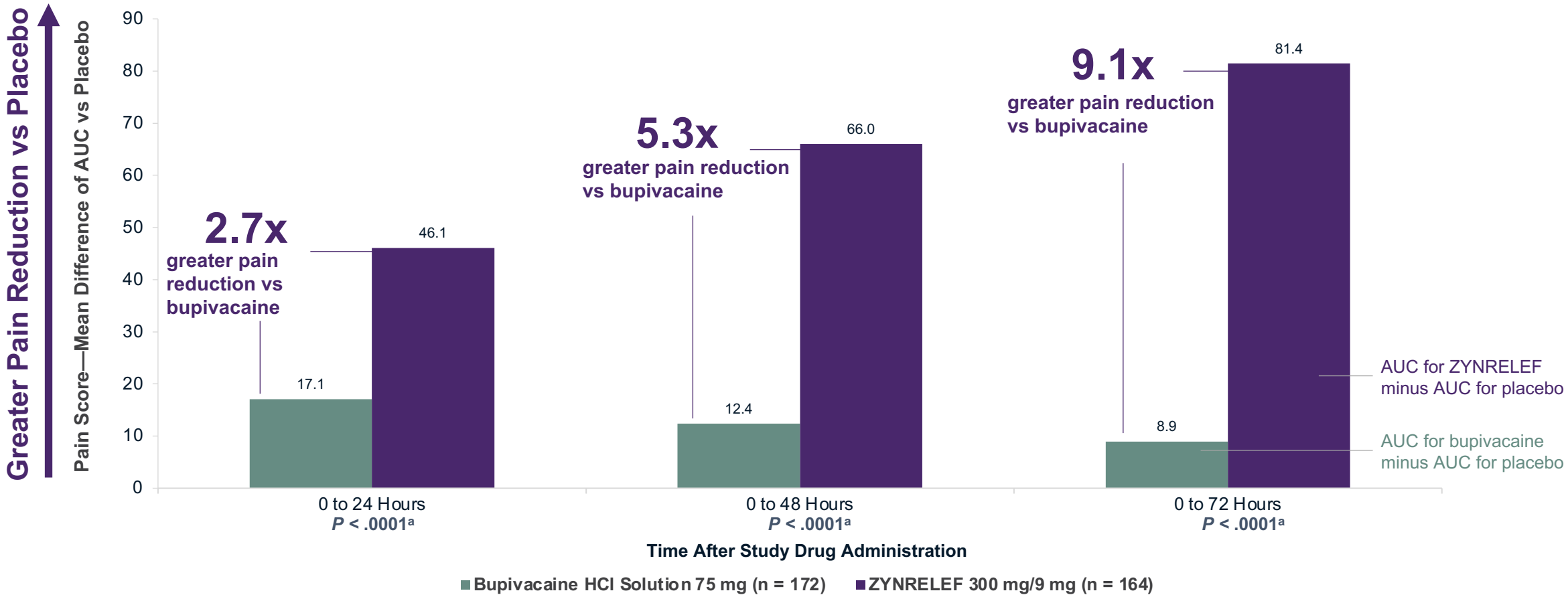
[b]Nominal *P* value not controlled for multiplicity.

Note: Pain scores were analyzed with adjustment for the analgesic duration of rescue medications.

SOC: standard-of-care. **NRS-A:** Numeric Rating Scale With Activity.
AUC: area under the curve.

References: 1. ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021.
2. Viscusi E, Minkowitz H, Winkle P, et al. *Hernia.* 2019;23(6):1071-1080.

EPOCH 2 Herniorrhaphy: Reduction in Pain Intensity (AUC) Versus Placebo Greater Than That of Bupivacaine HCl Solution Through 72 Hours[1-3]

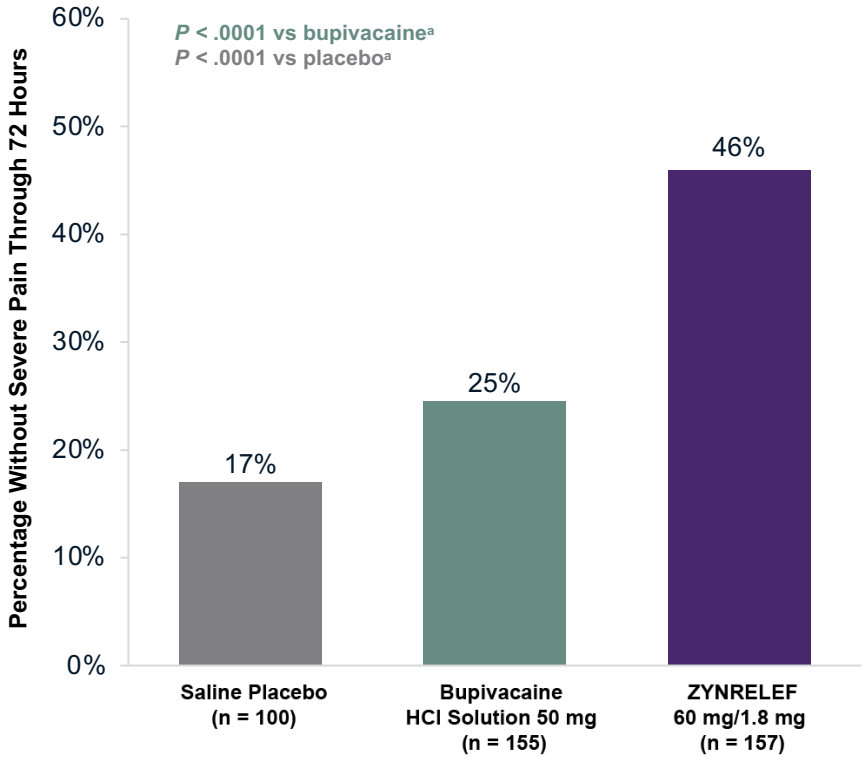


[a]Nominal *P* value not controlled for multiplicity.

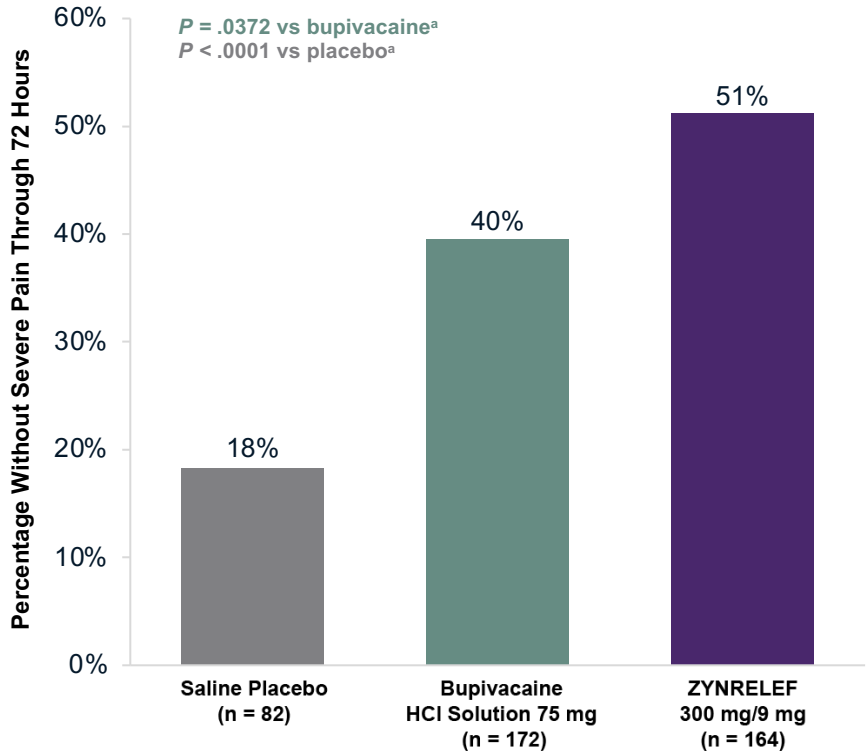
Note: Reduction in pain intensity: comparison of pain reduction vs placebo (LSMD of pain intensity score AUC) between groups, adjusting for the use of opioid rescue medication.
AUC: area under the curve. **LSMD:** least squares mean difference.
References: 1. Data on file. Study HTX-011-302. San Diego, CA: Heron Therapeutics Inc; 2018. **2.** Viscusi E, Minkowitz H, Winkle P, et al. *Hernia.* 2019;23(6):1071-1080. **3.** ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021.

More Patients Without Severe Pain Through 72 Hours Versus SOC Bupivacaine HCl Solution

EPOCH 1 Bunionectomy[1]



EPOCH 2 Herniorrhaphy[2]



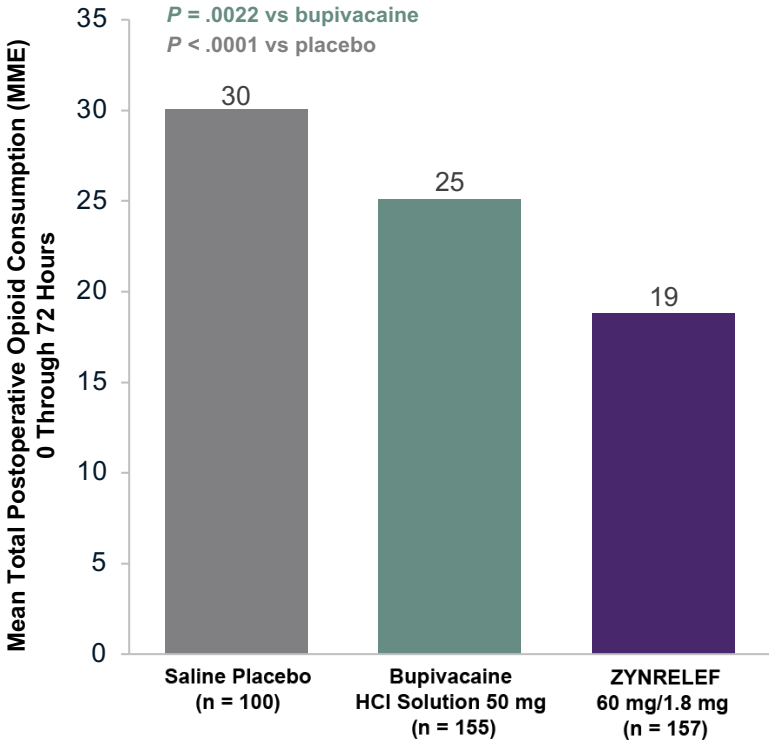
[a]Nominal *P* value not controlled for multiplicity.

SOC: standard-of-care. **Severe pain:** pain intensity score ≥7 on a Numeric Rating Scale of 0 to 10.

References: 1. Viscusi E, Gimbel JS, Pollack RA, et al. *Reg Anesth Pain Med*. 2019;44(7):700-706. **2.** Viscusi E, Minkowitz H, Winkle P, et al. *Hernia.* 2019;23(6):1071-1080.

Reduced Opioid Consumption Versus SOC Bupivacaine HCl Solution and Placebo Through 72 Hours

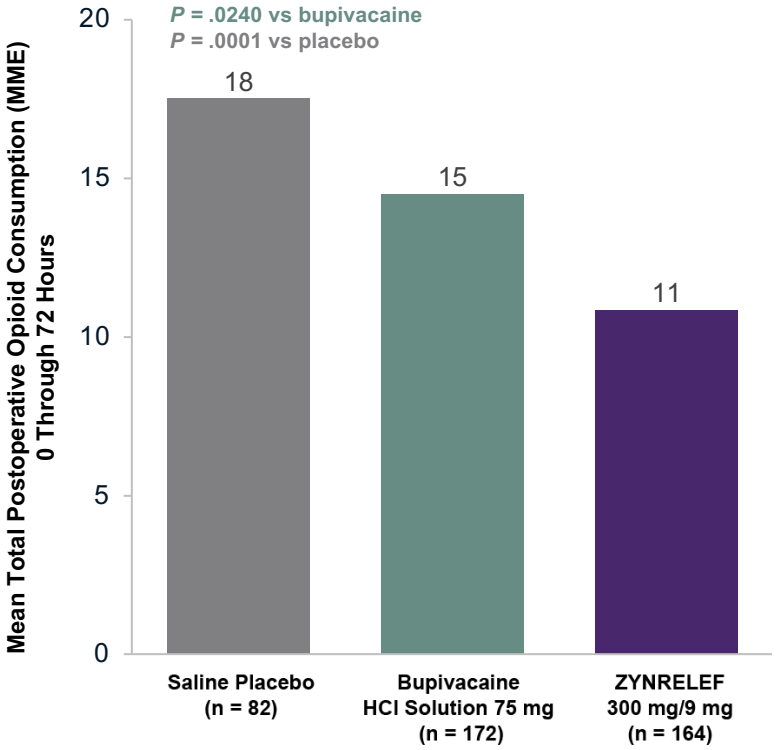
EPOCH 1 Bunionectomy[1]



⬇ 25% vs bupivacaine

⬇ 37% vs placebo

EPOCH 2 Herniorrhaphy[2]



⬇ 25% vs bupivacaine

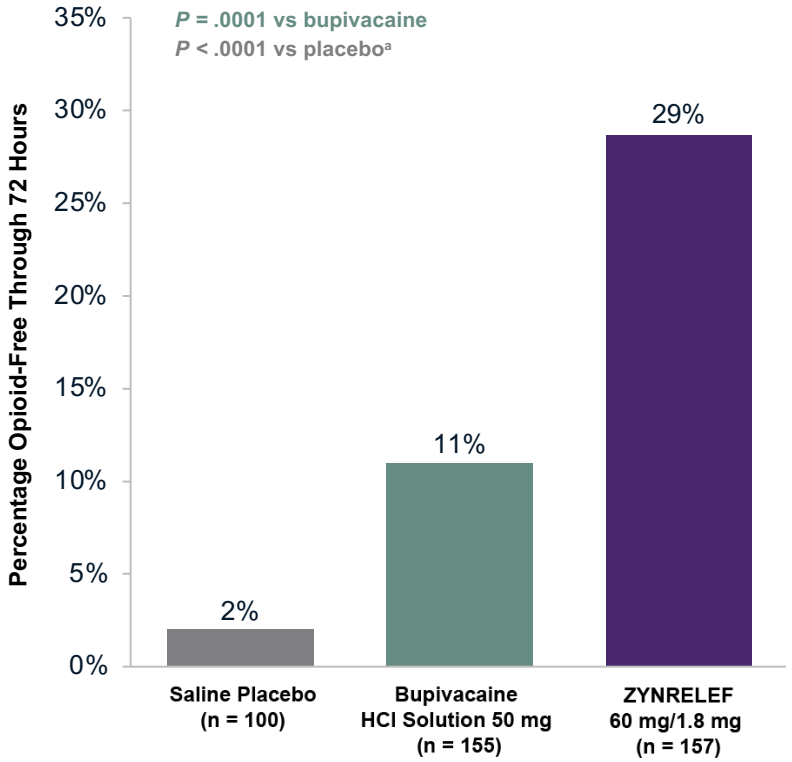
⬇ 38% vs placebo

SOC: standard-of-care. **MME:** morphine milligram equivalents.

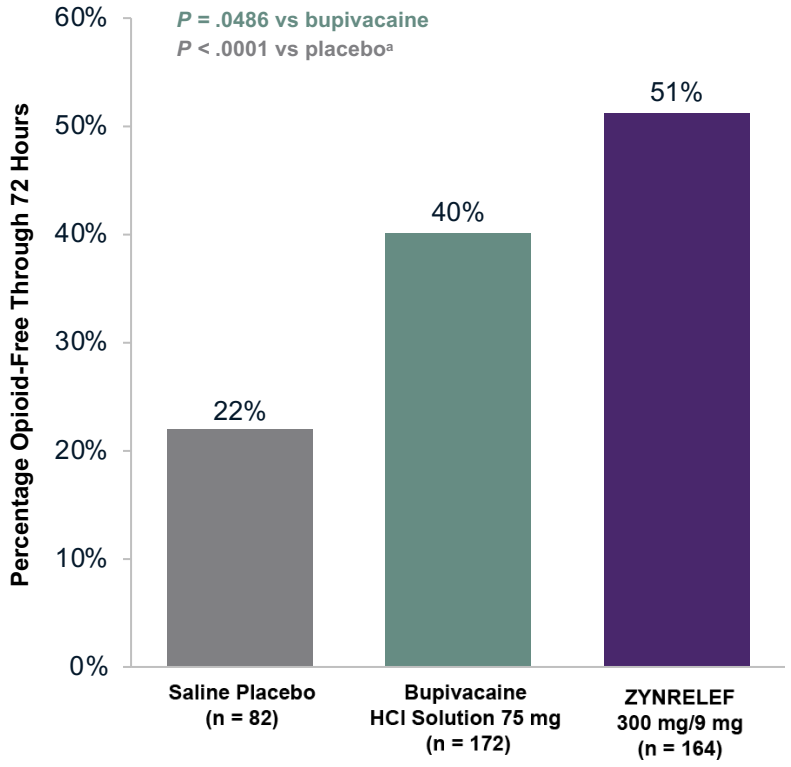
References: 1. Viscusi E, Gimbel JS, Pollack RA, et al. *Reg Anesth Pain Med*. 2019;44(7):700-706. **2.** Viscusi E, Minkowitz H, Winkle P, et al. *Hernia*. 2019;23(6):1071-1080.

Significantly More Patients Required No Opioids Through 72 Hours (Opioid-Free) Versus SOC Bupivacaine HCl Solution

EPOCH 1 Bunionectomy[1,2]



EPOCH 2 Herniorrhaphy[2,3]



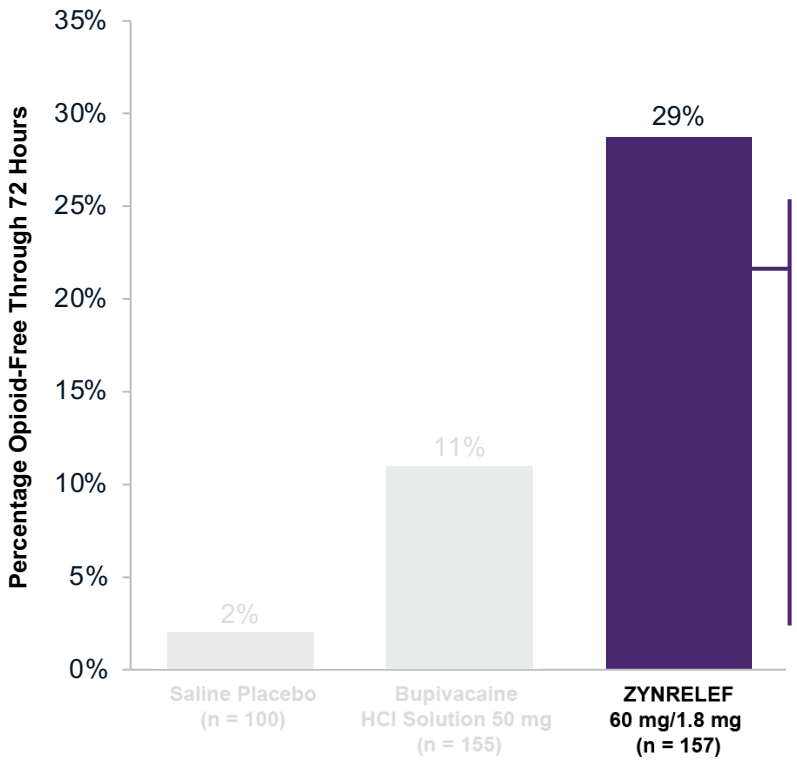
[a]Nominal *P* value not controlled for multiplicity.

SOC: standard-of-care.

References: 1. Viscusi E, Gimbel JS, Pollack RA, et al. *Reg Anesth Pain Med*. 2019;44(7):700-706. **2.** ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **3.** Viscusi E, Minkowitz H, Winkle P, et al. *Hernia.* 2019;23(6):1071-1080.

High Percentage of ZYNRELEF Patients Who Were Opioid-Free at 72 Hours Remained Opioid-Free Through Day 28 Recovery

EPOCH 1 Bunionectomy[1,2]

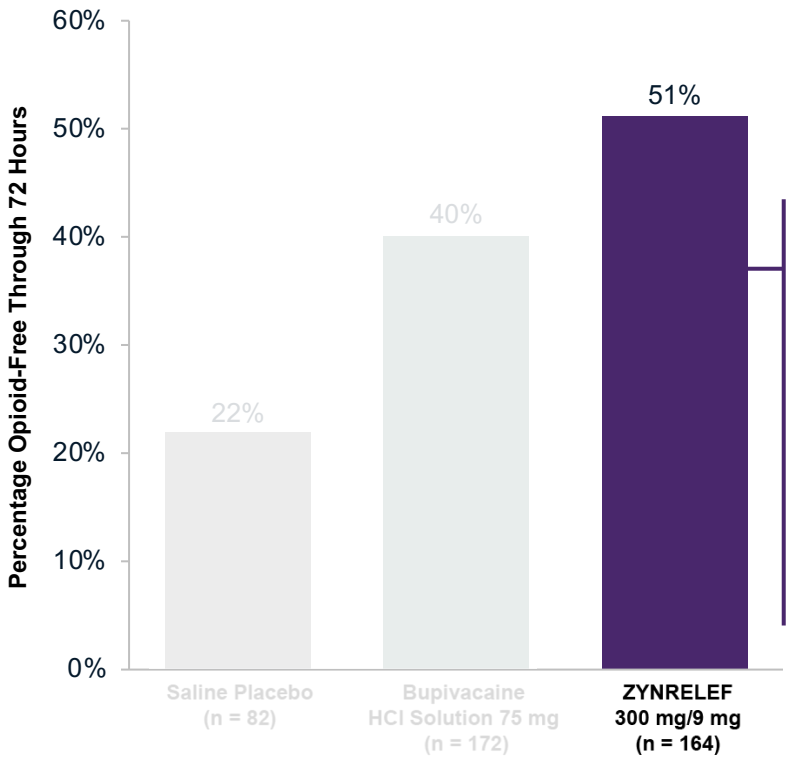


Of patients in the ZYNRELEF group who were opioid-free at 72 hours …

91%
remained opioid-free through **day 10**

82%
remained opioid-free through **day 28**

EPOCH 2 Herniorrhaphy[2,3]



Of patients in the ZYNRELEF group who were opioid-free at 72 hours …

95%
remained opioid-free through **day 10**

85%
remained opioid-free through **day 28**

References: 1. Viscusi E, Gimbel JS, Pollack RA, et al. *Reg Anesth Pain Med*. 2019;44(7):700-706. **2.** ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **3.** Viscusi E, Minkowitz H, Winkle P, et al. *Hernia*. 2019;23(6):1071-1080.

Incidence of Adverse Reactions[1-3]

EPOCH 1 Bunionectomy

	Saline Placebo (n = 101)	Bupivacaine HCl Solution 50 mg (n = 154)	ZYNRELEF 60 mg/1.8 mg (n = 157)
Dizziness	18%	23%	22%
Incision Site Edema	13%	14%	17%
Headache	10%	13%	14%
Incision Site Erythema	8%	12%	13%
Bradycardia	6%	8%	8%
Impaired Healing	1%	4%	6%
Muscle Twitching	5%	5%	6%

Local inflammatory adverse events occurring in ≥2% of patients treated with ZYNRELEF with a higher incidence than with saline placebo included incision site cellulitis (4% incidence with ZYNRELEF, compared to 1% with both bupivacaine HCl solution and saline placebo); wound dehiscence (4% with ZYNRELEF, compared to 1% with bupivacaine HCl solution and 2% with saline placebo); and incision site infection (3% with ZYNRELEF, compared to 1% with bupivacaine HCl solution and 0% with saline placebo).

In EPOCH 1 Bunionectomy, bone healing was assessed by X-ray on days 28 and 42. There was no difference in bone healing between treatment groups. A total of 4 subjects had delayed bone healing: 1 in the ZYNRELEF group, 1 in the saline placebo group, and 2 in the bupivacaine HCl group.

Note: Adverse reactions shown have incidence on ZYNRELEF ≥5% and higher than placebo incidence. Adverse reactions were coded using the *Medical Dictionary for Regulatory Activities*, Version 19.1. For each preferred term, patients are included only once, even if they experienced multiple events in that preferred term.

References: 1. ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **2.** Viscusi E, Gimbel JS, Pollack RA, et al. *Reg Anesth Pain Med*. 2019;44(7):700-706. **3.** Data on file. Study HTX-011-301. San Diego, CA: Heron Therapeutics Inc; 2018.

Incidence of Adverse Reactions[1-3]

EPOCH 2 Herniorrhaphy

	Saline Placebo (n = 82)	Bupivacaine HCl Solution 75 mg (n = 173)	ZYNRELEF 300 mg/9 mg (n = 163)
Headache	12%	14%	13%
Bradycardia	7%	9%	9%
Dysgeusia	4%	12%	9%
Skin Odor Abnormal[4,a]	1%	1%	8%

[a]All incidences of skin odor abnormal were recorded at a single site and by a single observer and are potentially related to the smell of dimethyl sulfoxide (DMSO) in ZYNRELEF.[2,4]

Note: Adverse reactions shown have incidence on ZYNRELEF ≥5% and higher than placebo incidence. Adverse reactions were coded using the *Medical Dictionary for Regulatory Activities*, Version 19.1. For each preferred term, patients are included only once, even if they experienced multiple events in that preferred term.

References: 1. ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **2.** Data on file. Study HTX-011-302. San Diego, CA: Heron Therapeutics Inc; 2018. **3.** Viscusi E, Minkowitz H, Winkle P, et al. *Hernia.* 2019;23(6):1071-1080. **4.** Tutolo M, Ammirati E, Castagna G, et al. *Int Braz J Urol*. 2017;43(1):134-141.

Lower Overall Incidence of Opioid-Related Adverse Events (ORAEs) Compared to Saline Placebo and Bupivacaine HCl Solution[1-4]

Patients Reporting at Least 1 Opioid-Related Treatment-Emergent Adverse Event

	Saline Placebo	Bupivacaine HCl Solution	ZYNRELEF
EPOCH 1 Bunionectomy[1,2]	53%	51%	44%
EPOCH 2 Herniorrhaphy[3,4]	44%	42%	33%

ORAEs were defined as nausea, vomiting, constipation, pruritus, pruritus generalized, somnolence, respiratory depression, and urinary retention.

References: 1. Viscusi E, Gimbel JS, Pollack RA, et al. *Reg Anesth Pain Med*. 2019;44(7):700-706. **2.** Data on file. Study HTX-011-301. San Diego, CA: Heron Therapeutics Inc; 2018. **3.** Viscusi E, Minkowitz H, Winkle P, et al. *Hernia*. 2019;23(6):1071-1080. **4.** Data on file. Study HTX-011-302. San Diego, CA: Heron Therapeutics Inc; 2018.

Phase 3 Safety Data Summary

- ZYNRELEF has a similar safety profile to that of bupivacaine HCl solution and placebo[1-5]
- ZYNRELEF was generally well tolerated with:
  - No premature discontinuations due to drug-related adverse events[2,3]
  - No deaths[2,3]
  - Comparable or fewer overall opioid-related adverse events versus placebo and bupivacaine HCl solution[2,3]
  - No evidence of drug-related local anesthetic systemic toxicity (LAST)[2,3]
  - No evidence of delayed bone healing compared to bupivacaine HCl solution[1,2]

References: 1. ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **2.** Viscusi E, Gimbel JS, Pollack RA, et al. *Reg Anesth Pain Med*. 2019;44(7):700-706. **3.** Viscusi E, Minkowitz H, Winkle P, et al. *Hernia*. 2019;23(6):1071-1080. **4.** Data on file. Study HTX-011-301. San Diego, CA: Heron Therapeutics Inc; 2018. **5.** Data on file. Study HTX-011-302. San Diego, CA: Heron Therapeutics Inc; 2018.

EPOCH 1 Single-Arm[a] Follow-On (Bunionectomy): Study Design[1]

Bunionectomy With Osteotomy and Internal Fixation

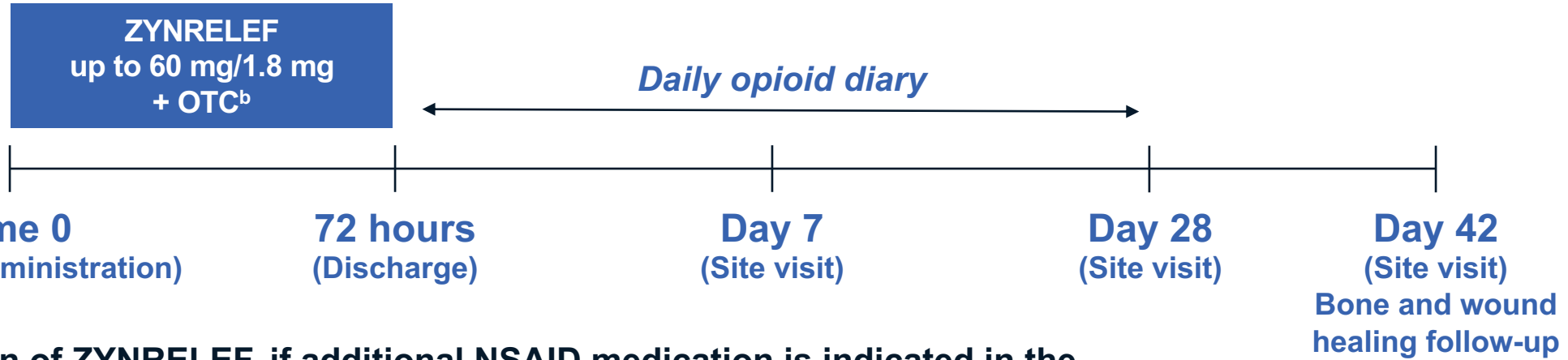
Screening (28 days)

- 2 sites in the United States
- n = 31
- **Protocol included an oral non-opioid MMA regimen**

Treatment and Inpatient Period

Study did not include comparator arms; superiority to SOC and placebo demonstrated in EPOCH 1 Bunionectomy[2,3]

Follow-Up Period



Following administration of ZYNRELEF, if additional NSAID medication is indicated in the postoperative period, monitor patients for signs and symptoms of NSAID-related GI adverse reactions.

[a]Single-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen. [b]OTC = Scheduled postoperative analgesic regimen of oral ibuprofen 600 mg q6h, then 3 hours later oral acetaminophen 1 g q6h, alternating for 72 hours, then as needed.

SOC: standard-of-care. **MMA:** multimodal analgesia. **OTC:** over-the-counter. **q6h:** every 6 hours.

References: 1. Pollak R, Cai D, Gan TJ. *J Am Podiatr Med Assoc.* 2021:20-204. doi:10.7547/20-204. **2.** Viscusi E, Gimbel JS, Pollack RA, et al. *Reg Anesth Pain Med.* 2019;44(7):700-706. **3.** ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021.

EPOCH 2 Single-Arm[a] Follow-On (Herniorrhaphy): Study Design[1]

Open Inguinal Herniorrhaphy

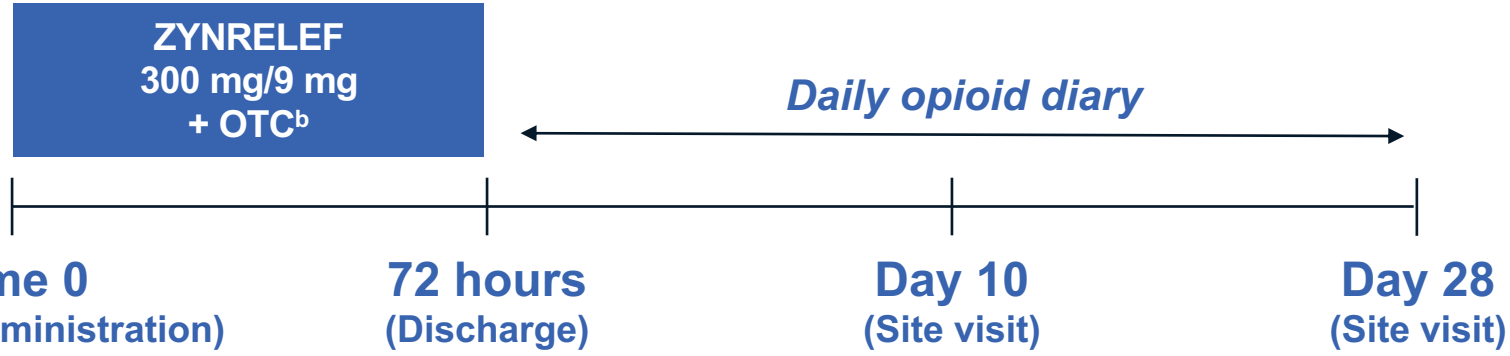
Screening (21 days)

- 3 sites in the United States
- n = 33
- **Protocol included an oral non-opioid MMA regimen**

Treatment and Inpatient Period

Study did not include comparator arms; superiority to SOC and placebo demonstrated in EPOCH 2 Herniorrhaphy[2,3]

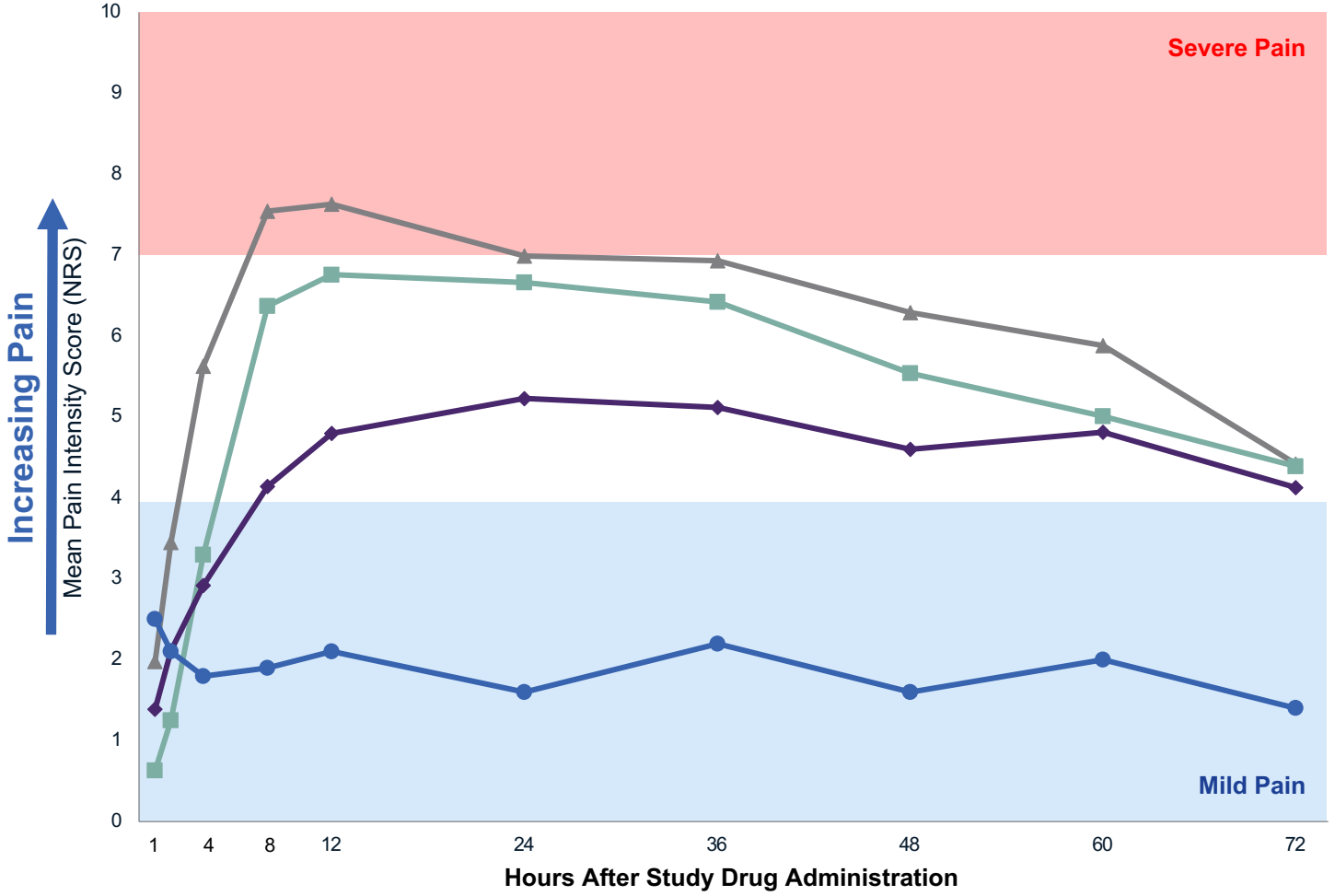
Follow-Up Period



Following administration of ZYNRELEF, if additional NSAID medication is indicated in the postoperative period, monitor patients for signs and symptoms of NSAID-related GI adverse reactions.

[a]Single-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen. [b]OTC = Scheduled postoperative analgesic regimen of oral ibuprofen 600 mg q6h, then 3 hours later oral acetaminophen 1 g q6h, alternating for 72 hours, then as needed. **Note:** Study was comprised of 2 cohorts. The Cohort 2 patients (n = 30) received the same OTC oral analgesics as Cohort 1 (n = 33), as well as a dose of IV ketorolac intraoperatively. The addition of IV ketorolac provided no additional benefit beyond oral acetaminophen and ibuprofen.[3] Figures on the subsequent efficacy slides reflect results from Cohort 1. **SOC:** standard-of-care. **MMA:** multimodal analgesia. **OTC:** over-the-counter. **q6h:** every 6 hours. **IV:** intravenous. **References: 1.** Singla N, Winkle P, Bertoch T, et al. *Surgery*. 2020;168(5):915-920. **2.** Viscusi E, Minkowitz H, Winkle P, et al. *Hernia*. 2019;23(6):1071-1080. **3.** ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021.

EPOCH 1 Single-Arm[a] Follow-On: In Bunionectomy, ZYNRELEF Plus a Scheduled Regimen of Oral Non-Opioid OTC Analgesics Kept Pain in the Mild Range Through 72 Hours[1-3]



EPOCH 1 Study[b]
Did not include the scheduled analgesic regimen

- **Saline Placebo (n = 100)**
- **Bupivacaine HCl Solution 50 mg (n = 155)**
- **ZYNRELEF 60 mg/1.8 mg (n = 157)**

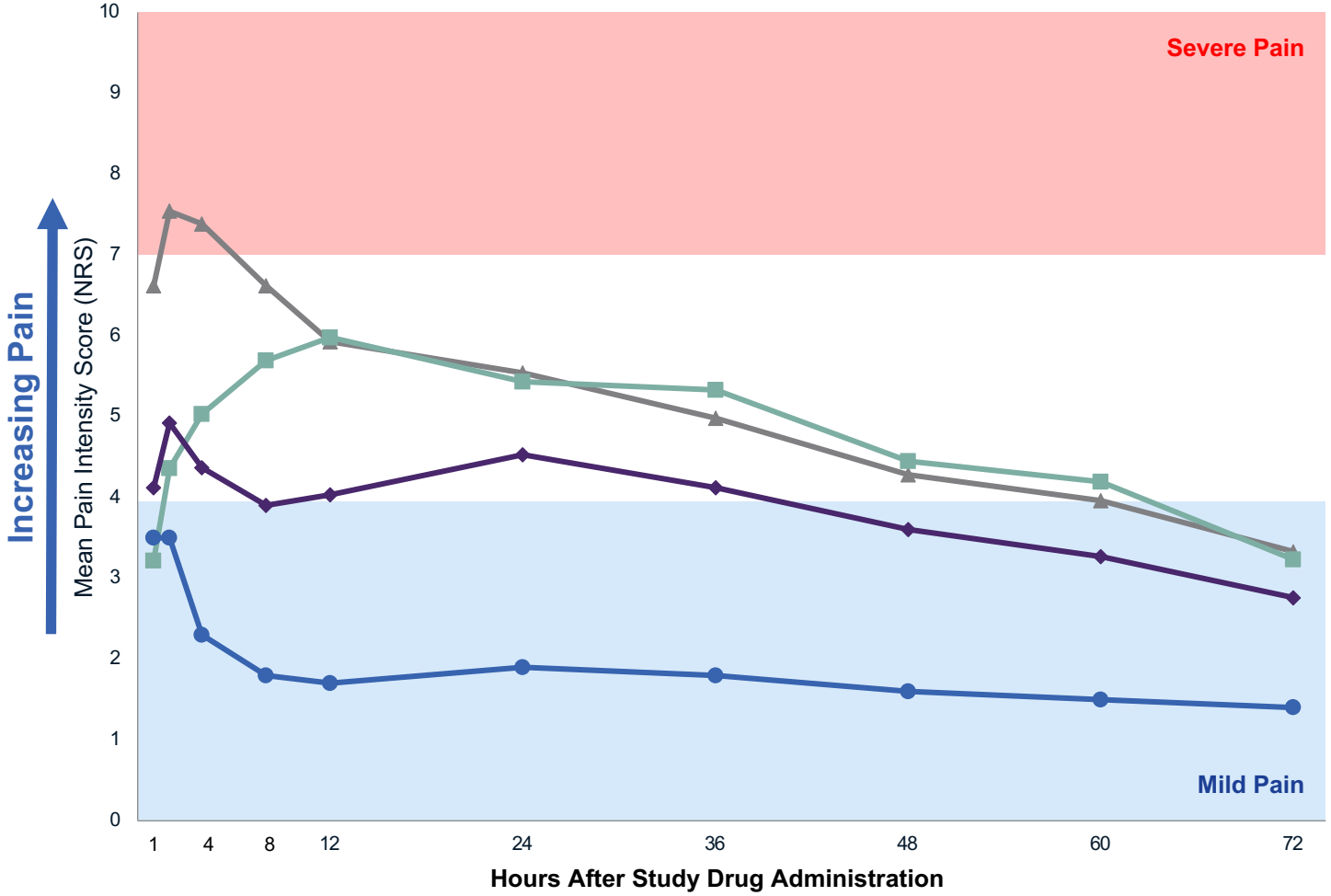
Follow-On Study

- **ZYNRELEF up to 60 mg/1.8 mg + OTC[c] (n = 31)**

[a]Single-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen. [b]EPOCH 1 had similar entry/exclusion criteria to that of the follow-on study but did not include the scheduled analgesic regimen. [c]EPOCH 1 Single-Arm Follow-On study included a scheduled regimen of readily available oral analgesics (acetaminophen and ibuprofen).

Note: Pain scores were analyzed with adjustment for the analgesic duration of rescue medications. **OTC:** over-the-counter. **NRS:** Numeric Rating Scale. **MMA**: multimodal analgesia. **References: 1.** Viscusi E, Gimbel JS, Pollack RA, et al. *Reg Anesth Pain Med*. 2019;44(7):700-706. **2.** Pollak R, Cai D, Gan TJ. *J Am Podiatr Med Assoc*. 2021:20-204. doi:10.7547/20-204. **3.** ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021.

EPOCH 2 Single-Arm[a] Follow-On: In Herniorrhaphy, ZYNRELEF Plus a Scheduled Regimen of Oral Non-Opioid OTC Analgesics Kept Pain in the Mild Range Through 72 Hours[1-5]



EPOCH 2 Study[b]
Did not include the scheduled analgesic regimen

- **Saline Placebo (n = 82)**
- **Bupivacaine HCl Solution 75 mg (n = 172)**
- **ZYNRELEF 300 mg/9 mg (n = 164)**

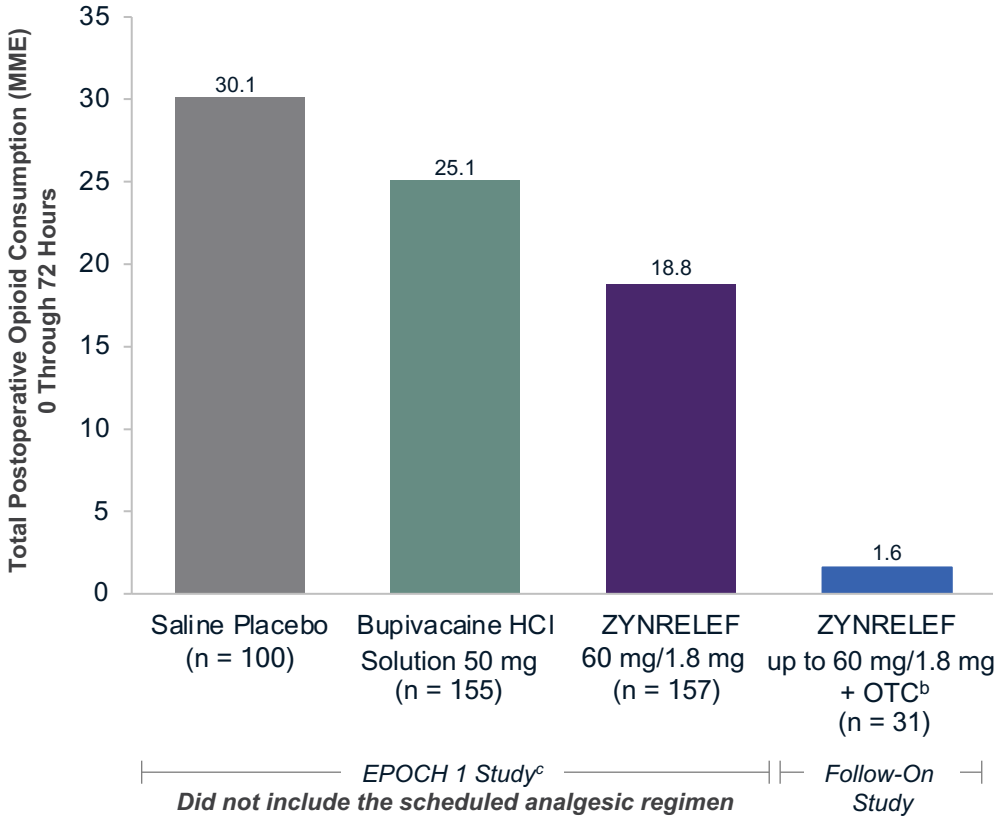
Follow-On Study

- **ZYNRELEF 300 mg/9 mg + OTC[c] (n = 33)**

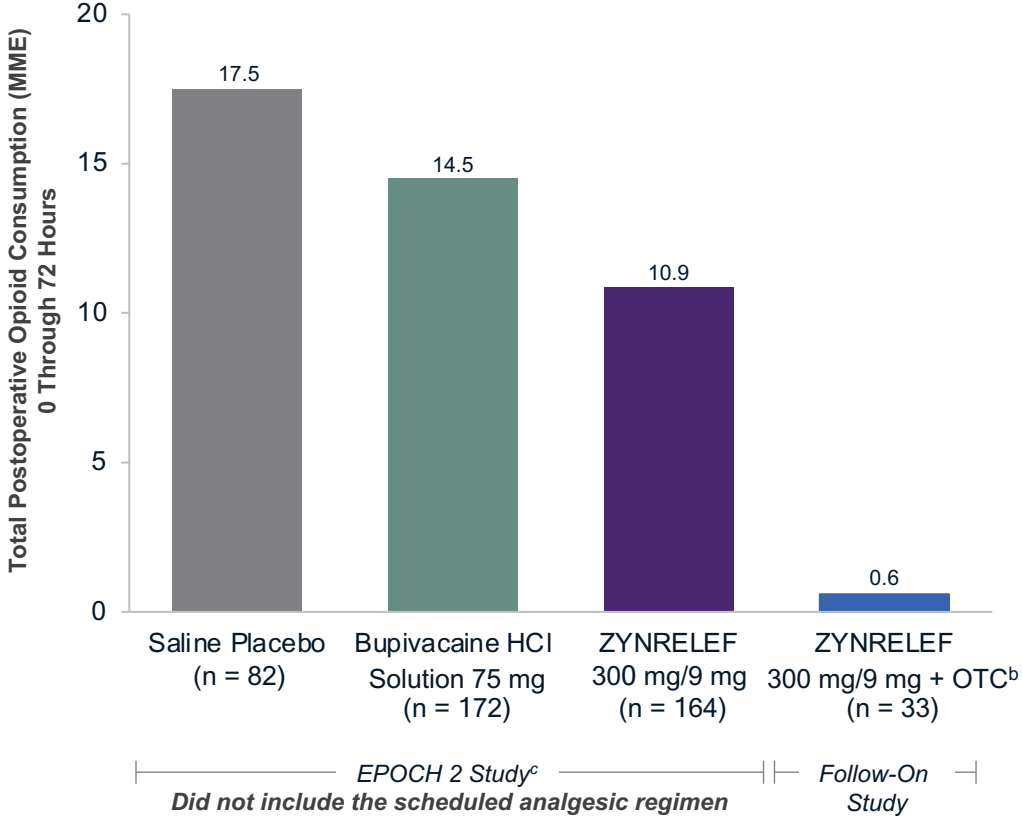
[a]Single-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen. [b]EPOCH 2 had similar entry/exclusion criteria to that of the follow-on study but did not include the scheduled analgesic regimen. [c]EPOCH 2 results reflect reported pain intensity with activity (after sitting up from a resting position); EPOCH 2 Follow-On study results reflect reported pain intensity at rest. EPOCH 2 Single-Arm Follow-On study included a scheduled regimen of readily available oral analgesics (acetaminophen and ibuprofen); Cohort 1 in the EPOCH 2 Follow-On study was used for analysis because addition of IV ketorolac provided no additional benefit beyond oral acetaminophen and ibuprofen. **Note:** Pain scores were analyzed with adjustment for the analgesic duration of rescue medications. **OTC:** over-the-counter. **NRS:** Numeric Rating Scale. **MMA**: multimodal analgesia. **References: 1.** Viscusi E, Minkowitz H, Winkle P, et al. *Hernia*. 2019;23(6):1071-1080. **2.** Data on file. Study HTX-011-302. San Diego, CA: Heron Therapeutics Inc; 2018. **3.** Singla N, Winkle P, Bertoch T, et al. *Surgery*. 2020;168(5):915-920. **4.** Data on file. Study HTX-011-215. San Diego, CA: Heron Therapeutics Inc; 2019. **5.** ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021.

ZYNRELEF + OTC Patients Consumed 1.6 and 0.6 MME Through 72 hours in Bunionectomy and Herniorrhaphy, Respectively

EPOCH 1 Bunionectomy/EPOCH 1 Single-Arm[a] Follow-On[1-3]



EPOCH 2 Herniorrhaphy/EPOCH 2 Single-Arm[a] Follow-On[3,4]



[a]Single-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen. [b]EPOCH 1 and EPOCH 2 Single-Arm Follow-On studies included a scheduled regimen of readily available oral analgesics (acetaminophen and ibuprofen); Cohort 1 of the EPOCH 2 Single-Arm Follow-On study was used for analysis as addition of IV ketorolac provided no additional benefit beyond oral acetaminophen and ibuprofen. [c]EPOCH 1 and EPOCH 2 had the same entry and exclusion criteria as the follow-on studies but did not include the scheduled analgesic regimen.
MME: morphine milligram equivalents. **OTC:** over-the-counter.

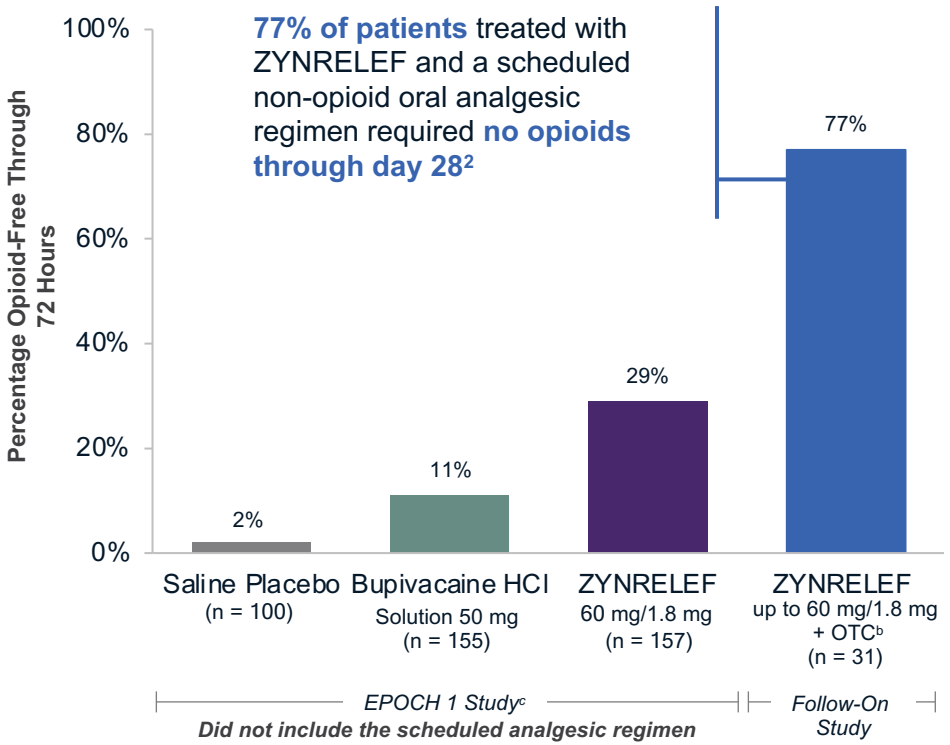
References: **1.** Viscusi E, Gimbel JS, Pollack RA, et al. *Reg Anesth Pain Med*. 2019;44(7):700-706. **2.** Pollak R, Cai D, Gan TJ. *J Am Podiatr Med Assoc*. 2021:20-204. doi:10.7547/20-204. **3.** Singla N, Winkle P, Bertoch T, et al. *Surgery*. 2020;168(5):915-920. **4.** Viscusi E, Minkowitz H, Winkle P, et al. *Hernia*. 2019;23(6):1071-1080.

Please see **IMPORTANT SAFETY INFORMATION** on pages 64 to 68 and full Prescribing Information, including **Boxed Warning**.

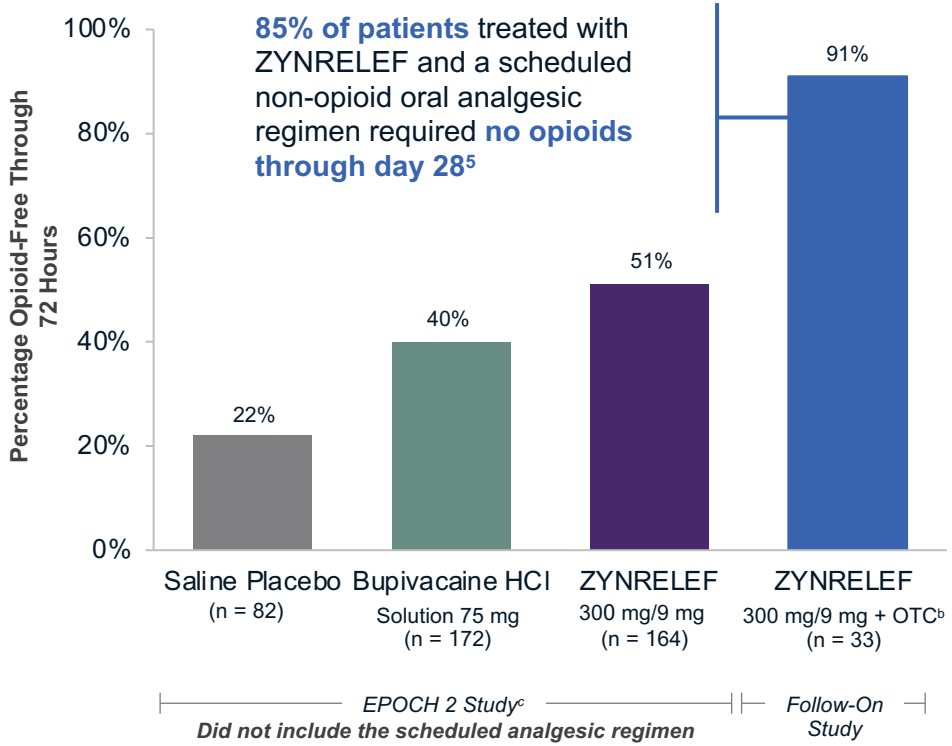
EPOCH 1 AND EPOCH 2 SINGLE-ARM FOLLOW-ON RESULTS

77% of Bunionectomy Patients and 91% of Herniorrhaphy Patients Remained Opioid-Free Through 72 Hours and Day 28 Recovery When Treated With ZYNRELEF + OTC[a]

EPOCH 1 Bunionectomy/EPOCH 1 Single-Arm[a] Follow-On[1-3]



EPOCH 2 Herniorrhaphy/EPOCH 2 Single-Arm[a] Follow-On[3-5]



[a]Single-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen. [b]EPOCH 1 and EPOCH 2 Single-Arm Follow-On studies included a scheduled regimen of readily available oral analgesics (acetaminophen and ibuprofen); Cohort 1 of the EPOCH 2 Single-Arm Follow-On study was used for analysis as addition of IV ketorolac provided no additional benefit beyond oral acetaminophen and ibuprofen. [c]EPOCH 1 and EPOCH 2 had the same entry and exclusion criteria as the follow-on studies but did not include the scheduled analgesic regimen. **OTC:** over-the-counter. **MMA**: multimodal analgesia

References: **1.** Viscusi E, Gimbel JS, Pollack RA, et al. *Reg Anesth Pain Med*. 2019;44(7):700-706. **2.** Pollak R, Cai D, Gan TJ. *J Am Podiatr Med Assoc.* 2021:20-204. doi:10.7547/20-204. **3.** ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **4.** Viscusi E, Minkowitz H, Winkle P, et al. *Hernia.* 2019;23(6):1071-1080. **5.** Singla N, Winkle P, Bertoch T, et al. *Surgery*. 2020;168(5):915-920.

Follow-On Studies: Incidence of Treatment-Emergent Adverse Events (TEAEs)

ZYNRELEF was well tolerated when used concomitantly with acetaminophen and ibuprofen, with no increase in NSAID-related toxicity.

EPOCH 1 Single-Arm[a] Follow-On: Bunionectomy[1,2]

	ZYNRELEF up to 60 mg/1.8 mg + OTC Analgesic Regimen (n = 31)
Any AE	**65%**
AE Possibly Related to Study Drug	0
Opioid-Related AE	29%
Local Inflammatory AE	3%
Potential LAST-Related AE	3%
AE Leading to Study Withdrawal	0
Severe AE	0
Serious AE	0
Fatal AE	0

EPOCH 2 Single-Arm[a] Follow-On: Herniorrhaphy[3,4]

	ZYNRELEF 300 mg/9 mg + OTC Analgesic Regimen (n = 33)	ZYNRELEF 300 mg/9 mg + OTC Analgesic Regimen + Ketorolac (n = 30)
Any AE	**36%**	**40%**
Severe AE	0	3%
Opioid-Related AE	6%	17%
Potential LAST-Related AE	3%	10%
Serious AE	0	0
AE Leading to Study Withdrawal	0	0

[a]Single-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen.
AE: adverse event. **OTC:** over-the-counter. **LAST:** local anesthetic systemic toxicity. **Severe Adverse Event:** any adverse event that interrupted daily activity or required systemic drug therapy or treatment. **Serious Adverse Event:** any adverse event that was life-threatening, resulted in substantial disruption to normal life, caused a birth defect, or required medical intervention. **MMA**: multimodal analgesia

References: 1. Data on file. Study HTX-011-218. San Diego, CA: Heron Therapeutics Inc; 2019. **2.** Pollak R, Cai D, Gan TJ. *J Am Podiatr Med Assoc.* 2021:20-204. doi:10.7547/20-204. **3.** Singla N, Winkle P, Bertoch T, et al. *Surgery*. 2020;168(5):915-920. **4.** Data on file. Study HTX-011-215. San Diego, CA: Heron Therapeutics Inc; 2019.

EPOCH TKA: Study Design[1,2]

Total Knee Arthroplasty

Screening (21 days)

- 15 sites in the United States
- N = 222
- **Protocol did not include a postoperative multimodal analgesic regimen**

Treatment and Inpatient Period

ZYNRELEF 400 mg/12 mg (n = 58)

ZYNRELEF 400 mg/12 mg + Ropivacaine 50 mg (n = 56)

Bupivacaine HCl 125 mg (n = 55)

Saline Placebo (n = 53)

Follow-Up Period

Daily opioid diary

Time 0 (Time of administration)

72 hours (Discharge)

Day 10 (Site visit)

Day 28 (Site visit)

Preoperatively/Intraoperatively:

- Acetaminophen ≤1 g IV x 1
- Pregabalin 150 mg PO x 1
- Tranexamic acid 1 g IV
- Fentanyl 75 µg IV[a]

ZYNRELEF Administration Technique:

- Needle-free instillation of 100 mg/3 mg to posterior capsule and 300 mg/9 mg to remaining tissue

Ropivacaine Administration Technique:

- Injection of 50 mg into posterior capsule

Postoperatively:

- Only opioid rescue on request
- Tranexamic acid 1 g IV x 1
- Aspirin 325 mg PO BID

[a]All patients were to receive 75 µg intravenous fentanyl just prior to the end of surgery.

Note: Patients requiring postoperative rescue medication were allowed opioid rescue with IV morphine and/or oral oxycodone.

TKA: total knee arthroplasty. **IV:** intravenous. **PO:** by mouth (oral). **BID:** twice daily.

References: 1. Lachiewicz PF, Lee G-C, Pollak R, et al. *J Arthroplasty*. 2020;35(10):2843-2851. **2.** ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021.

EPOCH TKA: Hierarchical Testing of Key Endpoints[1,2]

Hierarchical hypothesis testing ($P \leq .05$)

	Endpoint	*P* Value
Primary	Pain Intensity (AUC_{0-48}) ZYNRELEF 400 mg + Ropivacaine vs Placebo	$P < .0001$
	Pain Intensity (AUC_{0-48}) ZYNRELEF 400 mg vs Placebo	$P = .0002$
Key Secondary	Pain Intensity (AUC_{0-72}) ZYNRELEF 400 mg + Ropivacaine vs Placebo	$P < .0001$
	Pain Intensity (AUC_{0-72}) ZYNRELEF 400 mg vs Placebo	$P = .0004$

- In the primary analysis, ZYNRELEF demonstrated statistically superior pain reduction through 48 and 72 hours versus placebo[1,a]

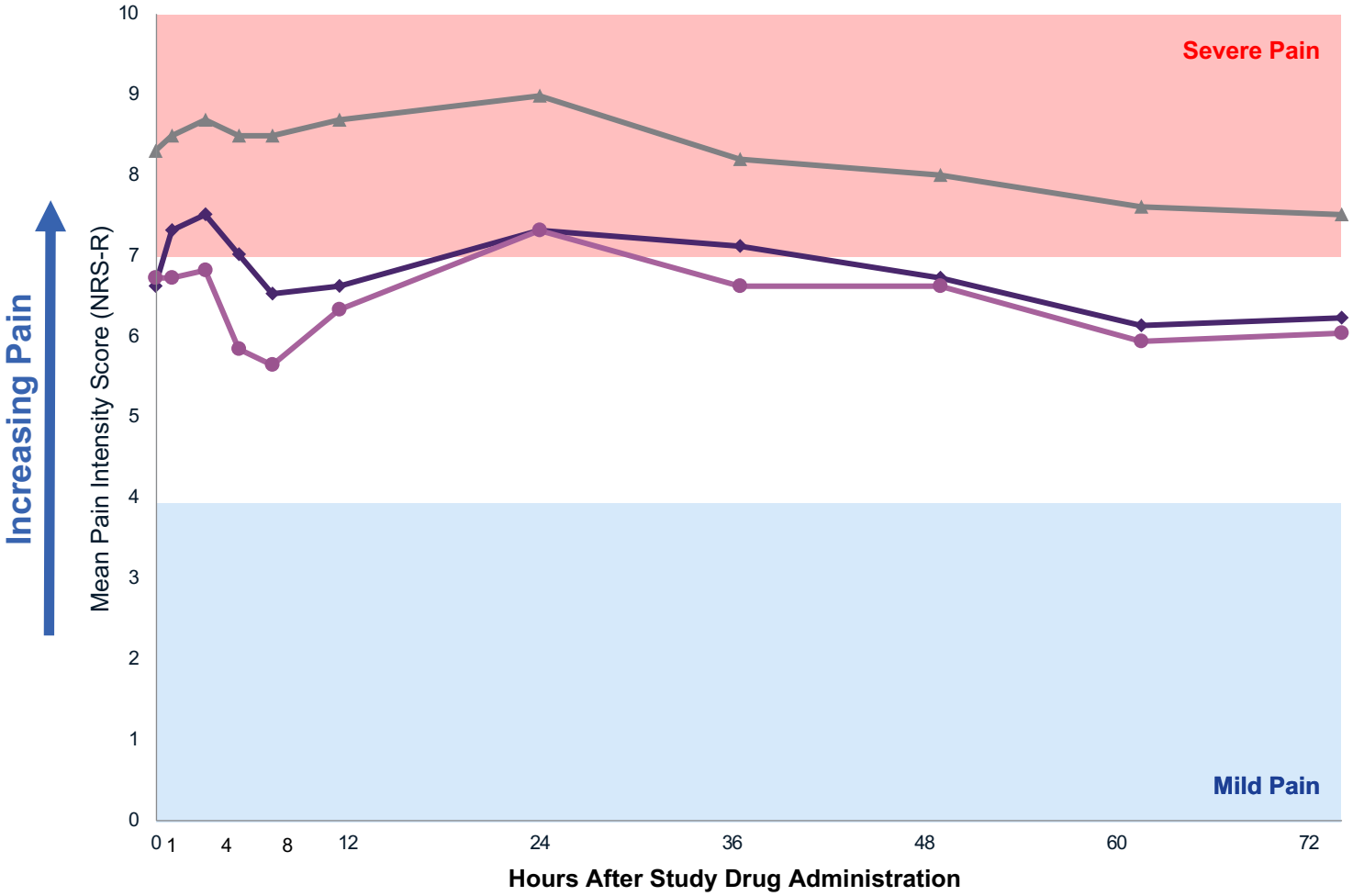
[a]Pain scores reported adjusting for opioid rescue medication use.

Note: A strict testing hierarchy was applied on the primary and key secondary endpoints to control the study-wise alpha at the .05 level. This means the primary endpoint had to reach significance ($P \leq .05$) before the first key secondary endpoint was tested, continuing through each additional key secondary endpoint.

TKA: total knee arthroplasty. **AUC:** area under the curve. **Placebo:** saline placebo.

References: 1. Lachiewicz PF, Lee G-C, Pollak R, et al. *J Arthroplasty*. 2020;35(10):2843-2851. **2.** ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021.

EPOCH TKA: Pain Intensity Score (NRS-R) Through 72 Hours, Adjusting for Opioid Rescue Medication Use[1,a]



ZYNRELEF vs placebo:

AUC_{0-48} *P* = .0002

AUC_{0-72} *P* = .0004

ZYNRELEF + Ropivacaine vs placebo:

AUC_{0-48} *P* < .0001

AUC_{0-72} *P* < .0001

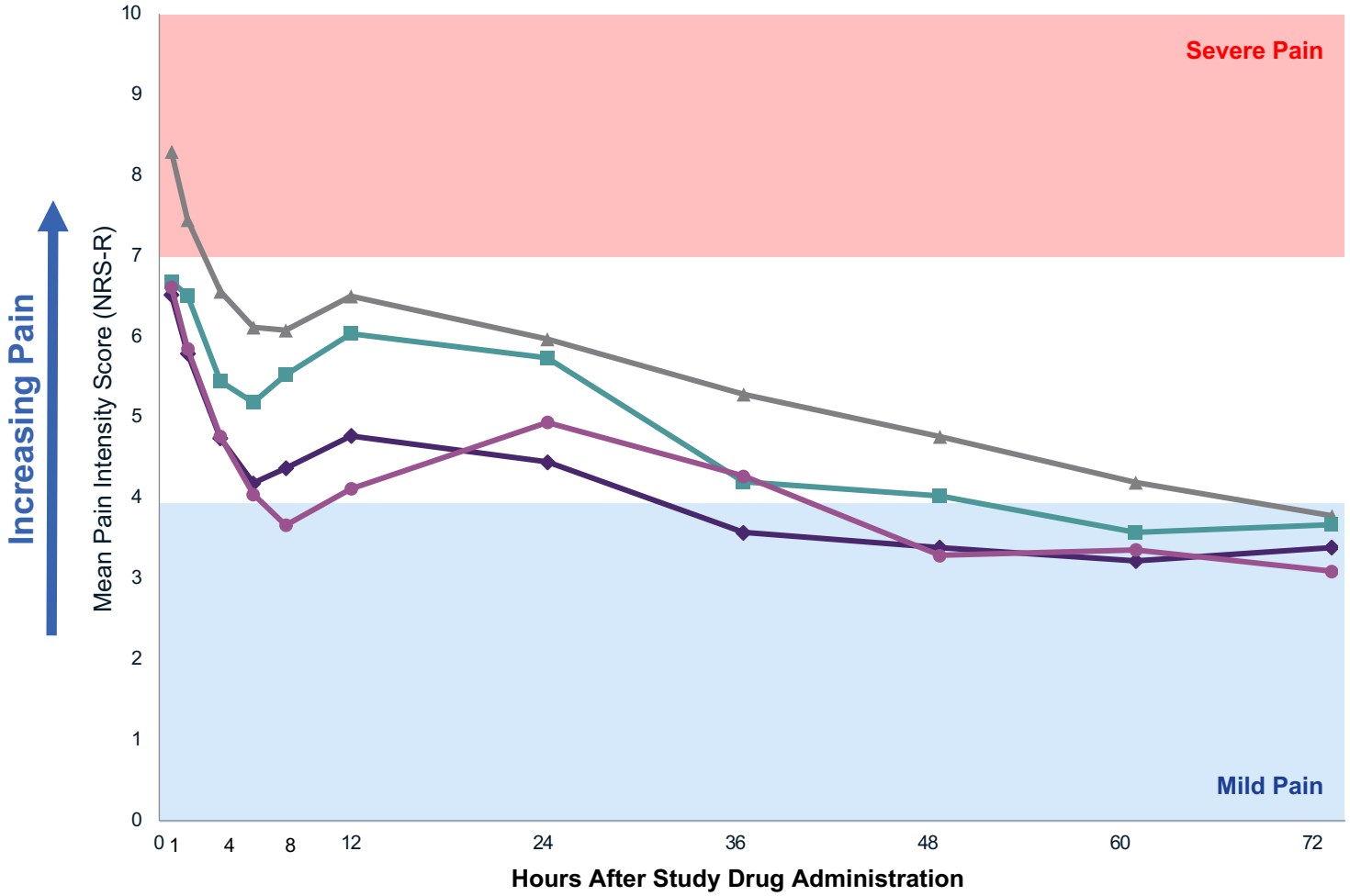
- **Saline Placebo (n = 53)**
- **ZYNRELEF 400 mg/12 mg (n = 58)**
- **ZYNRELEF 400 mg/12 mg + Ropivacaine 50 mg (n = 56)**

[a]Pain scores reported adjusting for opioid rescue medication use.

TKA: total knee arthroplasty. **NRS-R:** Numeric Rating Scale at Rest.

References: 1. ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021.

EPOCH TKA: Pain Intensity Score (NRS-R) Through 72 Hours Compared to Bupivacaine HCl Solution, Without Adjustment for Opioid Rescue Medication[1]



ZYNRELEF vs placebo:

$AUC_{0\text{-}48}$ *P* = .0001[a]

$AUC_{0\text{-}72}$ *P* = .0001[a]

ZYNRELEF vs bupivacaine:

$AUC_{0\text{-}48}$ *P* = .0070[a]

$AUC_{0\text{-}72}$ *P* = .0269[a]

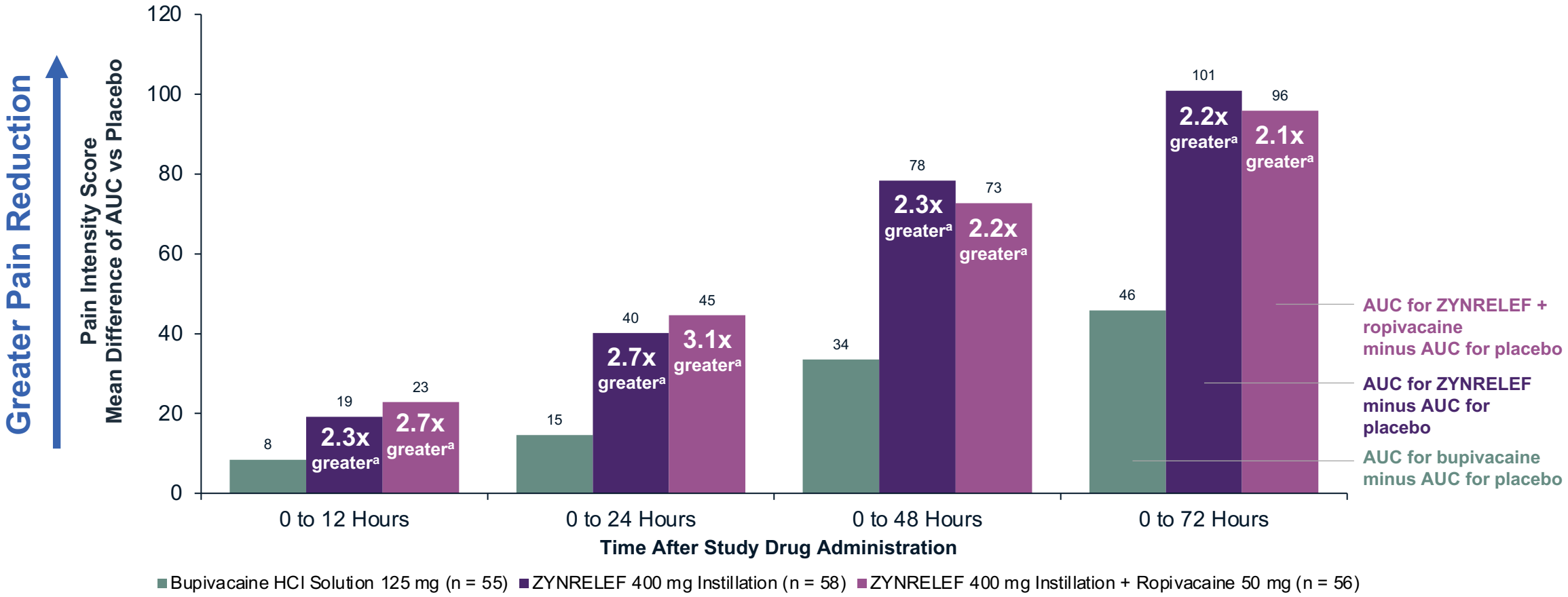
- **Saline Placebo (n = 53)**
- **Bupivacaine HCl Solution 125 mg (n = 55)**
- **ZYNRELEF 400 mg/12 mg (n = 58)**
- **ZYNRELEF 400 mg/12 mg + Ropivacaine 50 mg (n = 56)**

[a]Nominal *P* value not controlled for multiplicity. This analysis is appropriate since ZYNRELEF patients consumed fewer opioids, and is clinically meaningful because it demonstrates that ZYNRELEF patients experienced less pain even while consuming fewer opioids. Analysis represents data from Cohort 2.

TKA: total knee arthroplasty. **NRS-R:** Numeric Rating Scale at Rest.
AUC: area under the curve.

References: 1. Lachiewicz PF, Lee G-C, Pollak R, et al. *J Arthroplasty*. 2020;35(10):2843-2851.
2. Data on file. Study HTX-011-209. San Diego, CA: Heron Therapeutics Inc; 2018.

EPOCH TKA Secondary Analysis: Greater Pain Reduction With ZYNRELEF[1]



[a]Greater pain reduction versus placebo than SOC

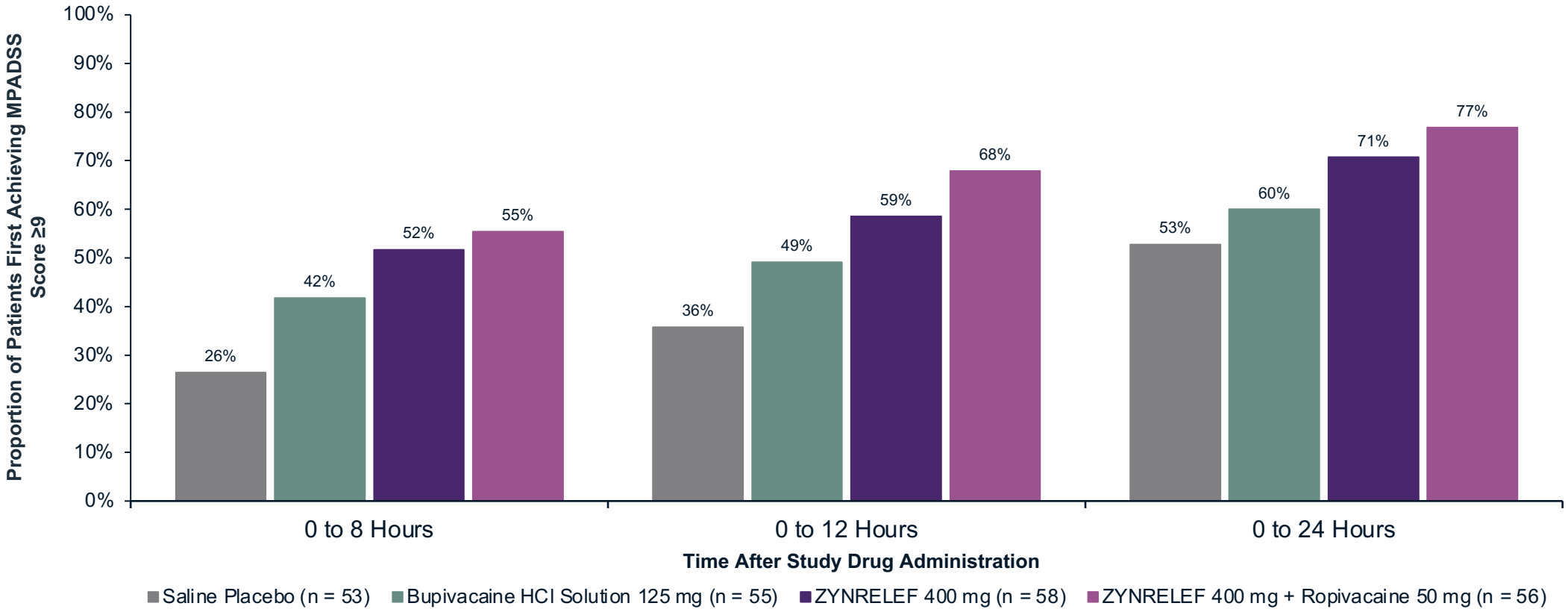
Note: Comparison of pain reduction versus placebo (LSMD of pain intensity score AUC) between groups without adjustment for opioid rescue medication use. This sensitivity analysis may be a more relevant comparison since patients were not given a multimodal analgesic regimen and almost all received opioids.

TKA: total knee arthroplasty. **AUC:** area under the curve. **SOC:** standard-of-care. **LSMD:** least squares mean difference.

References: 1. Lachiewicz PF, Lee G-C, Pollak R, et al. *J Arthroplasty*. 2020;35(10):2843-2851.

EPOCH TKA: Over 50% of ZYNRELEF Patients "Discharge Ready" by 8 Hours Following Surgery[1,a]

Discharge readiness was measured according to the MPADSS scale[2,a]



[a]MPADSS considers numerous clinical variables such as vital signs, ambulation, nausea/vomiting, pain, and surgical bleeding, with patients scoring ≥9 (on a scale of 0 to 10) considered ready for discharge.
The proportion of subjects who first achieved an MPADSS score ≥9 at each time point was analyzed cumulatively.
TKA: total knee arthroplasty. **MPADSS:** Modified Postanesthetic Discharge Scoring System.

References: 1. Lachiewicz PF, Lee G-C, Pollak R, et al. *J Arthroplasty*. 2020;35(10):2843-2851. **2.** Chung F. *Can J Anaesth.* 1995;42(11):1056-1058.

Incidence of Adverse Reactions[1-3]

	Saline Placebo (n = 53)	Bupivacaine HCl Solution 125 mg (n = 55)	ZYNRELEF 400 mg/12 mg (n = 58)
Nausea	47%	55%	50%
Constipation	23%	33%	24%
Vomiting	19%	27%	26%
Hypertension	15%	13%	19%
Pyrexia	4%	15%	14%
Leukocytosis	0	2%	7%
Pruritus	2%	5%	7%
Headache	0	7%	7%
Anemia	2%	0	5%
Hyperhidrosis	4%	0	5%
Hypotension	4%	2%	5%

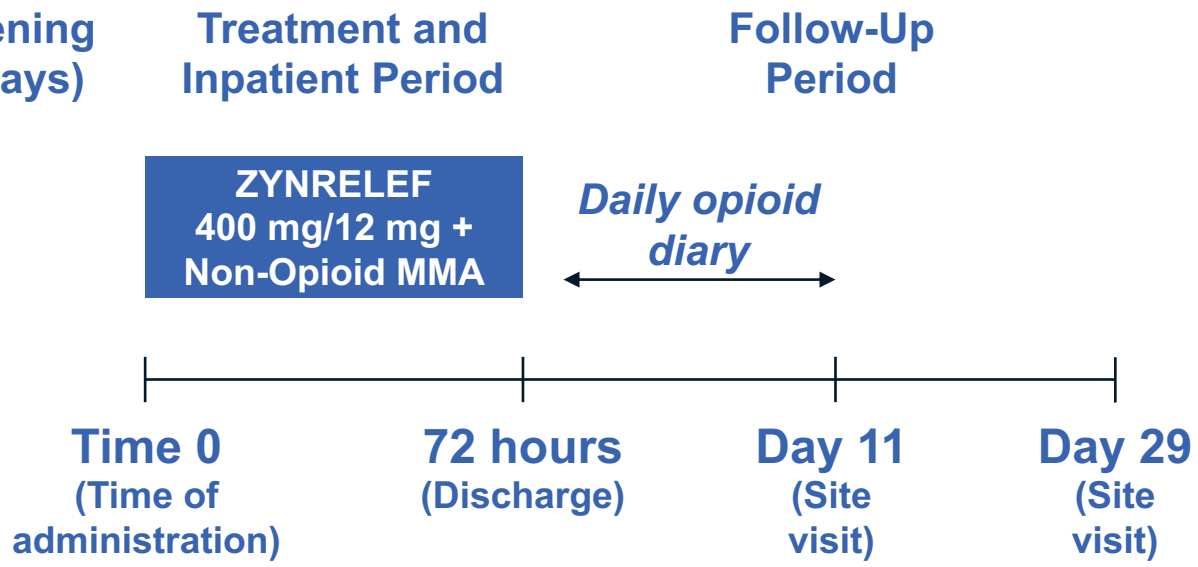
Note: Adverse reactions shown have incidence on ZYNRELEF ≥5% and higher than placebo incidence. Analysis represents data from Cohort 2. The adverse reactions for ZYNRELEF with or without low-dose ropivacaine were similar.

References: 1. ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **2.** Lachiewicz PF, Lee G-C, Pollak R, et al. *J Arthroplasty*. 2020;35(10):2843-2851. **3.** Data on file. Study HTX-011-209. San Diego, CA: Heron Therapeutics Inc; 2018.

EPOCH TKA Single-Arm[a] Follow-On Study (ZYNRELEF + Non-Opioid MMA)[1,2]

Total Knee Arthroplasty

- 6 sites in the United States
- n = 51
- **Protocol included an oral non-opioid postoperative MMA regimen[b]**



Pre-op: PO acetaminophen (1 g), PO celecoxib (200 mg), and PO pregabalin (300 mg). Surgery was performed under bupivacaine spinal anesthesia.

Intra-op: Intravenous fentanyl (≤4 µg/kg) permitted. No other opioids, analgesics, or anti-inflammatory agents (except ZYNRELEF) were permitted intraoperatively, unless needed to treat an adverse event, for pretreatment prior to needle placement, or to decrease venous irritation.

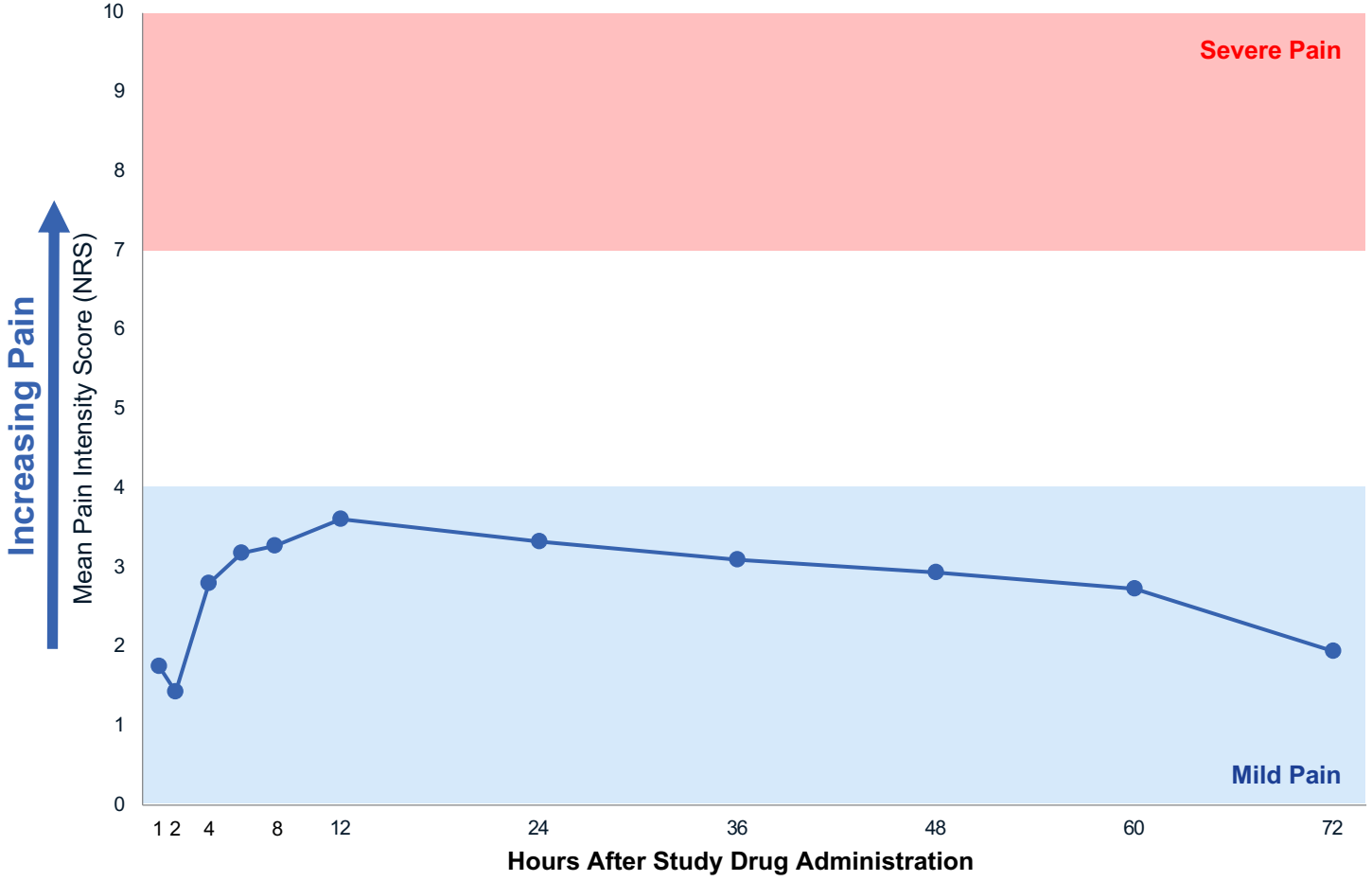
Post-op: For the first 3 days, PO acetaminophen (1 g q8h) and PO celecoxib (200 mg q12h). For the next 4 to 7 days, PO ibuprofen (600 mg q6h), then 3 hours later PO acetaminophen (1 g q6h), alternating for 72 hours, then as needed.

Following administration of ZYNRELEF, if additional NSAID medication is indicated in the postoperative period, monitor patients for signs and symptoms of NSAID-related GI adverse reactions.

[a]Single-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen. [b]The MMA regimen and primary endpoint were selected based on a published Phase 4 study of a long-acting liposomal bupivacaine with a scheduled, non-opioid MMA regimen in TKA.[3] **TKA:** total knee arthroplasty. **MMA:** multimodal analgesia. **PO:** by mouth (oral). **q6h/q8h/q12h:** every 6/8/12 hours.

References: 1. Data on file. Study HTX-011-306. San Diego, CA: Heron Therapeutics Inc; 2020. **2.** Hacker S. Poster presented at: Orthopedics Today Hawaii 2020; January 12-16, 2020; Koloa, HI. **3.** Mont MA, Beaver WB, Dysart SH, et al. *J Arthroplasty*. 2018;33(1):90-96.

EPOCH TKA Single-Arm[a] Follow-On Study: ZYNRELEF Plus Non-Opioid MMA Kept Pain in the Mild Range Through 72 Hours[1,b]



ZYNRELEF 400 mg/12 mg + Non-Opioid MMA (n = 51)

[a]Single-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen. [b]As reported without adjustment for opioid rescue medication use.

Note: Phase 2b data from Cohort 2. Phase 2b study surgeries performed under general anesthesia; follow-on study surgeries performed under bupivacaine spinal anesthesia.

TKA: total knee arthroplasty. **MMA:** multimodal analgesia. **NRS:** Numeric Rating Scale.

References: 1. Hacker S. Poster presented at: Orthopedics Today Hawaii 2020; January 12-16, 2020; Koloa, HI.

Topline Results of the EPOCH TKA Single-Arm[a] Follow-On Study (ZYNRELEF + MMA)[1]

- The majority of patients rated their pain control as “good” or “excellent”[1]

88% on day 1

90% on day 2

100% on day 3

- The mean consumption of opioids in the EPOCH TKA Single-Arm Follow-On study was 1 to 2 pills of oxycodone 10 mg per day through 72 hours (25 MME)[1]
- **39%** of TKA patients treated with ZYNRELEF and a non-opioid MMA regimen received **no opioid discharge prescription** and had no callbacks through day 11 of recovery[1,2]
- **37%** of TKA patients treated with ZYNRELEF and a scheduled non-opioid MMA regimen experienced **no severe pain through 72 hours**[2]

[a]Single-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen.

TKA: total knee arthroplasty. **MMA:** multimodal analgesia. **MME:** morphine milligram equivalent. **Severe pain:** pain intensity score of ≥7 on a Numeric Rating Scale of 0 to 10.

References: 1. Data on file. Study HTX-011-306. San Diego, CA: Heron Therapeutics Inc; 2020. **2.** Hacker S. Poster presented at: Orthopedics Today Hawaii 2020; January 12-16, 2020; Koloa, HI.

EPOCH TKA Single-Arm[a] Follow-On Study: Incidence of Treatment-Emergent Adverse Events[1]

	ZYNRELEF 400 mg/12 mg + Non-Opioid MMA Regimen (n = 51)
Any AE	**82%**
Nausea	57%
Vomiting	27%
Constipation	20%
Dizziness	12%
Anemia postoperative	6%
Bradycardia	6%
Urinary retention	6%

[a]Single-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen.

Note: Events included are AEs with an incidence of ≥5%.

TKA: total knee arthroplasty. **AE:** adverse event. **MMA:** multimodal analgesia.

References: 1. Data on file. Study HTX-011-306. San Diego, CA: Heron Therapeutics Inc; 2020.

Please see **IMPORTANT SAFETY INFORMATION** on pages 64 to 68 and full Prescribing Information, including **Boxed Warning**.

ZYNRELEF as the Foundation of a Non-Opioid MMA Regimen in a Real-World Setting[1,2]

HOPE Helping Opioid Prescription Elimination

Patients undergoing open inguinal herniorrhaphy were randomized to 1 of 2 parallel cohorts, each receiving different postoperative non-opioid MMA protocols with ZYNRELEF as the foundation:

- Cohort 1 (n = 46): Alternating OTC regimen (ibuprofen 600 mg q6h alternated 3 hours later with acetaminophen 1 g q6h)
- Cohort 2 (n = 47): Concurrent OTC regimen (ibuprofen 600 mg and acetaminophen 1 g, taken together q6h)

Endpoint[1]	
Primary	No Opioid Prescription Through Day 15
Secondary	No Opioid Prescription at Discharge
	No Opioid Prescription: Discharge Through Day 15
	Pain Intensity at Discharge
	Opioid Use: Discharge Through Day 15
	Satisfaction (TSQM-9 Scores) With Postoperative OTC Regimen

A simple algorithm was used to identify which patients were more likely to require postoperative opioid pain control[3]:

- Patients with an NRS score ≥6 within 2 hours after surgery
- Patients who required any postoperative opioids prior to discharge

This algorithm was prospectively validated in HOPE Hernia 1.

Following administration of ZYNRELEF, if additional NSAID medication is indicated in the postoperative period, monitor patients for signs and symptoms of NSAID-related GI adverse reactions.

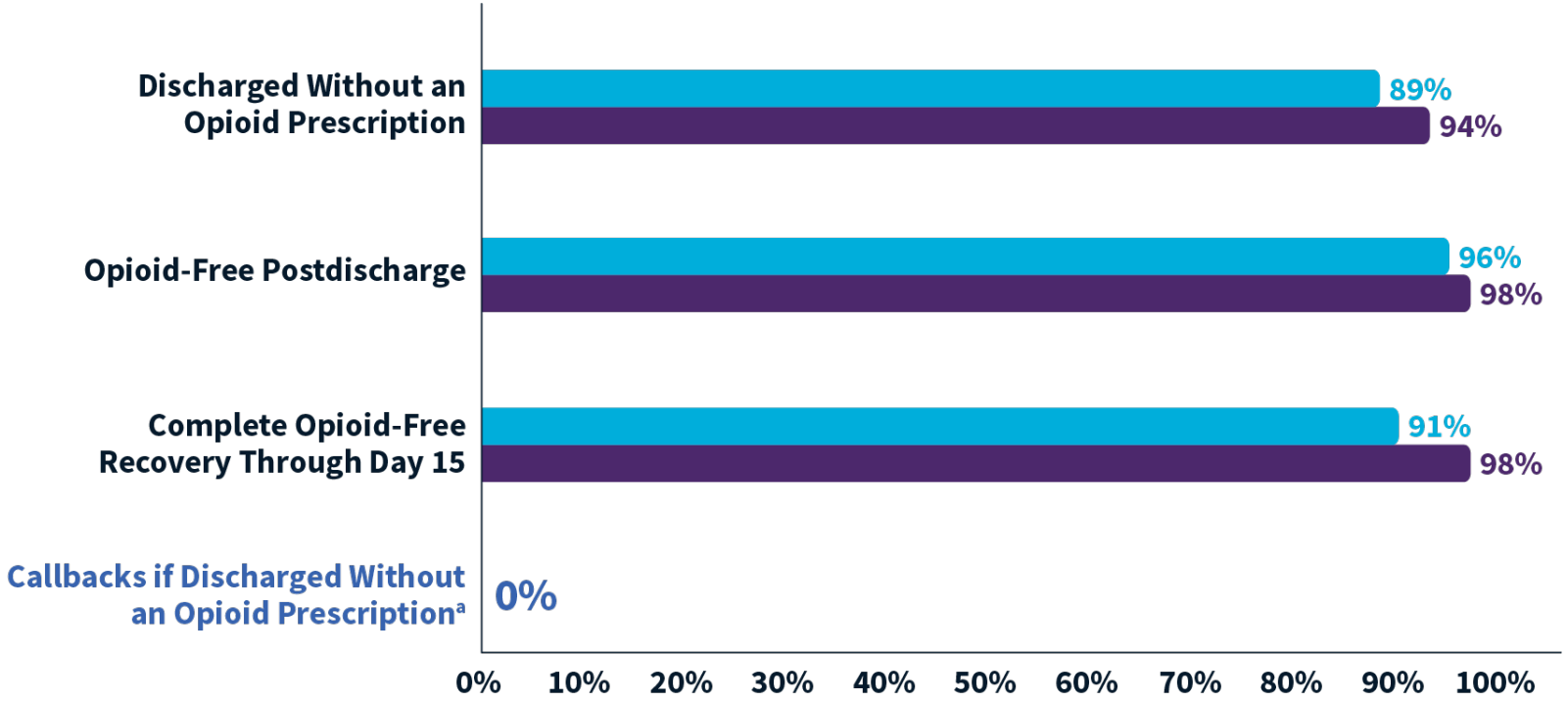
Note: The results in this presentation reflect Part 1 of the initial HOPE study in herniorrhaphy. Part 1 of this study was open label, with 2 parallel cohorts receiving different postoperative non-opioid MMA regimens. **MMA:** multimodal analgesia. **OTC:** over-the-counter. **q6h:** every 6 hours. **NRS:** Numeric Rating Scale. **TSQM-9:** Nine-item Treatment Satisfaction Questionnaire for Medication.[4]

References: 1. Minkowitz H, Soto R, Fanikos J, et al. Opioid-free recovery after hernia repair with HTX-011 as the foundation of a non-opioid, multimodal analgesia regimen in a real-world setting: a randomized, open-label study. *Pain Ther*. 2021;10(2):1295-1308. doi:10.1007/s40122-021-00289-2. **2.** Data on file. Study HTX-011-304. San Diego, CA: Heron Therapeutics Inc; 2020. **3.** Data on file. Algorithm to limit opioid prescriptions per administering HTX-011. San Diego, CA: Heron Therapeutics Inc; 2020. **4.** Bharmal M, Payne K, Atkinson MJ, et al. *Health Qual Life Outcomes*. 2009;7:36.

95% of ZYNRELEF Patients Opioid-Free Through Day 15 Recovery[1]

HOPE Helping Opioid Prescription Elimination

Of open inguinal hernia repair patients treated with ZYNRELEF and a scheduled non-opioid oral OTC analgesic regimen (N = 93):



- On average, patients were discharged 2.41 hours after surgery with only mild pain[1,2]
- Opioids were to be prescribed at discharge for patients who rated their pain at ≥6 (NRS) or received opioid rescue medication prior to discharge[1]

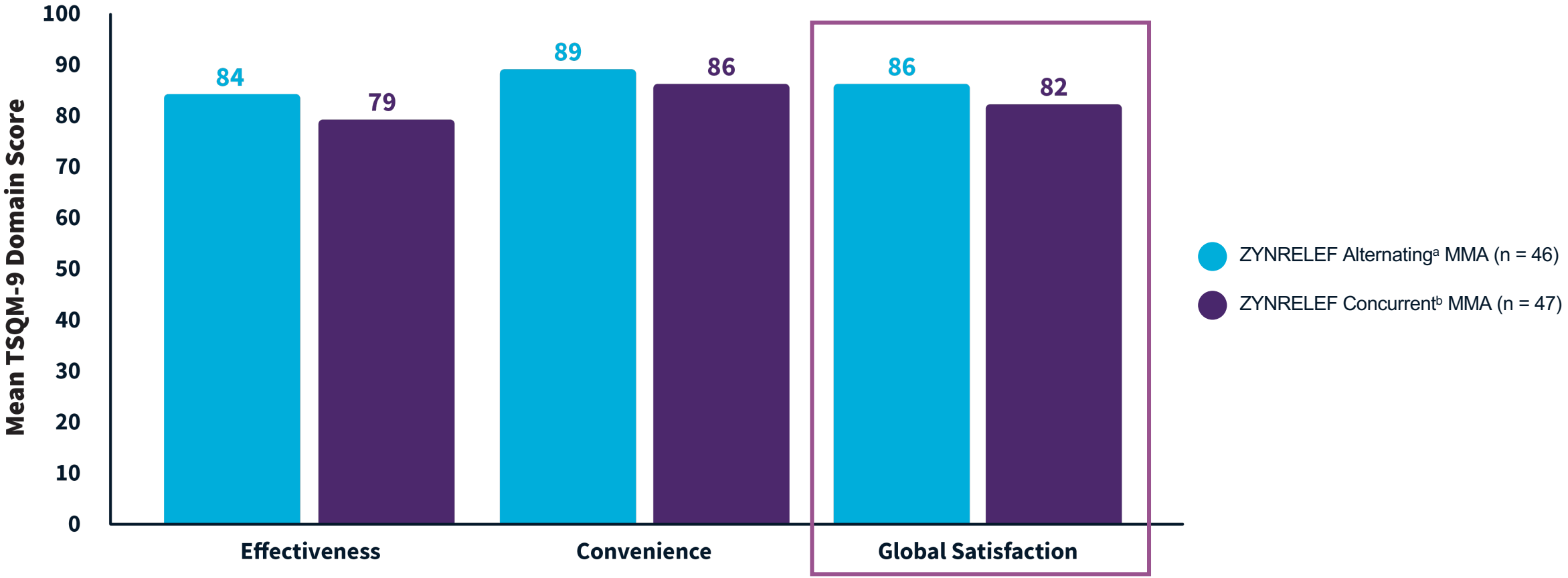
[a]Through day 15, 1 patient who received a discharge opioid prescription called the site for postoperative pain. [b]Alternating: OTC regimen of ibuprofen 600 mg q6h alternated 3 hours later with acetaminophen 1 g q6h. [c]Concurrent: OTC regimen of ibuprofen 600 mg and acetaminophen 1 g, taken together q6h.

OTC: over-the-counter. **NRS:** Numeric Rating Scale. **MMA:** multimodal analgesia. **q6h:** every 6 hours.

References: 1. Minkowitz H, Soto R, Fanikos J, et al. Opioid-free recovery after hernia repair with HTX-011 as the foundation of a non-opioid, multimodal analgesia regimen in a real-world setting: a randomized, open-label study. *Pain Ther*. 2021;10(2):1295-1308. doi:10.1007/s40122-021-00289-2. **2.** Data on file. Study HTX-011-304. San Diego, CA: Heron Therapeutics Inc; 2020.

High Patient Satisfaction With Pain Relief in Both MMA Regimens[1]

HOPE Helping Opioid Prescription Elimination



[a]Alternating: OTC regimen of ibuprofen 600 mg q6h alternated 3 hours later with acetaminophen 1 g q6h. [b]Concurrent: OTC regimen of ibuprofen 600 mg and acetaminophen 1 g, taken together q6h.

Note: Satisfaction assessed at day 15.

MMA: multimodal analgesia. **TSQM-9**: Nine-item Treatment Satisfaction Questionnaire for Medication.[2] **q6h:** every 6 hours.

References: 1. Minkowitz H, Soto R, Fanikos J, et al. Opioid-free recovery after hernia repair with HTX-011 as the foundation of a non-opioid, multimodal analgesia regimen in a real-world setting: a randomized, open-label study. *Pain Ther*. 2021;10(2):1295-1308. doi:10.1007/s40122-021-00289-2. **2.** Bharmal M, Payne K, Atkinson MJ, et al. *Health Qual Life Outcomes.* 2009;7:36.

HOPE Hernia 1: Incidence of Treatment-Emergent Adverse Events[1]

HOPE Helping Opioid Prescription Elimination

	Cohort 1: ZYNRELEF 300 mg/9 mg + Alternating MMA Regimen[a] (n = 46)	Cohort 2: ZYNRELEF 300 mg/9 mg + Concurrent MMA Regimen[b] (n = 47)
Any AE	**28%**	**38%**
Nausea	11%	15%
Constipation	2%	9%
Vomiting	7%	4%
Severe AE	0	0
Serious AE	0	0
AE Leading to Study Withdrawal	0	0

[a]Alternating: OTC regimen of ibuprofen 600 mg q6h alternated 3 hours later with acetaminophen 1 g q6h. [b]Concurrent: OTC regimen of ibuprofen 600 mg and acetaminophen 1 g, taken together q6h.

AE: adverse event. **MMA:** multimodal analgesia. **Severe Adverse Event:** any adverse event that interrupted daily activity or required systemic drug therapy or treatment. **Serious Adverse Event:** any adverse event that was life-threatening, resulted in substantial disruption to normal life, caused a birth defect, or required medical intervention. **q6h:** every 6 hours.

References: 1. Minkowitz H, Soto R, Fanikos J, et al. Opioid-free recovery after hernia repair with HTX-011 as the foundation of a non-opioid, multimodal analgesia regimen in a real-world setting: a randomized, open-label study. *Pain Ther*. 2021;10(2):1295-1308. doi:10.1007/s40122-021-00289-2.

Independent, Third-Party Research on ZYNRELEF

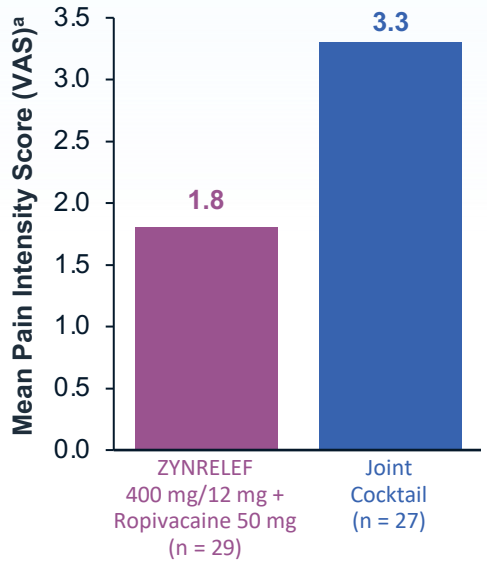
- In addition to Heron's clinical trials, independent third-party investigators have conducted real-world studies comparing ZYNRELEF with other treatments

ZYNRELEF Versus Joint Cocktail in Primary TKA (Retrospective, Real-World Study): Reduced Severe Pain, Opioid Consumption, and Length of Stay[1]

Independent, third-party, single-center, single-surgeon, retrospective chart review study.

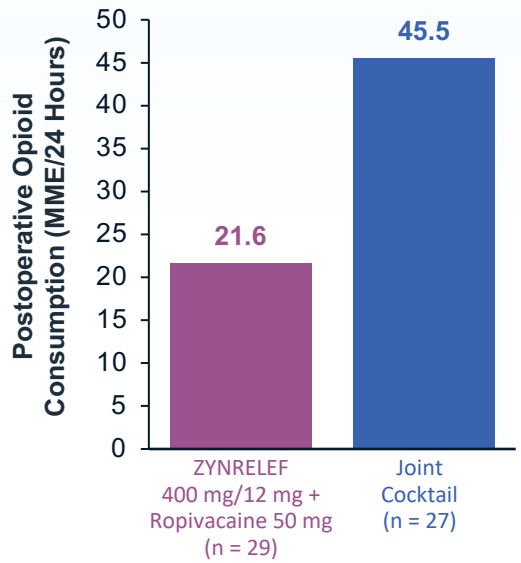
Pain Relief

- **45% lower pain scores[a] (*P* < .001)**
- **76% of ZYNRELEF patients experienced no severe pain (vs 45% for joint cocktail, *P* = .016)**



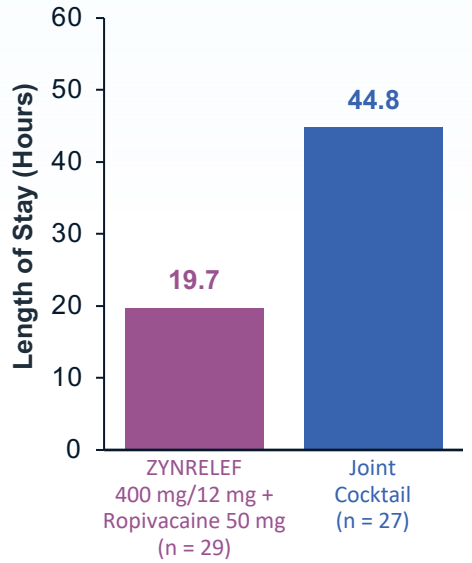
Opioid Consumption

- **53% lower opioid consumption (*P* < .05)**
- **41% of ZYNRELEF patients were opioid free (vs 33% for joint cocktail, *P* = .053)**



Length of Stay

- **56% shorter length of stay (*P* < .05)**
- **ZYNRELEF patients were discharged a day earlier on average**



Primary outcomes: difference in pain scores (VAS) and 24-hour opioid consumption (MME).

All patients were opioid naive and received spinal and regional (adductor canal block[b]) anesthesia as well as a standardized multimodal analgesic regimen.

ZYNRELEF + Ropivacaine 50 mg (n = 29)

- ZYNRELEF 400 mg/12 mg administered via instillation
- Ropivacaine 50 mg administered as a periarticular injection

Joint Cocktail (n = 27)

100 mL periarticular injection of:

- 400 mg ropivacaine
- 30 mg ketorolac
- 0.6 mg epinephrine
- 0.5 mg hydromorphone or 5 mg morphine

Note: The presented efficacy data is intended to comply with the FDA Guidance for Industry: Medical Product Communications That Are Consistent With the FDA-Required Labeling.
[a]Pain scores were assessed through time of discharge. [b]Adductor canal block of bupivacaine 0.5% 50 mg to 150 mg and ropivacaine LIA 0.5% 50 mg.
TKA: total knee arthroplasty. **VAS:** Visual Analog Scale. **MME:** morphine milligram equivalents. **Severe pain:** VAS score ≥7. **LIA:** local infiltration analgesia.
References: 1. Warner K, Bonkowski B, Melton K, Smith C, Turner A. Poster presented at: Orthopedics Today Hawaii; January 8-12, 2023; Koloa, HI.

Dosage and Administration

- Single-dose instillation; applied via a needle-free syringe into the surgical site following final irrigation and suction and prior to suturing[1]
- Prepare and administer ZYNRELEF using only the components provided in the kit[1]
- **No mixing with bupivacaine is required to achieve efficacy;** ZYNRELEF should not be diluted[1]
- Other local anesthetics can be administered before ZYNRELEF without causing release of the active ingredients all at once.[1-3] The toxic effects of local anesthetics are additive. Avoid additional use of local anesthetics within 96 hours following administration of ZYNRELEF.
- The recommended dose is based on the following factors[1]:
  - For foot and ankle surgical procedures, such as bunionectomy: up to 2.3 mL to deliver 60 mg of bupivacaine and 1.8 mg of meloxicam
  - For small-to-medium open abdominal surgical procedures, such as open inguinal herniorrhaphy: up to 10.5 mL to deliver 300 mg of bupivacaine and 9 mg of meloxicam
  - For lower extremity total joint arthroplasty surgical procedures, such as total knee arthroplasty: up to 14 mL to deliver 400 mg of bupivacaine and 12 mg of meloxicam

References: 1. ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **2.** Viscusi E, Gimbel JS, Pollack RA, et al. *Reg Anesth Pain Med*. 2019;44(7):700-706. **3.** Lachiewicz PF, Lee G-C, Pollak R, et al. *J Arthroplasty*. 2020;35(10):2843-2851.

ZYNRELEF Is Available in 2 Volumes

Suggested Vial Size for Example Procedures[1,2]

The recommended vial is based on the size of the surgical site and the volume required to cover the tissues within the surgical site that could result in pain generation. Maximum total dose is 400 mg bupivacaine/12 mg meloxicam (14 mL).

14-mL Vial Size

Example Procedures

- Appendectomy (Open)
- C-Section
- Herniorrhaphy[a] (Open)
- Hysterectomy (Open)
- Total Hip Arthroplasty
- Total Knee Arthroplasty

7-mL Vial Size

Example Procedures

- Bunionectomy and Phalangectomy
- Female Sterilization
- Fracture - Foot & Ankle
- Pelvic Floor Reconstruction
- Stoma Closure/Creation
- Suburethral Sling
- Total Ankle Arthroplasty

Small-to-Medium Laparoscopic Extraction Site Example Procedures[b]

- Appendectomy
- Cholecystectomy
- Colon and Small Bowel Resection
- Gastrectomy
- Hysterectomy
- Prostatectomy
- Roux-en-Y Gastric Bypass

Limit exposure to articular cartilage due to the potential risk of chondrolysis.

Note: Not all procedures listed under each vial size require full contents to cover affected tissues.

[a]Includes small-to-medium open hernia repair. [b]Extraction site is considered a small-to-medium open abdominal procedure.

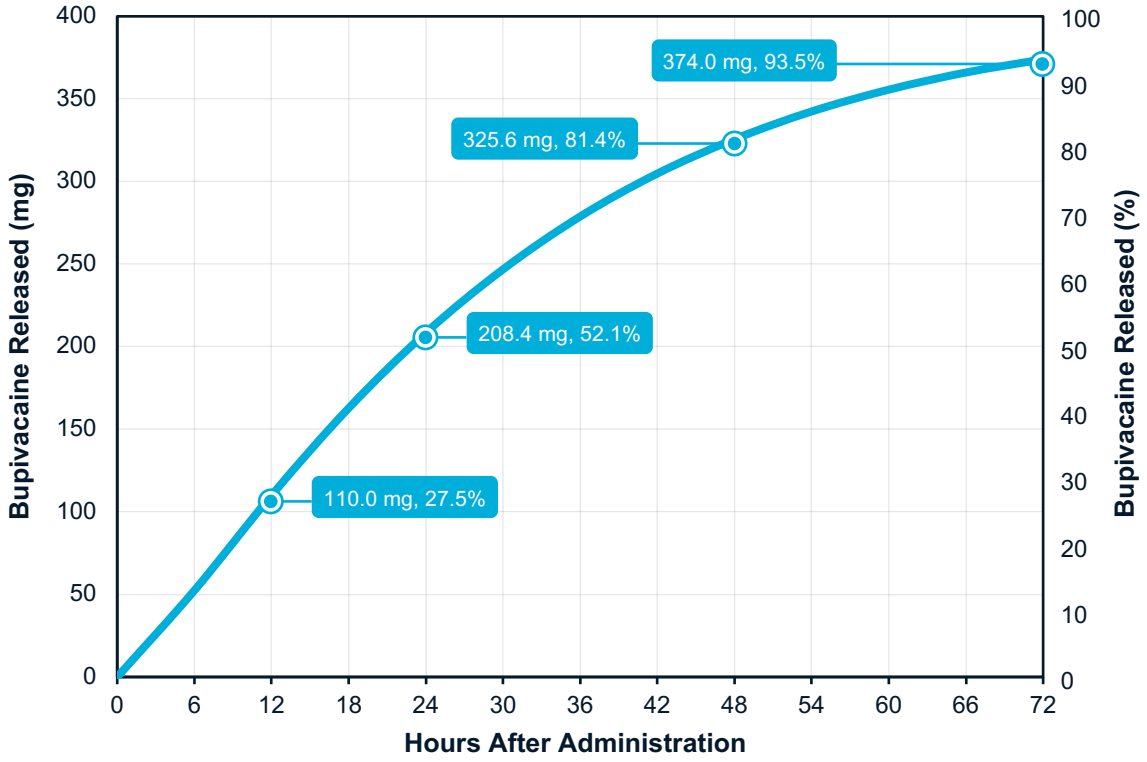
References: 1. ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **2.** Data on file. Assessment of dose by procedure. San Diego, CA: Heron Therapeutics Inc; 2018.

Please see **IMPORTANT SAFETY INFORMATION** on pages 64 to 68 and full Prescribing Information, including **Boxed Warning**.

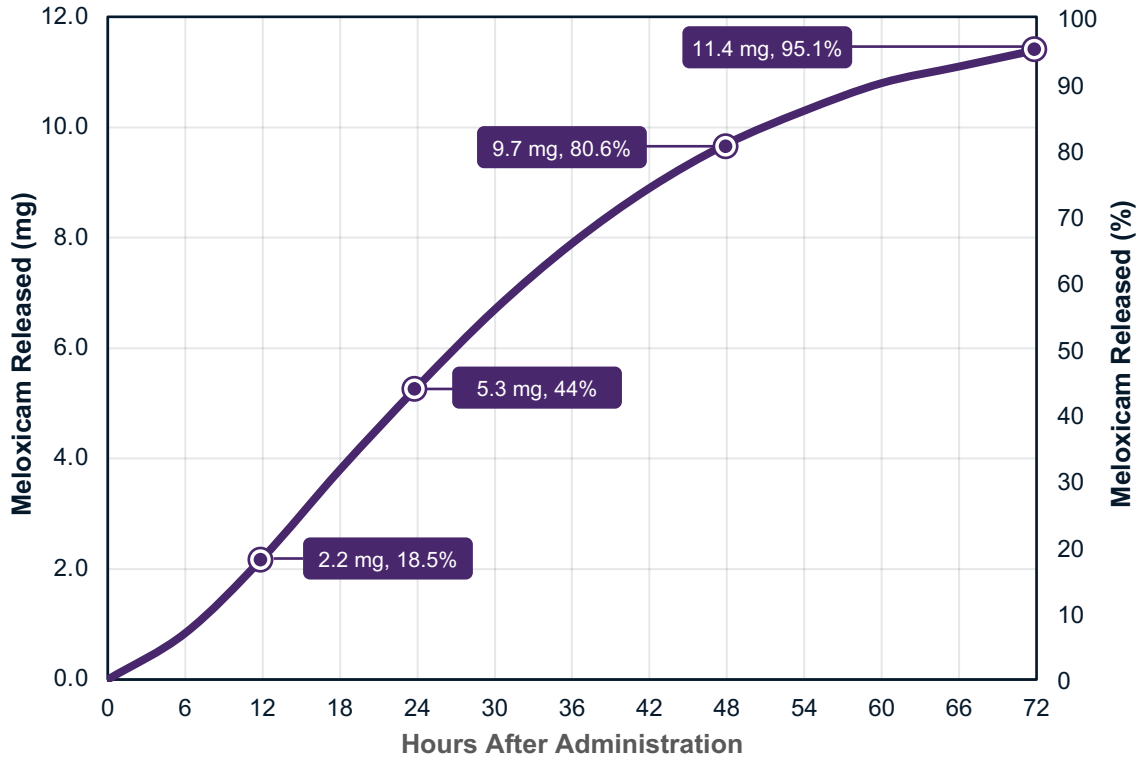
In Vitro Release Rates of Active Ingredients[1]

Maximum total dose: 400 mg bupivacaine/12 mg meloxicam (14 mL)

Bupivacaine 400 mg from ZYNRELEF



Meloxicam 12 mg from ZYNRELEF



Note: Milligram values extrapolated from in vitro release-rate percentages. ZYNRELEF was assayed in vitro.

References: 1. Data on file. Summary of biopharmaceutic studies and associated analytical methods. San Diego, CA: Heron Therapeutics Inc; 2018.

In Vitro Release Rates of Active Ingredients[1]

Maximum total dose: 400 mg bupivacaine/12 mg meloxicam (14 mL)

Time Elapsed After Dosing (hours)	6	12	18	24	30	36	42	48	54	60	66	72
400 mg Bupivacaine Released (mg)	52.4	110.0	162.8	208.4	246.8	278.8	304.8	325.6	342.4	355.6	366.0	374.0
400 mg Bupivacaine Released (%)	13.1	27.5	40.7	52.1	61.7	69.7	76.2	81.4	85.6	88.9	91.5	93.5
12 mg Meloxicam Released (mg)	0.8	2.2	3.8	5.3	6.7	7.9	8.9	9.7	10.3	10.8	11.1	11.4
12 mg Meloxicam Released (%)	7.0	18.5	31.4	44.0	55.5	65.5	73.9	80.6	85.9	89.9	92.9	95.1

Note: Milligram values extrapolated from in vitro release-rate percentages. ZYNRELEF was assayed in vitro.

References: 1. Data on file. Summary of biopharmaceutic studies and associated analytical methods. San Diego, CA: Heron Therapeutics Inc; 2018.

Please see **IMPORTANT SAFETY INFORMATION** on pages 64 to 68 and full Prescribing Information, including **Boxed Warning**.

Packaging, Storage, and Handling

- Controlled room temperature 20°C to 25°C (68°F to 77°F)[1]
  - Excursions permitted between 15°C to 30°C (59°F to 86°F)[1]
  - 36-month shelf life[2]
- Distribution through full-line wholesalers and specialty distributors; prime vendor discounts apply
- 2 SKUs for different surgery requirements[1]
  - SKUs identifiable by different colors on package
- Kit includes all necessary components[1,a]
  - Sized to fit in standard OR medication carts (eg, Pyxis™)
  - Kits have the same outer package dimensions

[a]Kit components include single-dose glass vial, Luer lock syringe(s), vented vial spike, Luer lock applicator(s), and tip cap(s). **SKU:** stock keeping unit.

References: 1. ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021. **2.** Roca R; Center for Drug Evaluation and Research. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/211988Orig1s000ltr.pdf. Accessed May 13, 2021.

Packaging, Storage, and Handling (cont)

Product Presentation[1]			Vented Vial Spike	Luer Lock Syringe(s)	Luer Lock Applicator(s)	Syringe Tip Cap(s)
NDC	Bupivacaine/ Meloxicam	Volume				
47426-301-02	400 mg/12 mg	14 mL	1	2 x 12 mL	2	2
47426-303-01	200 mg/6 mg	7 mL	1	1 x 12 mL	1	1

Order Replacement Kit Components for ZYNRELEF

ZYNRELEF should be prepared and administered using only the components provided in the ZYNRELEF kit. In case parts are dropped or mishandled during preparation, replacement kit components can be ordered for $0.01 per carton. Search “ZYNRELEF” on your distributor’s ordering website and add 1 carton of each component[a] to your initial order.

[a]Luer lock cone-shaped applicators (GTIN 00347426902106), vented vial spikes (GTIN 00347426903059), 12-mL Luer lock syringes (GTIN 00347426904087).

References: 1. ZYNRELEF [package insert]. San Diego, CA: Heron Therapeutics Inc; 2021.

ZYNRELEF Is Priced to Reduce Average Cost Across the Surgical Mix

ZYNRELEF Pricing[a]		
SKU	**WAC**	**340B[b]**
14 mL: 400 mg/12 mg	$280.87	$204.49
7 mL: 200 mg/6 mg	$142.27	$103.31

GPO and sub-WAC discounts available. Prime vendor discounts apply.

Cost Information for Other Longer-Acting Local Anesthetics

Exparel®[c,d] *Not including bupivacaine cost*		WAC	340B
	20 mL	**$365.16**	**$266.00**
	10 mL	**$214.75**	**$151.00**
Catheter-based pump cost[1,e]		**$318-$630**	

Cost comparisons do not imply safety or efficacy. WAC and list prices may not reflect discounts available to customers through manufacturers or other parties.

ZYNRELEF Estimated Average Cost, SKU Mix, and Savings by Setting of Care Compared With Exparel

	ZYNRELEF[2,a,f]			Exparel[3,d,g]			Estimated Savings With ZYNRELEF
	Estimated Average Cost	Estimated SKU Mix		Average Cost	SKU Mix		
		400 mg	200 mg		20 mL	10 mL	
Hospital	~$187	32%	68%	~$321	71%	29%	42%
ASC	~$170	20%	80%	~$287	48%	52%	41%

[a]ZYNRELEF pricing as of January 1, 2023. 340B prices update quarterly. Confirm current pricing with your Heron representative. [b]340B pricing allows purchases by eligible customers for outpatient use at a minimum discount of 23.1%. [c]Exparel (bupivacaine liposome injectable suspension) is a trademark of Pacira Pharmaceuticals, Inc. [d]Figures reflect Exparel prices as of January 1, 2023. [e]Pump cost varies based on components, drug, and rate of delivery. [f]Based on national average procedure volumes for common procedures; individual organizations may vary. Estimated average cost at WAC; not inclusive of GPO, sub-WAC, or distributor discounts. [g]Estimated average cost at WAC.

SKU: stock keeping unit. **WAC:** wholesale acquisition cost. **GPO:** group purchasing organization. **ASC:** ambulatory surgical center.

References: 1. Data on file. On-Q competitive intelligence. San Diego, CA: Heron Therapeutics Inc; 2019. **2.** Data on file. DRG procedure volume analysis. San Diego, CA: Heron Therapeutics Inc; 2020. **3.** US non-retail pharmacy sales data, January-December 2022. Horsham, PA: Symphony Health; 2023.

Please see **IMPORTANT SAFETY INFORMATION** on pages 64 to 68 and full Prescribing Information, including **Boxed Warning**.

ZYNRELEF Reimbursement Overview

Medicare: ZYNRELEF Is Reimbursed Separately in HOPDs and ASCs Through 2027

Through March 2025	**HOPD, ASC:** Separate reimbursement at **ASP + 6%** *(pass-through status)*
April 2025 – December 2027	**HOPD, ASC:** Separate reimbursement under law promoting access to non-opioids *(HR 2617 §4135, signed December 2022)*

2023 Q1 Medicare Reimbursement and Pricing

ZYNRELEF	Medicare Reimbursement (Allowed Amount)[a,b]	Pricing[c]	
SKU	**HOPD, ASC**	**WAC**	**340B**
14 mL: 400 mg/12 mg	$276.00	$280.87	$204.49
7 mL: 200 mg/6 mg	$138.00	$142.27	$103.31

Note: Outpatient procedures include those expected to require a hospital stay spanning less than 2 midnights.

Exparel is not currently separately reimbursed in the HOPD.[d]
Pumps and generic local anesthetics like bupivacaine HCl are currently packaged across all settings of care.[e]

C9088

☑ **HOPD, ASC: Separate Payment Through 2027 (Medicare)**

Commercial: Separate Payment Available for Many Patients

- Commercial payers have been notified that **C9088** has been assigned for ZYNRELEF; many customers have reported separate commercial payment
- Commercial reimbursement varies by payer and site of care; contact payers to verify coverage
- Heron offers resources to assist with billing and coding and to support separate payment requests

[a]HOPD coverage under 3-year transitional pass-through status (effective April 1, 2022). [b]Q1 2023 Medicare payment rate: ZYNRELEF $0.69/mg. Medicare reimbursement is subject to CMS updates, co-pay amounts, sequestration, and other factors. [c]ZYNRELEF pricing as of January 1, 2023. 340B prices update quarterly. Confirm current pricing with your Heron representative. [d]From January 1, 2025 through December 31, 2027, Medicare will reimburse separately in HOPDs and ASCs for certain non-opioid drugs without pass-through status, per HR 2617 §4135. [e]Reimbursement comparisons do not imply safety or efficacy.
HOPD: hospital outpatient department. **ASC:** ambulatory surgical center. **ASP:** average sales price. **SKU:** stock keeping unit. **WAC:** wholesale acquisition cost. **CMS:** Centers for Medicare & Medicaid Services.

Q1 2023 Medicare Reimbursement by SKU: ZYNRELEF vs Exparel®[a]

ZYNRELEF is separately reimbursed in HOPDs by Medicare, Exparel currently is not[b]

ZYNRELEF	Medicare Reimbursement (Allowed Amount)[b,c]	Pricing[d]	
SKU	**HOPD, ASC**	**WAC**	**340B**
14 mL: 400 mg/12 mg	$276.00	$280.87	$204.49
7 mL: 200 mg/6 mg	$138.00	$142.27	$103.31

Exparel	Medicare Reimbursement (Allowed Amount)[c]		Pricing[e]	
SKU	**HOPD**	**ASC**	**WAC**	**340B**
266 mg (20 mL)	Packaged	$367.08	$365.16	$266.00
133 mg (10 mL)	Packaged	$183.54	$214.75	$151.00

Cost and reimbursement comparisons do not imply safety or efficacy. WAC and list prices may not reflect discounts available to customers through manufacturers or other parties.

[a]Exparel (bupivacaine liposome injectable suspension) is a trademark of Pacira Pharmaceuticals, Inc. [b]ZYNRELEF HOPD coverage under 3-year transitional pass-through status (effective April 1, 2022). [c]Q1 2023 Medicare payment rate: ZYNRELEF $0.69/mg, Exparel $1.38/mg. Medicare reimbursement is subject to CMS updates, co-pay amounts, sequestration, and other factors. [d]ZYNRELEF pricing as of January 1, 2023. 340B prices update quarterly. Confirm current pricing with your Heron representative. [e]Exparel prices as of January 1, 2023.

SKU: stock keeping unit. **HOPD:** hospital outpatient department. **ASC:** ambulatory surgical center. **WAC:** wholesale acquisition cost. **CMS:** Centers for Medicare & Medicaid Services.

Please see **IMPORTANT SAFETY INFORMATION** on pages 64 to 68 and full Prescribing Information, including **Boxed Warning**.

Important Safety Information

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use.**
- **ZYNRELEF is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.**
- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.**

Contraindications

ZYNRELEF is contraindicated in patients with a known hypersensitivity (eg, anaphylactic reactions and serious skin reactions) to any amide local anesthetic, NSAIDs, or other components of ZYNRELEF; with history of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (severe, sometimes fatal, anaphylactic reactions to NSAIDS have been reported in such patients); undergoing obstetrical paracervical block anesthesia; or undergoing CABG.

Important Safety Information (cont)

Warnings and Precautions

Dose-Related Toxicity: Monitor cardiovascular and respiratory vital signs and patient's state of consciousness after application of ZYNRELEF. When using ZYNRELEF with other local anesthetics, overall local anesthetic exposure must be considered through 72 hours.

Hepatotoxicity: If abnormal liver tests persist or worsen, perform a clinical evaluation of the patient.

Hypertension: Patients taking some antihypertensive medication may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure.

Heart Failure and Edema: Avoid use of ZYNRELEF in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure.

Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of ZYNRELEF in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal failure.

Important Safety Information (cont)

Warnings and Precautions (cont)

Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs.

Chondrolysis: Limit exposure to articular cartilage due to the potential risk of chondrolysis.

Methemoglobinemia: Cases have been reported with local anesthetic use.

Serious Skin Reactions: NSAIDs, including meloxicam, can cause serious skin adverse reactions. If symptoms present, evaluate clinically.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): If symptoms are present, evaluate clinically.

Fetal Toxicity: Due to the risk of oligohydramnios/fetal renal dysfunction and premature closure of the ductus arteriosus with NSAIDS, limit use of ZYNRELEF between about 20 to 30 weeks gestation, and avoid use after about 30 weeks.

Hematologic Toxicity: Monitor hemoglobin and hematocrit in patients with any signs or symptoms of anemia.

Important Safety Information (cont)

Drug Interactions

Drugs That Interfere with Hemostasis: Monitor patients for bleeding who are using ZYNRELEF with drugs that interfere with hemostasis (eg, warfarin, aspirin, SSRIs/SNRIs).

ACE Inhibitors, Angiotensin Receptor Blockers (ARBs), or Beta-Blockers: Use with ZYNRELEF may diminish the antihypertensive effect of these drugs. Monitor blood pressure.

ACE Inhibitors and ARBs: Use with ZYNRELEF in elderly, volume-depleted, or those with renal impairment may result in deterioration of renal function. In such high-risk patients, monitor for signs of worsening renal function.

Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects.

Important Safety Information (cont)

Use in Specific Populations

Infertility: NSAIDs are associated with reversible infertility. Consider avoidance of ZYNRELEF in women who have difficulties conceiving.

Severe Hepatic Impairment: Only use if benefits are expected to outweigh risks; monitor for signs of worsening liver function.

Severe Renal Impairment: Not recommended.

Adverse Reactions

Most common adverse reactions (incidence ≥10%) in controlled clinical trials with ZYNRELEF are constipation, vomiting, and headache.

Report side effects to Heron at 1-844-437-6611 or to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see full Prescribing Information, including Boxed Warning, at ZYNRELEF.com.

ZYNRELEF®
(bupivacaine and meloxicam)
extended-release solution
29.25 mg/mL and 0.88 mg/mL

THANK YOU

PP-HTX011-0371 | 03/23