Jefferies Conference Corporate Update

June 1, 2021

HERON THERAPEUTICS

Forward-Looking Statements

This presentation contains "forward-looking statements" as defined by the Private Securities Litigation Reform Act of 1995. We caution investors that forward-looking statements are based on management's expectations and assumptions as of the date of this presentation, and involve substantial risks and uncertainties that could cause our clinical development programs, future results, performance or achievements to differ significantly from those expressed or implied by the forward-looking statements. These risks and uncertainties include, but are not limited to, those associated with: risks associated with achieving the full-year 2021 net product sales guidance for the CINV franchise; the timing of the commercial launch of ZYNRELEF in the U.S.; the timing of the commercial launch of ZYNRELEF in Europe; the potential market opportunity for ZYNRELEF in the US and Europe; the timing of Health Canada's NDS review process for HTX-011; whether Health Canada issues a Notice of Compliance for the NDS for HTX-011; the timing and results of studies for HTX-011, the HTX-034 development program, and the HTX-019 development program; the expected future balances of Heron's cash, cash equivalents and short-term investments; the expected duration over which Heron's cash, cash equivalents and short-term investments balances will fund its operations; the extent of the impact of the ongoing Coronavirus Disease 2019 (COVID-19) pandemic on our business; and other risks and uncertainties identified in the Company's filings with the Securities and Exchange Commission. Forward-looking statements reflect our analysis only on their stated date, and we take no obligation to update or revise these statements except as may be required by law.

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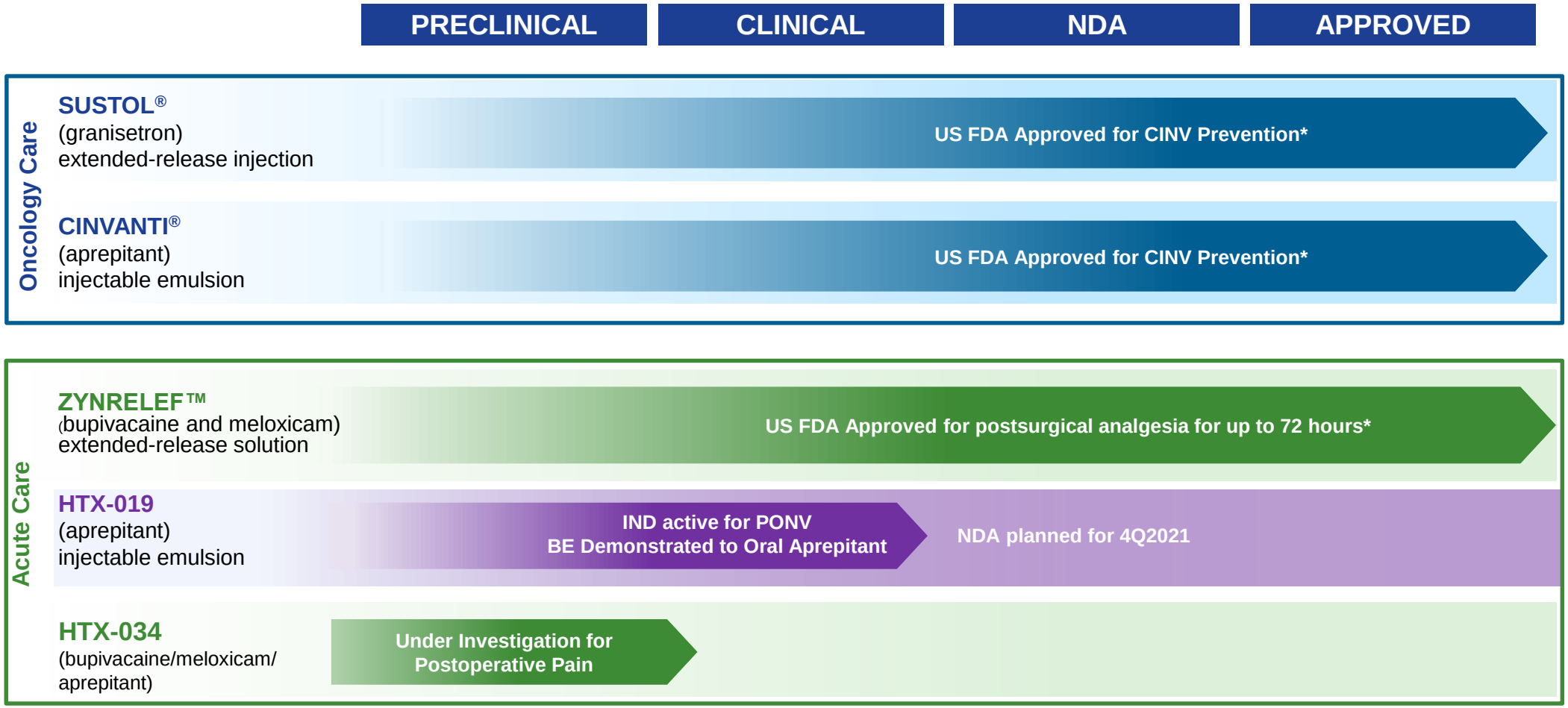
Heron Pipeline



CINV: Chemotherapy-induced nausea and vomiting. **SUSTOL® (granisetron) extended-release injection** is indicated in combination with other antiemetics in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens. **CINVANTI® (aprepitant) injectable emulsion**, in combination with other antiemetic agentsis indicated in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin as a single-dose regimen, delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) as a single-dose regimen, and nausea and vomiting associated with initial and repeat courses of MEC as a 3-day regimen. CINVANTI has not been studied for treatment of established nausea and vomiting. **ZYRNELEF (bupivacaine and meloxicam) extended-release solution** is indicated in adults for soft tissue or periarticular instillation to produce postsurgical analgesia for up to 72 hours after bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty. Safety and efficacy have not been established in highly vascular surgeries, such as intrathoracic, large multilevel spinal, and head and neck procedures.

HTX-034 and HTX-019 are investigational new drugs and are not approved by the FDA

Heron's Top Priorities for Remainder of 2021

1. **Successfully launch ZYNRELEF™ and work with the FDA to expand ZYNRELEF's indication as quickly as possible**
   - Commercial Product available July 1, 2021
   - Actively pursuing formulary approvals – initial formulary acceptance within 24 hours
   - Expanded salesforce hiring underway
   - Initiated additional PK and safety studies to support label expansion

2. **Continue to grow the Oncology Care Franchise sales and profitability**

3. **Submit NDA for HTX-019 for postoperative nausea and vomiting**

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Why Approval of ZYNRELEF is so Important

Postoperative Opioids Can Be a Doorway to Addiction

More than 50 million
surgical procedures happen in the United States.[1]

67% of patients
filled an opioid prescription between 30 days before through 14 days after surgery.[2*]

> 2 million Americans
may become persistent opioid users annually after surgery. [1]

In 2020, drug overdoses were linked to more than
90,000 deaths
the highest number ever recorded in a single year.[3]

In addition, most patients take fewer opioids than the amount prescribed after surgery, resulting in excess opioid pills that are accessible to others.[4]

80%
of patients report unused opioid tablets[4]

Up to **77%**
of opioid pills remain inside the home in unsecured locations[4]

51%
of nonmedical users of opioids received them from friends and family[5]

More than
$23.4 billion
in annual healthcare costs associated with persistent opioid users can be attributed to postoperative pain management.[1,6]

* This was determined using a 20% national sample of Medicare claims among beneficiaries aged 65 and older with Medicare Part D claims who underwent a major or minor surgical procedure between January 1, 2009 and June 30, 2015.

References: 1. Brummett CM, Waljee JF, Goesling J, et al. New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults [published correction appears in JAMA Surg. 2019 Mar 1;154(3):272]. *JAMA Surg*. 2017;152(6):e170504. doi:10.1001/jamasurg.2017.0504. **2.** Santosa KB, Hu HM, Brummett CM, et al. New persistent opioid use among older patients following surgery: A Medicare claims analysis. *Surgery*. 2020;167(4):732-742. doi:10.1016/j.surg.2019.04.016. **3.** NCHS, National Vital Statistics System. Estimates for 2020 are based on provisional data. Estimates for 2015-2019 are based on final data (available from: https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm). **4.** Bicket MC, Long JJ, Pronovost PJ, Alexander GC, Wu CL. Prescription Opioid Analgesics Commonly Unused After Surgery: A Systematic Review. *JAMA Surg*. 2017;152(11):1066–1071. doi:10.1001/jamasurg.2017.0831. **5.** Substance Abuse and Mental Health Services Administration . Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; Rockville, MD: 2019. Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health (HHS Publication No. PEP19-5068, NSDUH Series H-54). https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHNationalFindingsReport2018/NSDUHNationalFindingsReport2018.pdf. Accessed April 19, 2021. **6.** Brummett CM, Evans-Shields J, England C, Kong AM, Lew CR, Henriques C, Zimmerman NM, Sun EC. Increased health care costs associated with new persistent opioid use after major surgery in opioid-naive patients. *J Manag Care Spec Pharm*. 2021 Feb 24:1-12. doi: 10.18553/jmcp.2021.20507. Epub ahead of print. PMID: 33624534.

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ZYNRELEF Approved Indications and Limitations of Use

Indication

- ZYNRELEF is indicated in adults for soft tissue or periarticular instillation to produce postsurgical analgesia for up to 72 hours after bunionectomy, open inguinal herniorrhaphy, and total knee arthroplasty.

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.

ZYNRELEF is First of a New Class of Local Anesthetic

- ZYNRELEF granted broadest indication by FDA for a local anesthetic (Exparel NB, Xaracoll, Posimir) since analgesics guidance withdrawn, with significantly fewer limitations of use
- Standard NSAID class warnings included, with modifications due to single-dose local application allowing for additional NSAID use in multimodal analgesia (MMA)
- ZYNRELEF is first and only local anesthetic to be classified by FDA as “extended-release” based on superiority to bupivacaine HCl for 72 hours
- FDA recognized ZYRELEF’s unique Mechanism of Action (MOA)
  - Compared with bupivacaine alone in both studies, ZYNRELEF (at the same bupivacaine doses) demonstrated greater and longer analgesia through 24, 48, and 72 hours
  - The only dual-acting extended-release local anesthetic
- ZYNRELEF is only local anesthetic demonstrating superiority to bupivacaine (standard of care):
  - Statistically superior pain reduction
  - Statistically superior opioid-free results
- ZYNRELEF has superior reduction in pain for total knee arthroplasty (TKA), most painful surgery, included in label

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Positive Labeling and Results for ZYNRELEF Use in TKA

- ZYNRELEF has unique labeling for use in TKA

Product	Labeling
ZYNRELEF	Positive results for TKA in Clinical Trials section.
Exparel	Negative results for femoral nerve block for TKA in Clinical Trials section. Limitation of Use for nerve blocks other than brachial plexus.
Xaracoll	Limitation of Use against use for orthopedic and boney procedures.
Posimir	Limitation of Use against use for orthopedic and boney procedures.

- Exparel failed TKA studies for infiltration use and as nerve block (NB)
  - Failed Phase 3 infiltration TKA study[1]
  - Failed femoral NB TKA study, with increased falls in 2 TKA studies[2]
  - Published studies do not support Exparel use in TKA[3]
    - Phase 4 PILLAR study used non-standard analyses to achieve statistical significance for pain and opioid use[4]

[1] SIMPLE TKA Study 311: NCT00745290; Exparel liposomal European Public Assessment Report (EMA/CHMP/528272/2020)
[2] Exparel USPI 2021
[3] Jain 2016l: https://doi.org/10.1016/j.arth.2016.03.036; DeClaire 2017: https://doi.org/10.1016/j.arth.2017.03.062; Zlotnicki 2018: https://doi.org/10.1016/j.arth.2018.03.014; Amundson 2017: https://doi.org/10.1097/ALN.0000000000001586; Hussain 2021: https://doi.org/10.1097/ALN.0000000000003651
[4] Mont et al 2018: https://doi.org/10.1016/j.arth.2018.12.026

ZYNRELEF Clinical Development

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.

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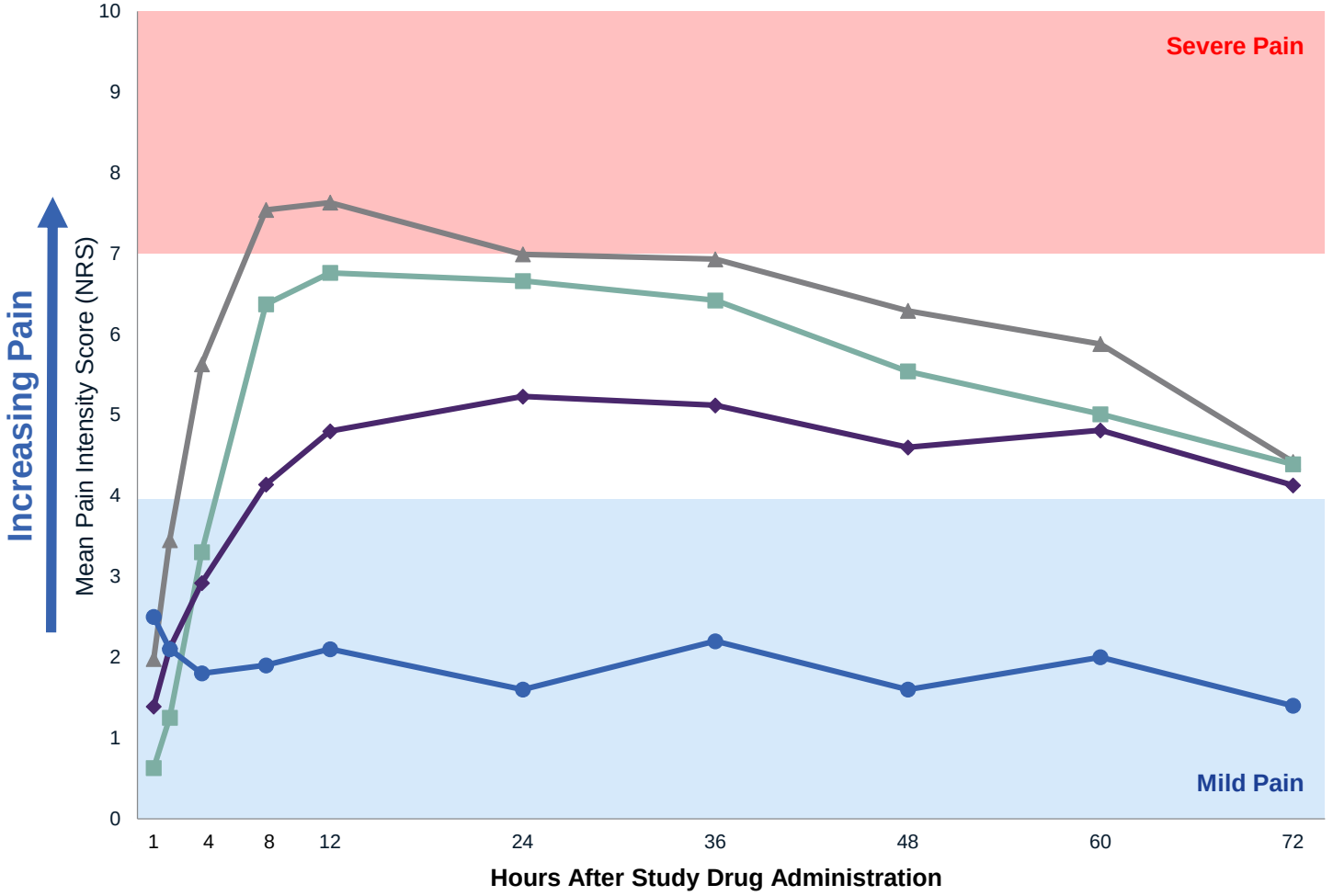
EPOCH 1 Single-Arm[a] Follow-On: In Bunionectomy, ZYNRELEF Plus a Scheduled Regimen of Oral Non-Opioid OTC Analgesics Kept Pain in the Mild Range Through 72 Hours[1-3]



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)**

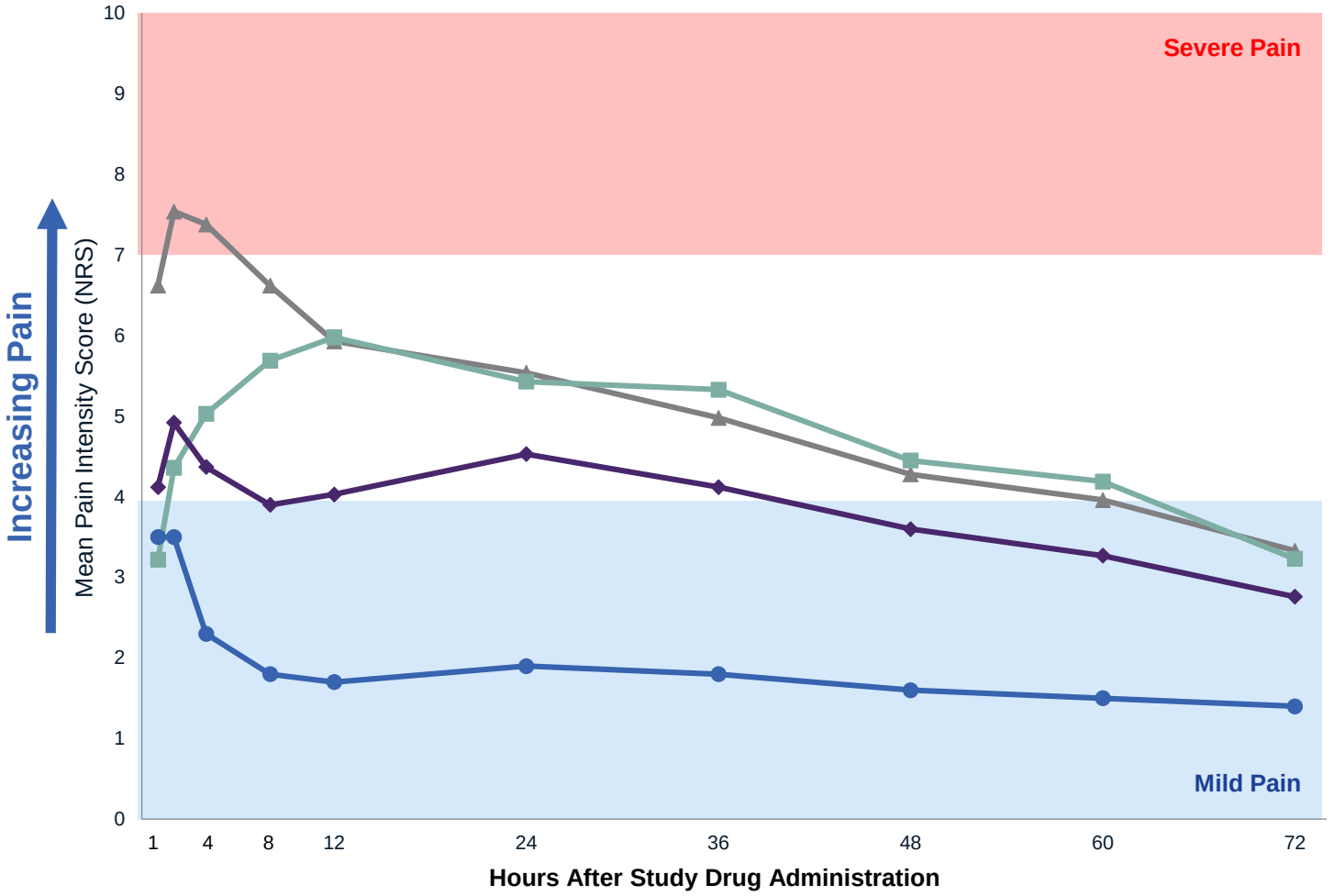
Follow-On Study

- **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.

Please see **IMPORTANT SAFETY INFORMATION** on pages 32 to 33 and full Prescribing Information, including **Boxed Warning**.
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.

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)**

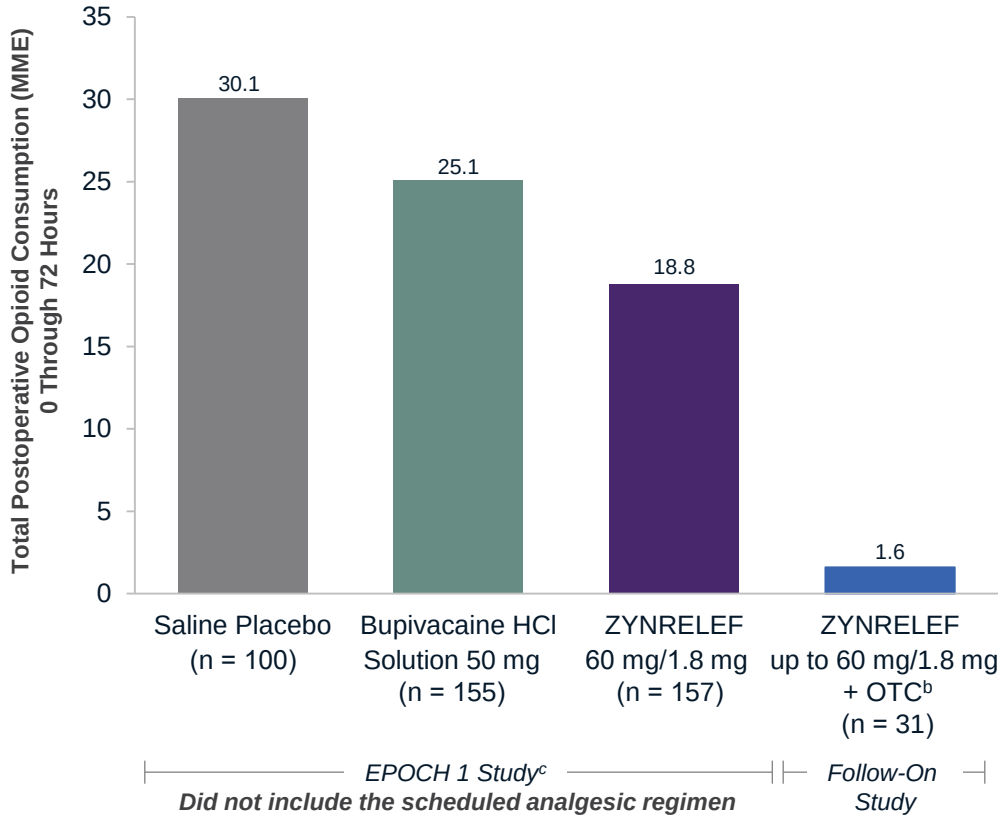
Follow-On Study

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

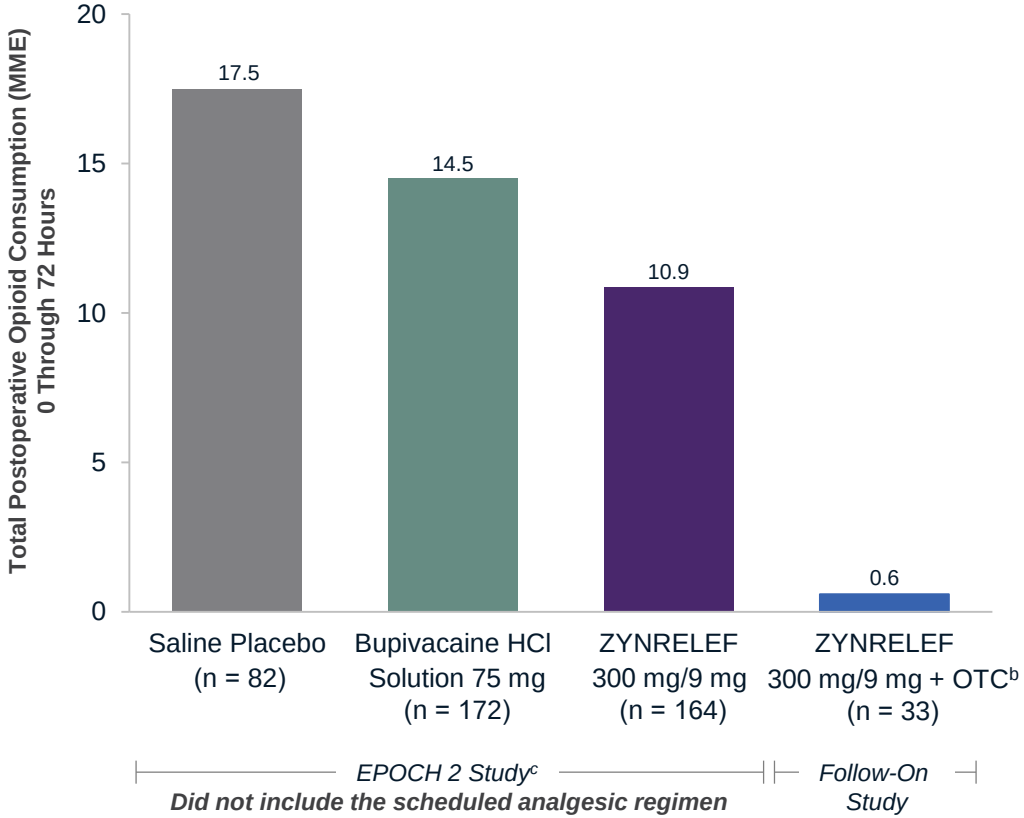
[a]Single-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen. [b]EPOCH 2 had similar entry/exclusion criteria to that of the follow-on study but did not include the scheduled analgesic regimen. [c]EPOCH 2 results reflect reported pain intensity with activity (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]



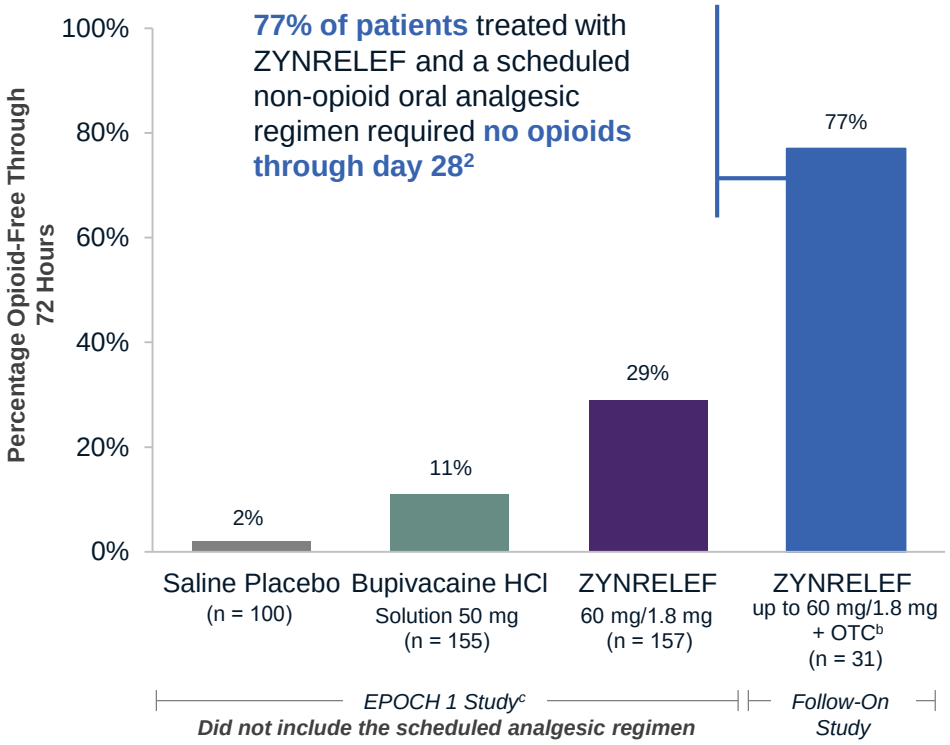
EPOCH 2 Herniorrhaphy/EPOCH 2 Single-Arm[a] Follow-On[3,4]



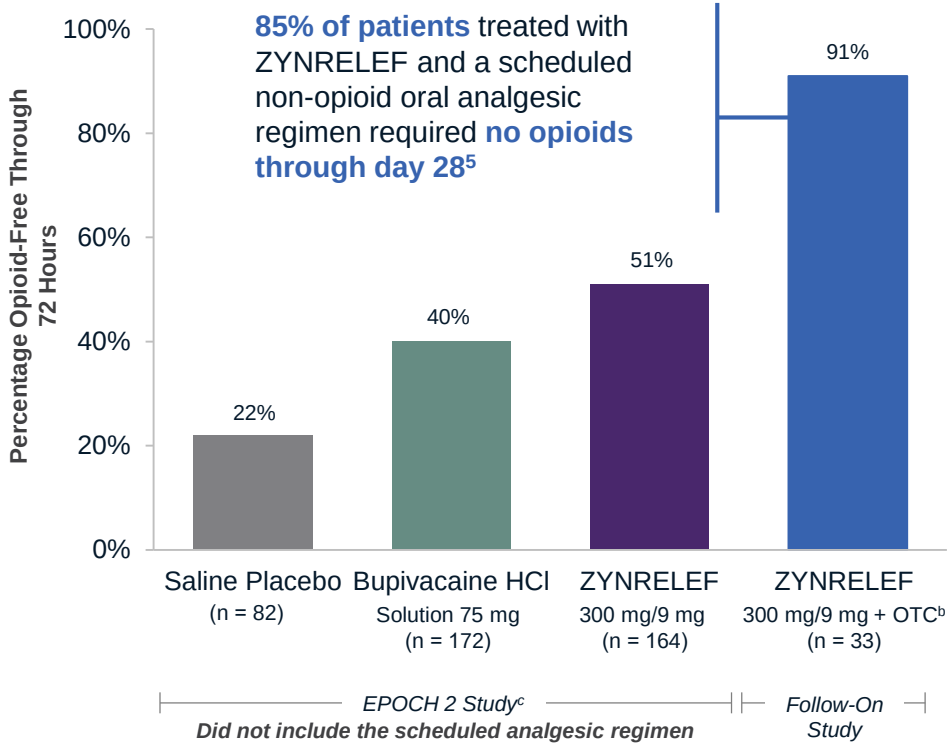
[a]Single-arm, open-label, uncontrolled study. ZYNRELEF was given with a scheduled non-opioid MMA regimen. [b]EPOCH 1 and EPOCH 2 Single-Arm Follow-On studies included a scheduled regimen of readily available oral analgesics (acetaminophen and ibuprofen); Cohort 1 of the EPOCH 2 Single-Arm Follow-On 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.

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[1,2]



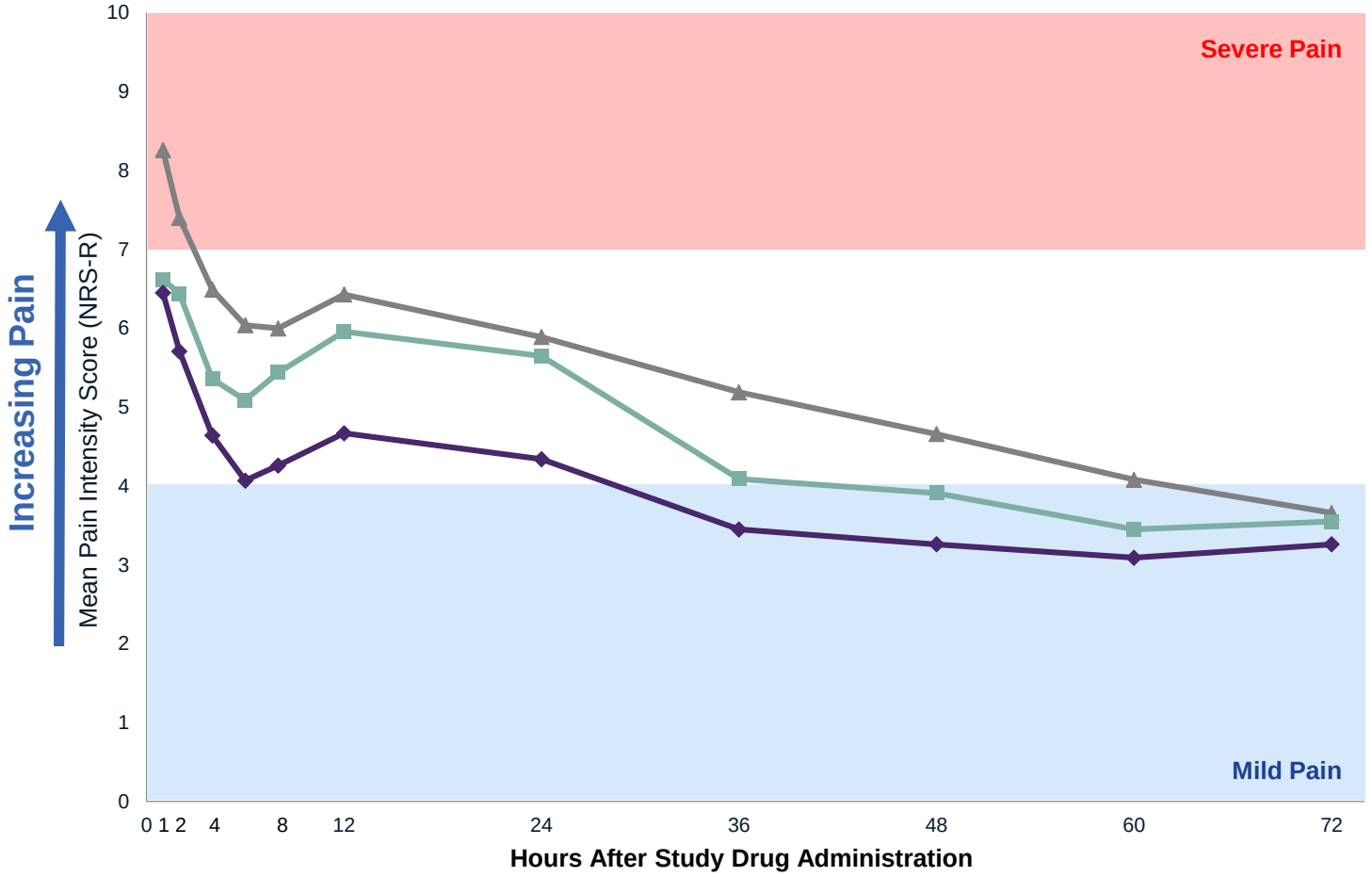
EPOCH 2 Herniorrhaphy/EPOCH 2 Single-Arm[a] Follow-On[3-5]



[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.

EPOCH TKA (Study 209): ZYNRELEF Patients Experienced a Greater Reduction in Pain Scores[a] Versus Bupivacaine Solution Group[1]



ZYNRELEF vs bupivacaine:

$AUC_{0\text{-}24}$ *P* = .0022[b]

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

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

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

[a]As reported without adjustment for opioid rescue medication use.

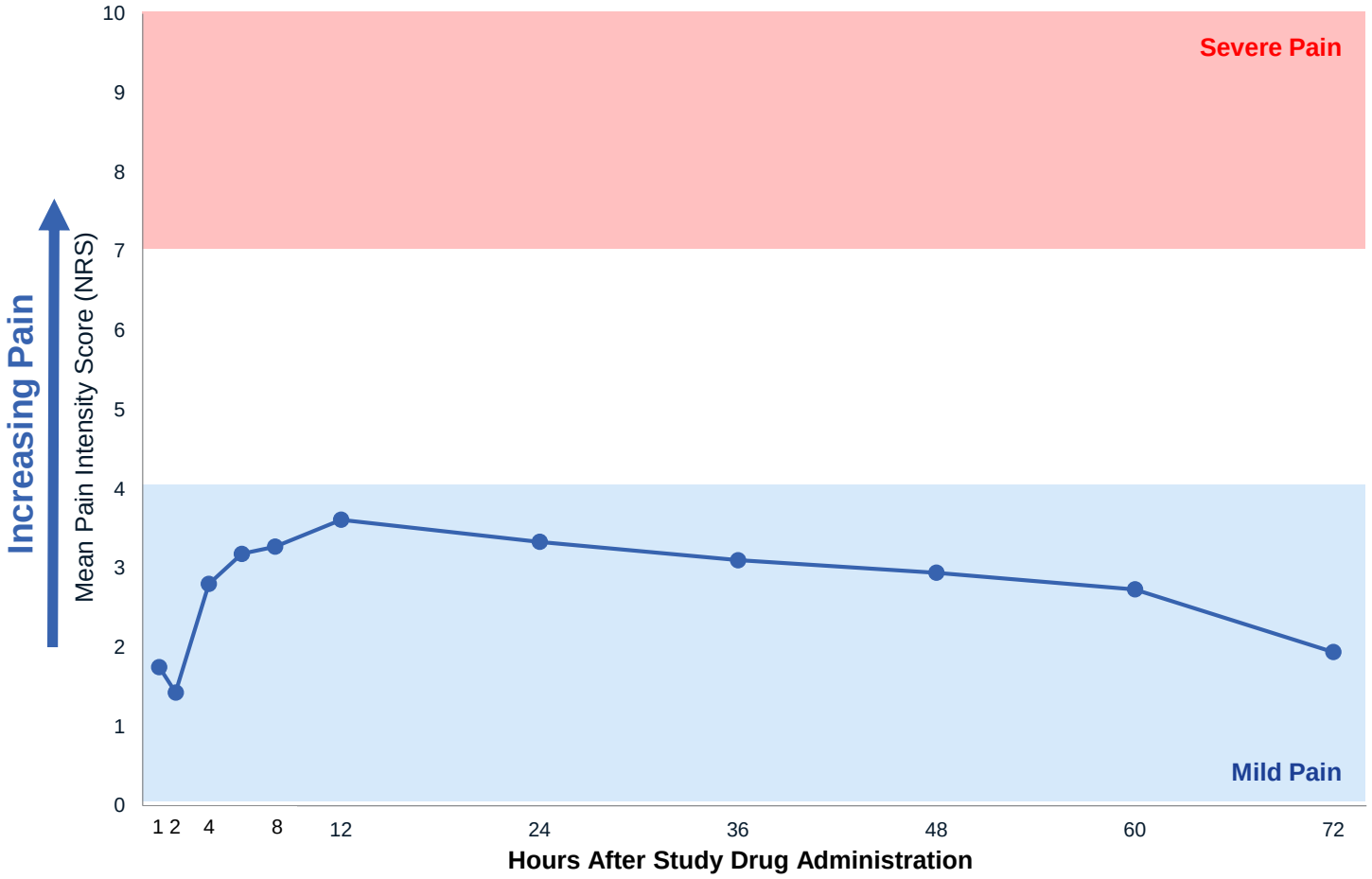
[b]Nominal *P* value not controlled for multiplicity.

Note: 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 of Phase 2b study. Prescribing Information presents pain scores analyzed with adjustment for the analgesic duration of rescue medications.

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.

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.

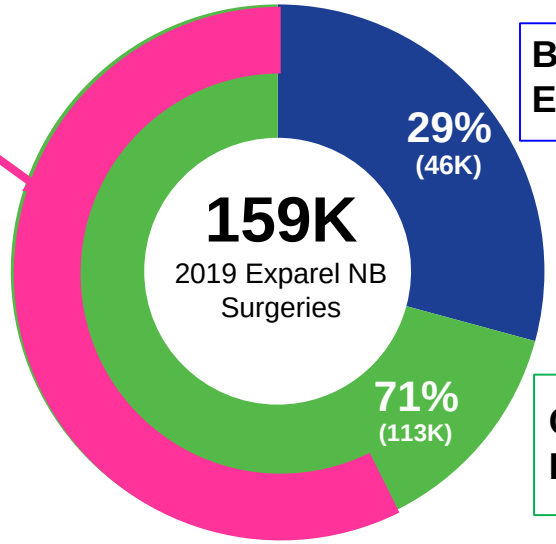
TKA: total knee arthroplasty. **MMA:** multimodal analgesia. **NRS:** Numeric Rating Scale.

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

Majority of Exparel Nerve Block Usage is Off-Label for TKA

Additional EXPAREL Failure in TKA Nerve Block Study Gives ZYNRELEF Important Advantage

81% Exparel NB Off-Label Surgeries were TKA



Brachial Plexus Exparel NB Surgeries

Off-Label Exparel NB Surgeries

Brachial Plexus Exparel NB Surgeries	FY 2019
Rotator Cuff Repair	28,464
Shoulder Arthroplasty	12,227
Fracture - Arm (Surgical)	3,979
Fracture - Shoulder (Surgical)	1,799
Brachial Plexus Exparel NB Surgeries	**46,469**

Off-Label Exparel Nerve Block Surgeries	FY 2019
Knee Arthroplasty (TKA)	91,277
Hip Arthroplasty	4,489
Fracture - Hip (Surgical)	1,880
Bunionectomy & Phalangectomy	1,394
Mastectomy	1,346
Fracture - Ankle (Surgical)	1,268
Hysterectomy - Laparoscopic	1,205
Carpal Tunnel Release	957
*Other Off-Label Surgeries	8,844
Total Off-Label Exparel NB Surgeries	**112,660**

*Other Off-Label Surgeries: Fracture - Leg (Surgical)-858 Mammoplasty-800 Insertion of Breast Tissue Expander-760 Fracture - Foot (Surgical)-651 Cholecystectomy - Laparoscopic-548 Inguinal Hernia Repair - Open-536 Roux-en-Y Gastric Bypass-519 Inguinal Hernia Repair - Laparoscopic-486 Ventral Hernia Repair - Laparoscopic-382 Ventral Hernia Repair - Open-378 Fracture - Hand (Surgical)-335 Nephrectomy-318 Fracture - Knee (Surgical)-310 Female Sterilization-279 Hysterectomy - Open-264 Ankle Arthrodesis-216 Pelvic Floor Reconstruction-206 Gastrectomy-147 Other Hernia Repair - Laparoscopic-136 Elbow Arthroplasty-125 Other Hernia Repair - Open-82 Stoma Creation-81 Laminectomy, Foraminotomy, Discectomy-76 Appendectomy - Open-54 Suburethral Sling-50 Appendectomy - Laparoscopic-49 Abdominoplasty-48 Splenectomy-46 Spinal Fusion-40 Myomectomy - Open-32 Nissen Fundoplication-13 Myomectomy - Laparoscopic-10 Prostatectomy-9

DRG Exparel Procedure Claims 2019 – Exparel NB Surgeries uses a projection methodology

CONCLUSION: WE BELIEVE ZYNRELEF WILL DOMINATE TKA MARKET OF 1,051,000 PROCEDURES/YEAR

Please see **IMPORTANT SAFETY INFORMATION** on pages 32 to 33 and accompanying full Prescribing Information, including **Boxed Warning**.

HERON THERAPEUTICS®
Developing Best-in-Class Medicine. Improving Lives.™

An Extensive Body of Peer-Reviewed Data Will Be Available for Launch

MANUSCRIPTS

EPOCH 1 (301), *RAPM*—May 2019

EPOCH 2 (302), *Hernia*—Aug 2019

MOA (Inflammation and PK/PD), *RAPM—Jan 2020*

TKA (209), *JoA—Oct* 2020

Truven HEOR–opioid naive, *JMCP*—July 2019

Hernia (215), *Surgery* – Sept 2020

Bunion (218), *JAPMA*—Jan 2021

Truven HEOR, persistent users, *JMCP*—Feb 2021

POSTERS & ABSTRACTS

Bunion (202, 208, 301, 218)

HOPE Hernia 1

Hernia (215, 302)

TKA (209, 306)

MOA PK/PD

Truven HEOR

502/PK

211 (Augmentation Mammoplasty)

220 (PK in breast milk and plasma concentrations)

Healthagen TKA/THA opioid use

All Studies—Lack of LAST (C_{max})

All Studies—Max Dose and Release Rates

HOPE Algorithm, HOPE Regimen and Patient Satisfaction

Safety with NSAID containing MMA in the elderly

Accepted for 2021 Congresses:

Bone Healing

Safety with NSAID containing MMA

HERON THERAPEUTICS

The Commercialization of ZYNRELEF

Advancing Postoperative Pain Management

May 2021

HERON THERAPEUTICS®
Developing Best-In-Class Medicine. Improving Lives.™

ZYNRELEF is Launching with an Unprecedented Value Proposition

- FDA Indicated Label Market includes **> 2.1 million** procedures
  - ~ 1.3 million (60%) of indicated procedures are in the outpatient setting (HOPD & ASC)
  - ZYNRELEF additional economic advantages in ~ 650,000 (50%) of outpatient procedures
    - ~ 492k (38%) of indicated outpatient procedures are eligible for 340B pricing
    - ~ 298k (23%) of indicated outpatient procedures are eligible for C-code pass-through status reimbursement for Medicare patients (140.6k patients are overlapping with the 492k eligible 340B patients)
- ZYNRELEF is launching with a 22% to 28% WAC discount to Exparel which will be beneficial under the surgical bundle payment model with commercial payers & Medicare inpatient procedures
- Additional ZYNRELEF benefits will be realized by customers through GPO contracts & FLW prime vendor agreements
- We believe these significant economic benefits will accelerate access for ZYNRELEF which is critical to a fast start during our launch

ASC: ambulatory surgical center. **HOPD:** hospital outpatient department. **GPO:** Group Purchasing Organization **FLW:** Full Line Wholesaler.

Positioning

The first and only extended-release, dual-acting local anesthetic (DALA), keeping more patients out of severe pain and opioid-free for 72 hours after surgery[1-3]

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.

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Developing Best-in-Class Medicine. Improving Lives.™

ZYNRELEF Offers Superior Clinical Value Over Bupivacaine, Not Demonstrated with Exparel

Exparel Share is an early opportunity for ZYNRELEF

- > $400M in sales
- Exparel has never demonstrated head-to-head superiority to bupivacaine
- Exparel has efficacy challenges beyond 24 hours
- Surveyed pharmacy directors state that they would provide better access to ZYNRELEF than to Exparel[6]

	ZYNRELEF	Exparel
Extended-Release Local Anesthetic[1]	✓	✗
Overcomes Challenges of Inflammation at Surgical Site[2]	✓	✗
Pain Reduction Through 72 Hours vs Bupivacaine[1,3-5]	✓	✗
Superior Pain Reduction vs Bupivacaine[1,3,4]	✓	✗
Greater Reduction in Severe Pain vs Bupivacaine[3-4]	✓	✗
Significant Increase in Opioid-Free Patients vs Bupivacaine[1,3,4]	✓	✗
Greater Decrease of Opioid-Related AEs vs Bupivacaine[3]	✓	✗
Needle-free Application[1]	✓	✗

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.** Viscusi E, Minkowitz H, Winkle P, et al. *Hernia*. 2019;23(6):1071-1080. **4.** Viscusi E, Gimbel JS, Pollack RA, et al. *Reg Anesth Pain Med*. 2019;44(7):700-706. **5.** Lachiewicz PF, Lee G-C, Pollak R, et al. *J Arthroplasty*. 2020;35(10):2843-2851. **6.** DRG Pharmacy Director Surveys.

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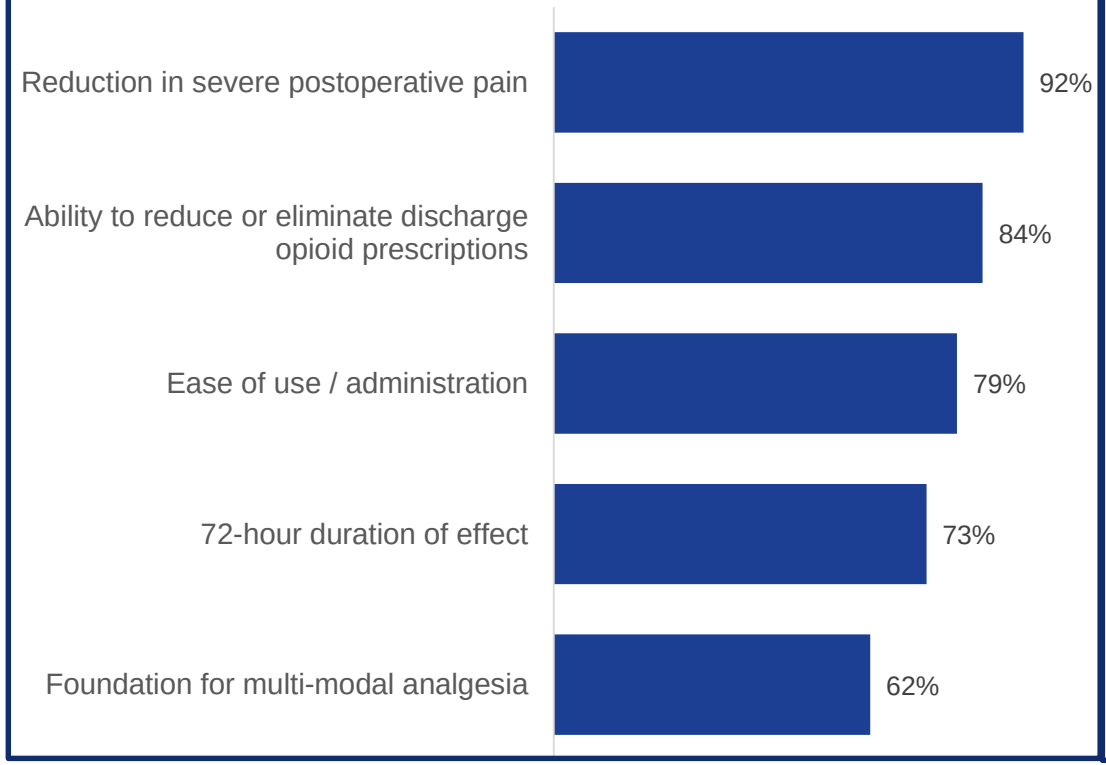
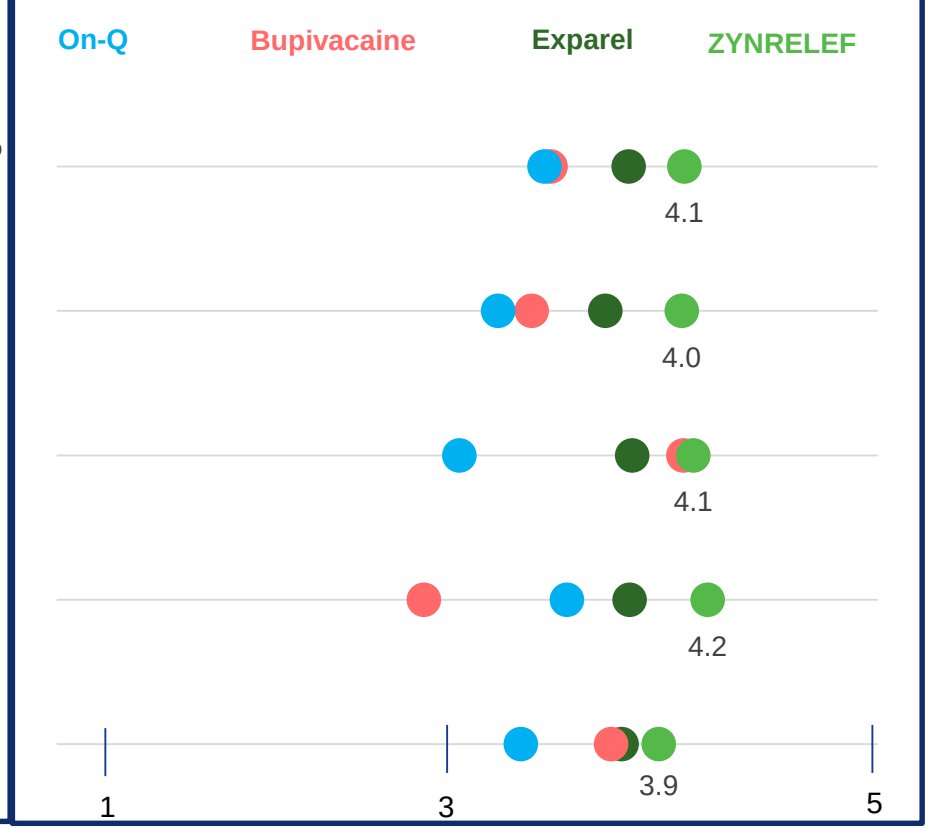
ZYNRELEF Is Well Positioned on Core Drivers to Create Fast Access and Early Uptake

Importance of Core Attributes in Selecting a LA
Top 2 Boxes



Mean Product Rating on Core Attributes
1-5 Scale



Source: Company-sponsored ATU Study July 2020 – Survey of 386 surgeons, anesthesiologists, pharmacists, NP/Pas of potential use of an approved product with the attributes for which ZYRELEF was developed

Please see **IMPORTANT SAFETY INFORMATION** on pages 32 to 33 and accompanying full Prescribing Information, including **Boxed Warning**.

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Targeting ~2.1M Procedures at Launch With $450M Potential Value With Data Supporting Fast Uptake with Influential Specialties

Indicated Launch Targets		
Inguinal Hernia 617,100	**Bunion** 481,300	**TKA** 1,051,000
Closely-Related Procedures Without Promotion		
Other Hernia 831,000	Other Foot & Ankle 197,900	THA 630,000
Potential Combined Opportunity		
Total 1,448,100	**Total 679,200**	**Total 1,681,000**

- Orthopedic and general surgeons account for 10.6M procedures or 76% of the 14M high value market procedures
- Orthopedic and general surgeons account for 82% of Exparel market utilization
- Orthopedic surgeons are heavy influencers (P&T, new drugs, profitability) across all settings of care

Reference: DRG Claims Analysis, 2019 / May 2021 DRG USPI Market Research. High value market procedures selected on severity and duration of pain and opioid use validated thorough medical review

ZYNRELEF's Unprecedented Value Proposition

ZYNRELEF Go-to-Market Strategy Comparison

	ZYNRELEF	Exparel
Lower Acquisition and Average Cost to Support Broad Access	✓	✗
340B Pricing	✓	✗
Pass-Through Status: Separate Reimbursement in HOPD*	✓	✗
Positive Net Cost Recovery	✓	✗
Full-Line Wholesaler Distribution	✓	✗
GPO Contracting	✓	✗

*Medicare Reimbursement only, pass-through status is for 3 years.
GPO = Group Purchasing Organization. **HOPD** = Hospital Outpatient Department.

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ZYNRELEF Reimbursement & Pricing Creates Economic Benefits Across All Settings of Care

Medicare: ZYNRELEF Is Reimbursed Separately in HOPD and ASC

Setting of Care	At Launch *C9399*	3-Year Pass-Through[a] *Product-specific C-code /J-code*
Inpatient	Diagnosis-Related Group (DRG) Payment	
HOPD	95% of AWP	ASP + 6%[c]
HOPD (304B)	95% of AWP	ASP + 6%[c]
ASC	95% of AWP	ASP + 6%[c,d]

Heron will apply for a C-Code with expected grant date of October 1, 2021

Commercial Reimbursement Varies by Payer

- Heron will apply for a J-code to facilitate separate reimbursement with expected grant date of January 1, 2022
- Like all new products, until CMS assigns a permanent code, commercial payers will require a miscellaneous code (J3490 or C9399) for ZYNRELEF
- Heron Connect helps customers navigate coding and reimbursement for ZYNRELEF

a. Heron will apply for transitional pass-through status for ZYNRELEF. Typically, pass-through status is for 3 years. **b.** Exparel (bupivacaine liposome injectable suspension) is a trademark of Pacira Pharmaceuticals, Inc. **c.** ZYNRELEF will be reimbursed at WAC + 3% until ASP is established. **d.** Effective January 1, 2019, ASCs are reimbursed at ASP + 6% for non-opioid postoperative pain management drugs, like ZYNRELEF, when administered during a surgical procedure.
HOPD: hospital outpatient department. **AWP:** average wholesale price. **ASP:** average selling price. **ASC:** ambulatory surgical center. **WAC:** wholesale acquisition cost.

ZYNRELEF's Significant Economic Benefits Designed to Support Rapid Share Conversion and Broad Access

ZYNRELEF	WAC	340B
400 mg/12 mg	$267.50	$203.57
200 mg/6 mg	$135.50	$103.12

Exparel	WAC	340B
266 mg (20 mL)	$344.20	$344.20
133 mg (10 mL)	$189.37	$189.37

ZYNRELEF Savings vs Exparel

WAC $/unit	WAC %	340B $/unit	340B %
~ $77	22%	~$141	41%
~ $54	28%	~$86	46%

Medicare NCR By Site of Care†

	NCR 340B	NCR HOPD	ASC
ZYNRELEF 400 mg/12 mg	$71.53	$10.37	ASP +6%
Exparel 266 mg	($344.20)	($344.20)	ASP +6%
ZYNRELEF 200 mg/6 mg	$34.50	$3.45	ASP +6%
Exparel 133 mg	($189.37)	($189.37)	ASP + 6%

ZYNRELEF Economic Benefit vs. Exparel*

- 340B accounts: >$415 (400 mg to 266 mg) and >$223 (200 mg to 133 mg)
- HOPD accounts: >$354 (400 mg to 266 mg) and >$192 (200 mg to 133 mg)
- Research has shown all customer segments were more sensitive to and favored acquisition cost over reimbursement**
- Based on expected use of two vials at launch and 340b discounts, average price projected to be $225

Does not include additional cost of bupivacaine to admix with Exparel to achieve efficacy

*Comparing WAC acquisition cost to NCR reimbursement under Medicare/Exparel NCR assumes ASCs purchasing at WAC.
†Medicare NCRs are shown based on estimated ASP reimbursement for ZYNRELEF and Exparel Q2'21 published ASP reimbursement.
WAC: wholesale acquisition cost. NCR: net cost recovery. HOPD: hospital outpatient department. ASC: ambulatory surgical center.
**DRG Research Pricing Research 2018 and Mock P&T Research 2019

We Expect the Economic Benefits in ~ 650k (31%)* of the 2.1M FDA Indicated Procedures Will Support Rapid Access for ZYNRELEF

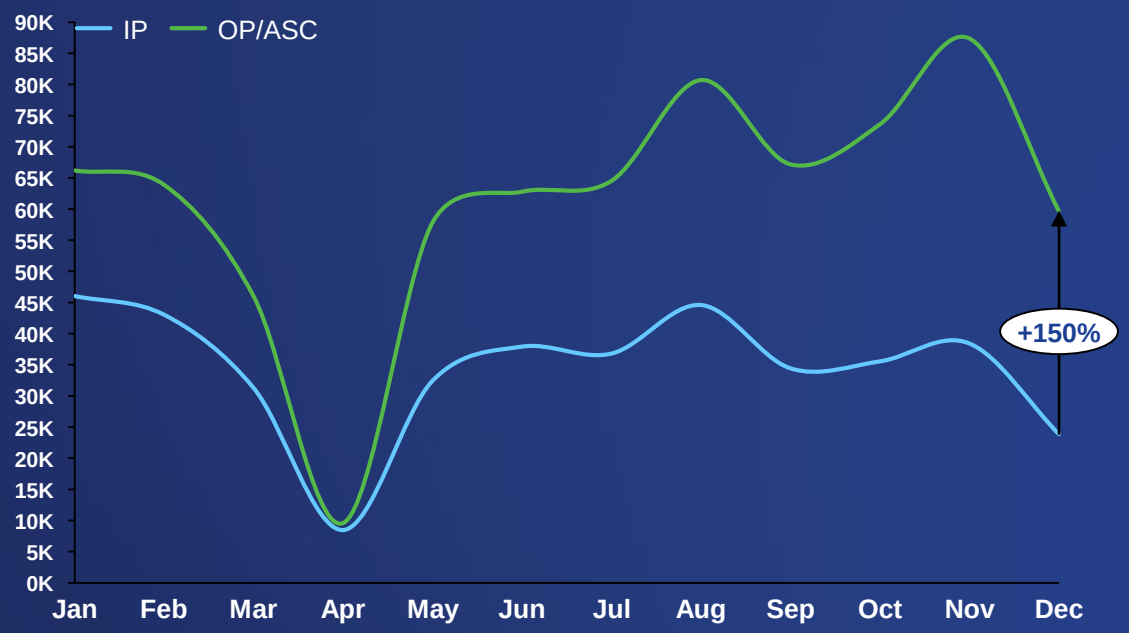
2019 Claims Data	Open Inguinal Hernia	Bunion	TKA	Totals
Indicated Procedures (000s)	617.0	481.3	1,051.0	2,149.3
% Hospital Outpatient	66.1%	41.5%	24.4%	40.2%
Procedures HOPD (000s)	407.8	199.7	256.4	864.0
% Medicare HOPD Patients	21.3%	20.3%	34.8%	10.1%
HOPD C-code Passthrough reimbursement (000s)	86.9	40.5	89.2	216.7
% 340B HOPD Patients	60.4%	54.6%	53.1%	22.9%
340B Pricing (000s)	246.3	109.1	136.2	491.6
% ASC Patients	22.5%	50.0%	4.3%	19.8%
ASC Procedures (000s)	138.8	240.7	45.2	424.7
% Medicare Patients	21.3%	20.8%	4.0%	3.8%
ASC C-code Passthrough reimbursement (000s)	29.6	50.1	1.8	81.4

HOPD: hospital outpatient department. 1. **Reference:** 2019 DRG Claims Data
*140.6k HOPD C-code passthrough patients are overlapping with the 491.6k eligible 340B patients.

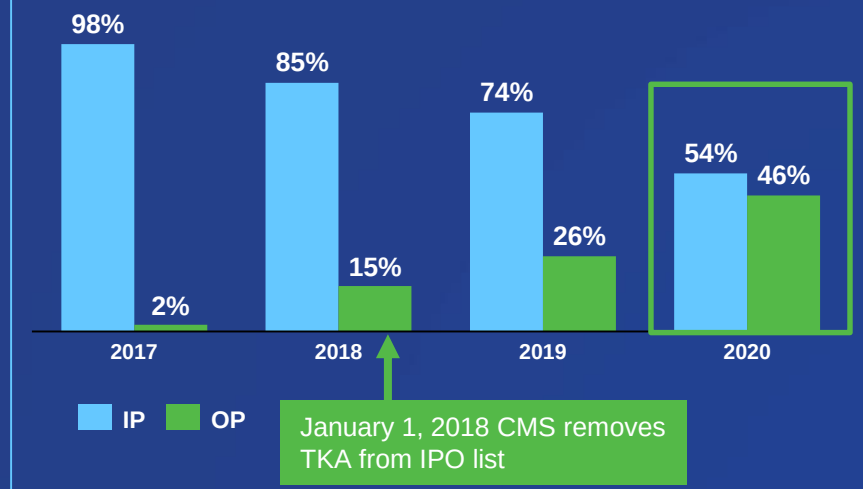
We believe current TKA procedures are much higher in the ASC Setting of Care

- Claims data in the previous slide were from 2019 – in January 2020, CMS allowed TKA in ASCs
- CMS has expanded the ASC-Covered Procedures List including Total Hip Arthroplasty
- CMS has eliminated their exclusion criteria leaving the determination of appropriate site of care to the physician

Launch Procedure Outpatient Shift in 2020



TKA Outpatient Shift



Reference: Surgical procedure volume data, 2017-2020. New York, NY: LexisNexis; 2021.

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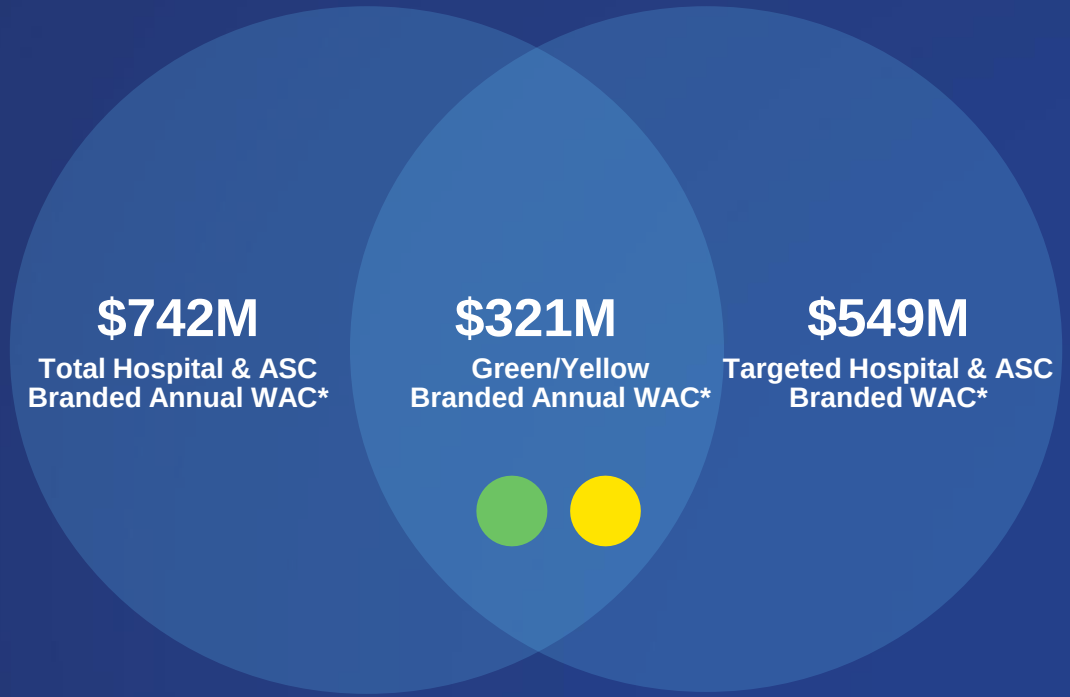
Who Will Determine Speed and Magnitude of Uptake?

- ZYNRELEF's superior clinical profile and lower price will drive acceptance by P&T Committees
- 340B pricing provides substantial economic benefits for ~ 492k procedures
- Medicare coverage under C-code in HOPD (~ 217k procedures) for three years and indefinitely in the ASC (~ 81k) provides strong incentive for use
- Commercial insurance does not reimburse outside the surgical bundle thus not involved **BUT** acquisition cost plays significant role with pharmacy directors
- Heron commercial organization will drive formulary acceptance then pull-through with surgeons (i.e., preference cards)

58% of Prioritized Target Accounts are Fast Moving



	Accts	340B %	high value market Procedures	Indicated Launch Procedures	Branded Utilization
Hospitals	705	*53%*	4.6M	1.2M	$309M
ASC	398	*0%*	414K	144K	$13M

0-3 Months
When will the account order post commercial availability of ZYNRELEF

4-8 Months
When will the account order post commercial availability of ZYNRELEF

*Includes Exparel and Offirmev. **ASC:** ambulatory surgical center. **WAC:** wholesale acquisition cost.

References: 1. Symphony Drug Market – 2020. **2.** LexisNexis Procedure Data August 2019 YTD.

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Important Safety Information for Patients

Important Safety Information

ZYNRELEF contains an NSAID (non-steroidal anti-inflammatory drug), a type of medicine which:

- **can increase the risk of a heart attack or stroke that can lead to death. This risk increases with higher doses and longer use of an NSAID.**
- **cannot be used during heart bypass surgery**
- **can increase the risk of gastrointestinal bleeding, ulcers, and tears.**

ZYNRELEF should also not be used:

- if you are allergic to any components of ZYNRELEF, aspirin or other NSAIDs (such as ibuprofen or naproxen), or have had an asthma attack, hives, or other allergic reaction after taking any of these medicines.
- as a paracervical block, during childbirth.

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Important Safety Information for Patients (cont)

The most common side effects of ZYNRELEF are constipation, vomiting, and headache.

The medicines in ZYNRELEF (a local anesthetic and an NSAID) can affect the nervous and cardiovascular system; may reduce the effects of some blood pressure medications; should be avoided if you have severe heart failure; may cause liver or kidney problems, a rare blood disorder or life-threatening skin or allergic reactions; may harm your unborn baby if received at 20 weeks of pregnancy or later; and may cause low red blood cells (anemia).

Tell your healthcare provider about all your medical conditions and about all the medicines you take including prescription or over-the-counter medicines, vitamins, or herbal supplements to discuss if ZYNRELEF is right for you.

Talk to your healthcare provider for medical advice about side effects. Report side effects to Heron at 1-844-437-6611 or to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

The information provided here is not comprehensive.

Please see full Prescribing Information, including Boxed Warning

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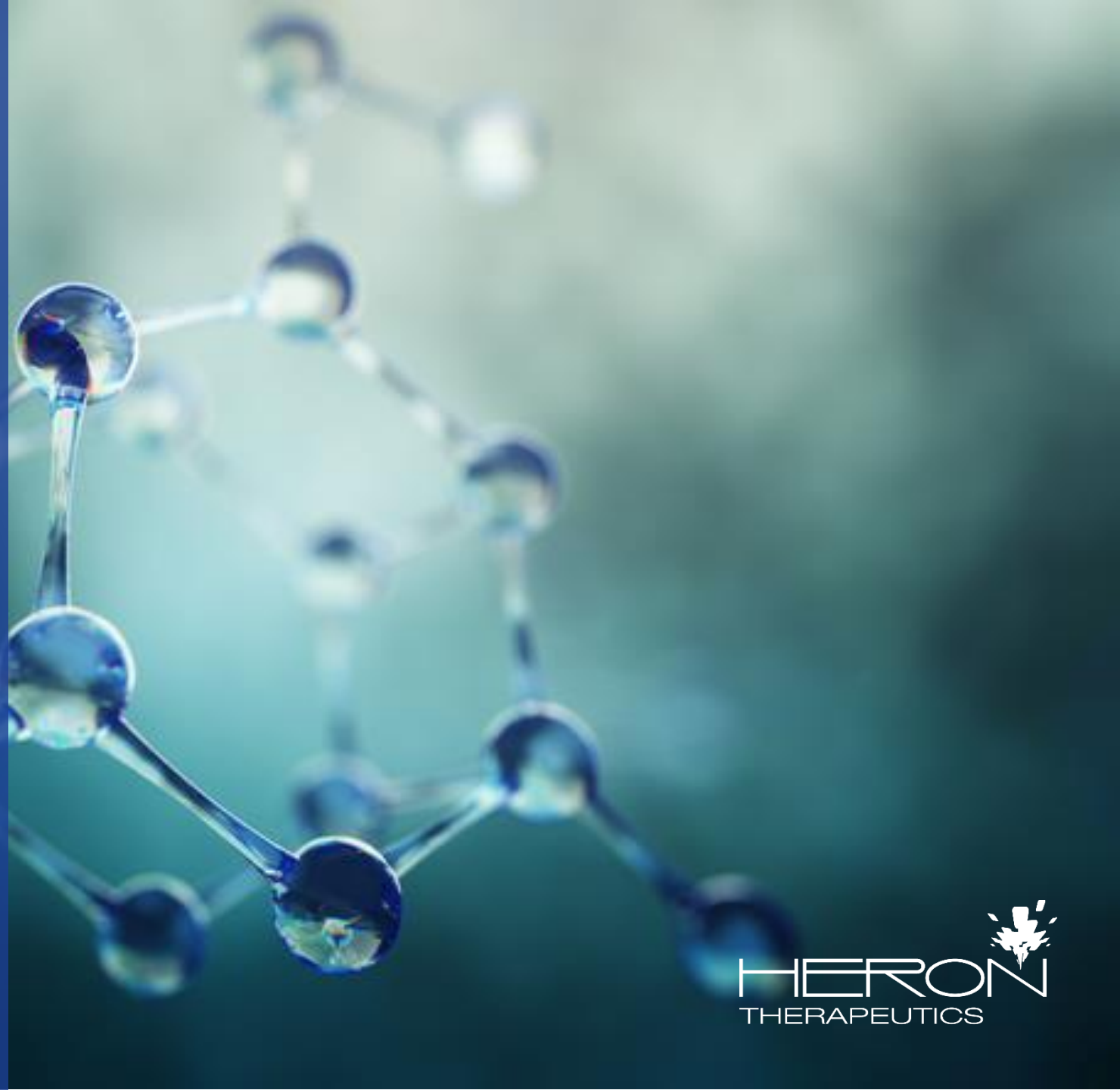
CINV Franchise Q1’21 Review



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Review of Q1’21 CINV Market Dynamics

COVID-19 Impact on Clinics

- Year-over-year (March – Nov. 2020): cancer screening procedures declined **~ 25%** on average[1]
  - Mammogram, colon, lung & prostate

- Year-over-year (March – Nov. 2020): new & established patient visits declined **~ 35%** on average[1]

- Q1’21 weekly average anti-emetic units declined vs. Q4’20[2]
  - 5HT3 units declined **14%**
  - NK-1 units declined **3.7%**

CINV Competitive Factors

Two unexpected events occurred in Q1’21:

- IV Akynzeo ASP reimbursement of $696 in Q1’21 vs. $375 in Q3’20 allowed for greater contracting value[3]
  - Q2’21 ASP reimbursement drops to $641[3]
  - Unit volume past year: 22k – 27k per QTR[2]
- IV fosaprepitant arbitrage continued for another quarter with drop in acquisition costs for generic down to ~$30 compared to projected $40 leading to improved NCR with $63 ASP reimbursement in Q1’21[3]
  - Q2’21 ASP reimbursement drops to $51[3]

Sources [1]: Avalere Health & COA analysis of Inovalon Provider Clearinghouse data published online ahead of publication in the November issue of JCO
[2]: IMS DDD Weekly 3-26-2021 [3]: All ASP reimbursement based on CMS quarterly files

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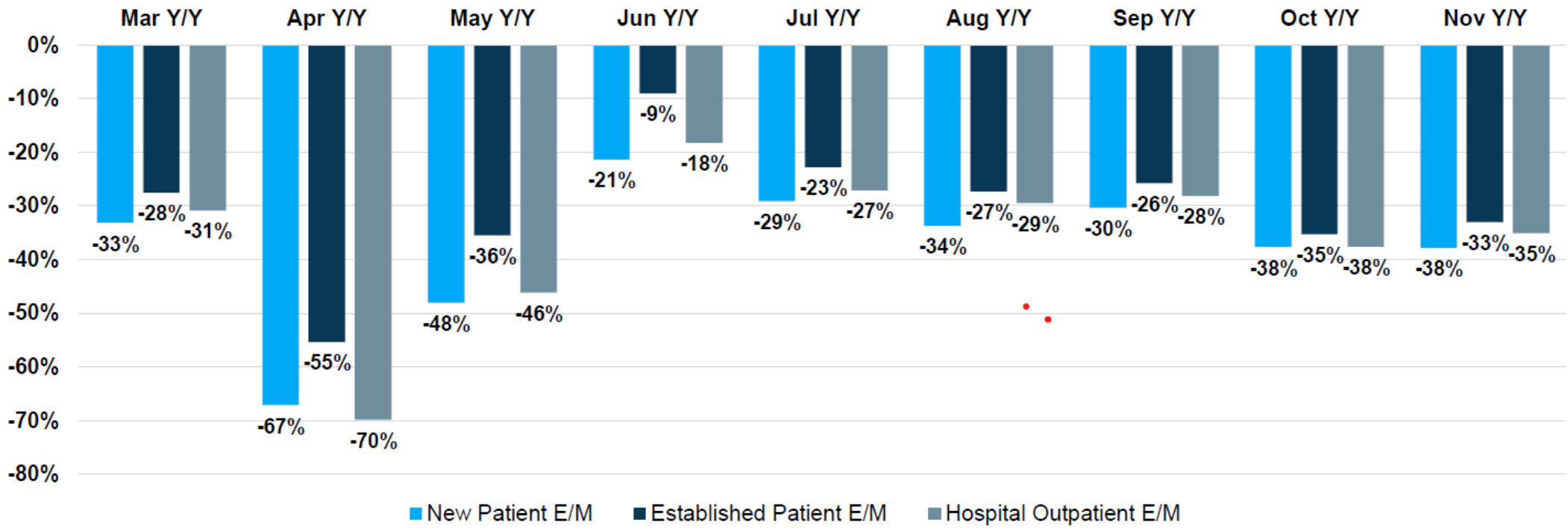
Barriers to Care Caused by COVID-19 Complications Have Resulted in Significant Reductions in Patient Visits

Relative Change in Billing Frequencies for Cancer-Related E/M Services

(March-November 2019 vs. March-November 2020)



The relative change in utilization was higher for new patient E/M than established patient E/M, which could reflect patient reluctance to visit providers due to COVID-19 concerns, as well as lowered rates of screening

Avalere Health and COA analysis of Inovalon Provider Clearinghouse data published online ahead of publication in the November issue of JCO Clinical Cancer Informatics. Supported, in part, by Amgen, BMS, Daiichi-Sankyo, Eisai, Janssen, Genentech & Pfizer
Note: Claims on average represent 5-7% of Medicare FFS nationally and include CMS-1450 claims from Institutional providers and CMS-1500 claims from Non-Institutional or Professional providers

E/M – Evaluation and management

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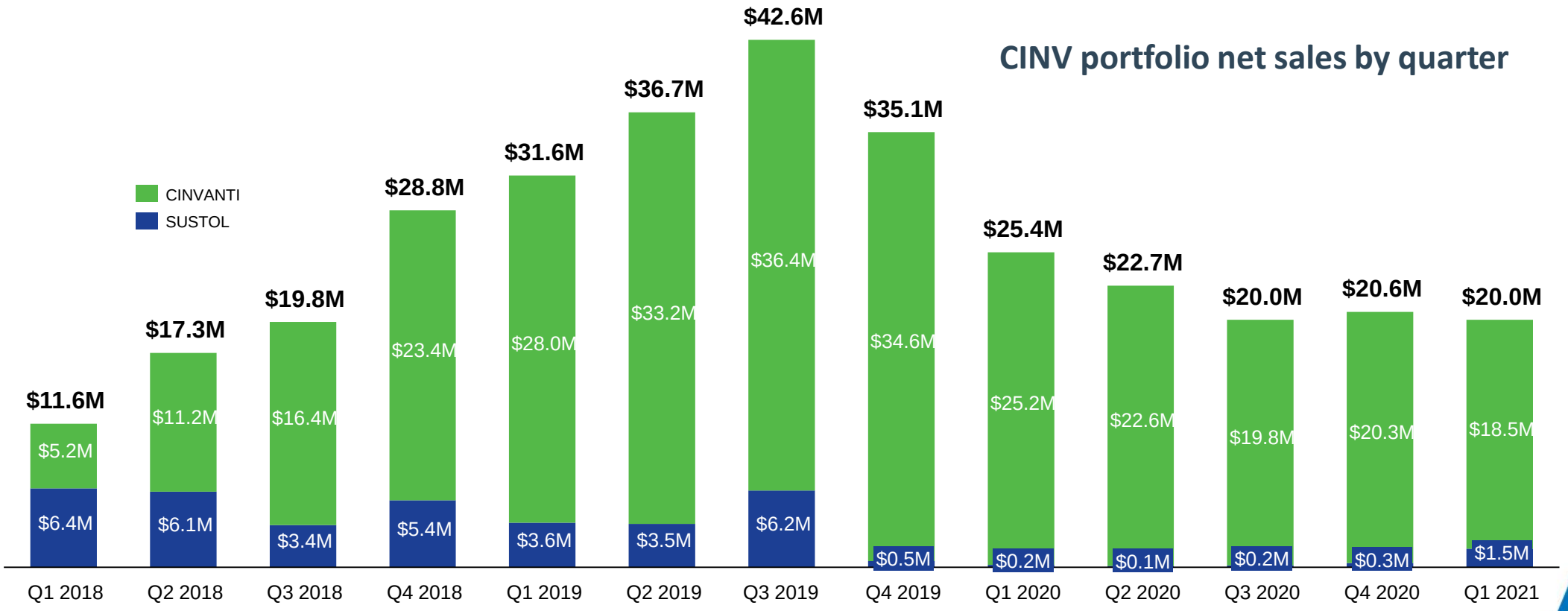
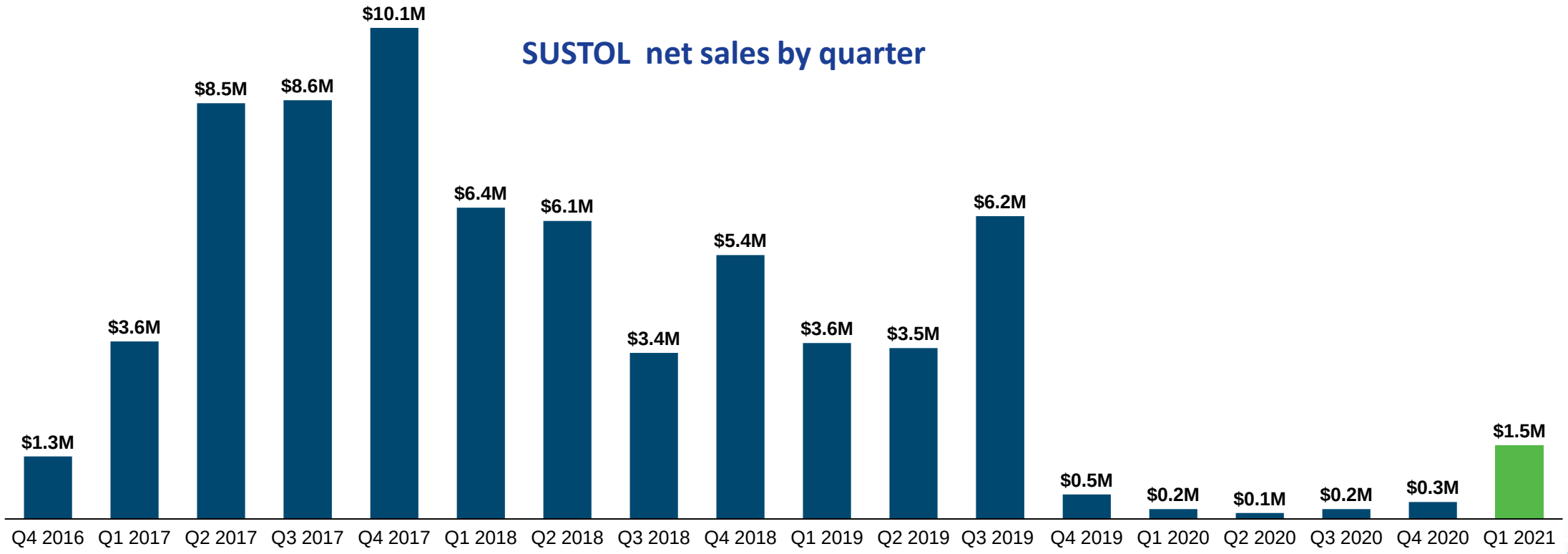
Even with a 35% Decline in Patient Visits in Q4, Heron's CINV Portfolio Overall was Flat

- CINVANTI units are expected to increase in Q2 and build throughout 2021
- SUSTOL sales began to rebound after reinstating promotion & contracting in Q1



Note: SUSTOL sales from Q4 2016- Q4 2017 of $32.05M not shown in graph

SUSTOL Refresh Program Completed & Return to Growth in Q1



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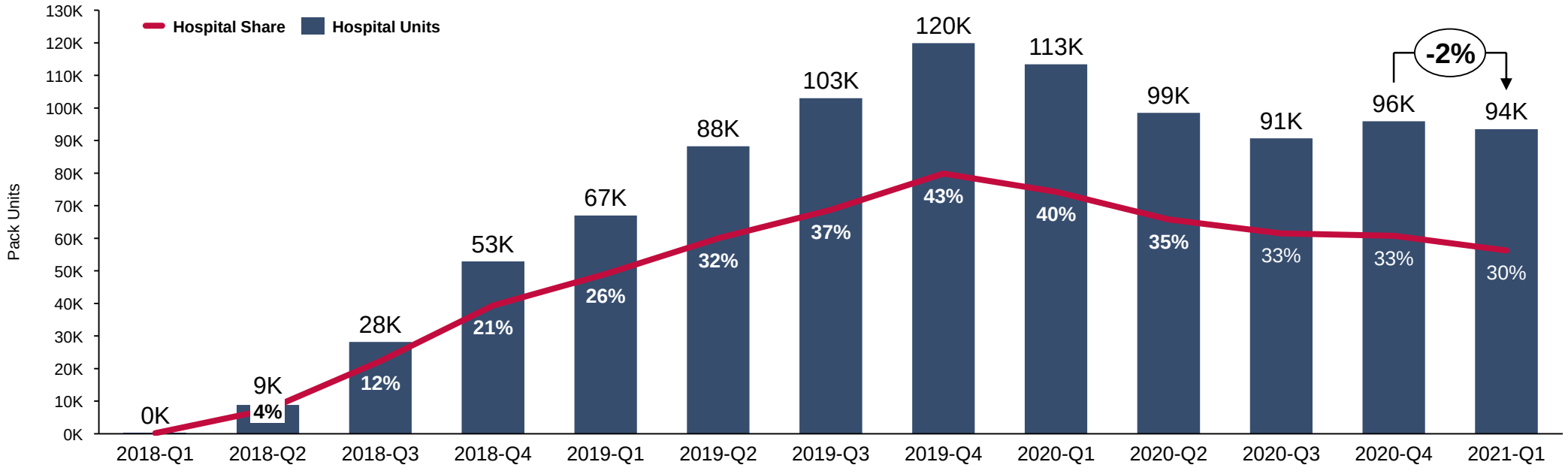
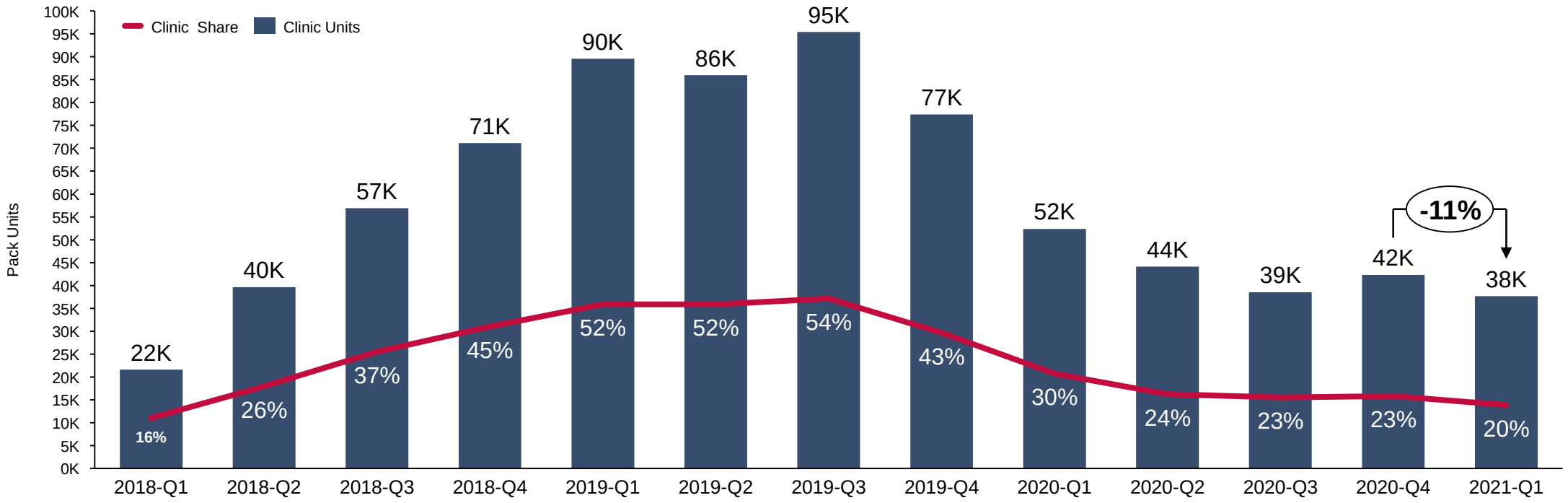
CINVANTI – Hospital Units Generally Maintained During the Past Year Despite Significantly Lower Acquisition Cost of Generic Emend IV



SOURCE:867 4.21.21, : IMS DDD 4.2.21

CINVANTI – Clinic Units have Declined Due to the Emend IV Generic Arbitrage & Offer Significant Potential for Growth in 2021



SOURCE:867 4.21.21, : IMS DDD 4.2.21

HTX-019 for Postoperative Nausea and Vomiting (PONV)

HTX-019 is an investigational new drug for PONV and not approved by the FDA

HTX-019 for PONV

- PONV is a large market ~20x the size of CINV
- HTX-019 has significant potential advantages over oral aprepitant and fosaprepitant
- IND active, BE to oral aprepitant demonstrated and 505(b)(2) NDA for PONV prevention planned for Q4 2021
- Several hundred million dollar a year potential market opportunity, taking the majority of the oral aprepitant market and use in high risk procedures

HTX-019 is an investigational new drug for PONV and not approved by the FDA

Aprepitant Efficacy – Large Differential in Vomiting Episodes Compared to Ondansetron*

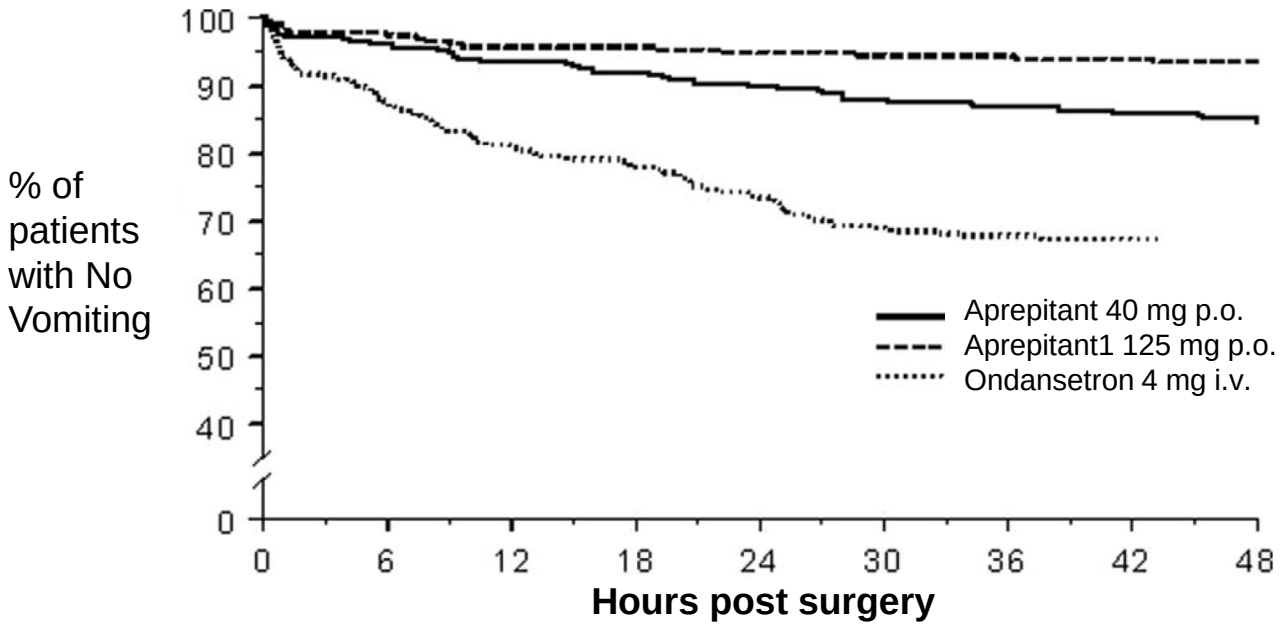


Figure 5. Kaplan-Meier curves for the time to first vomiting during the 48 h following surgery. The time to first vomiting was delayed by aprepitant; *P* 0.001 based on the log-rank test.

Aprepitant delayed the time to first vomiting episode compared with ondansetron.

***Published results from Gan TJ, et al. *Ambul Anesth*. 2007; 1082-89.

HTX-019 is an investigational new drug for PONV and not approved by the FDA

2020 Cochrane Meta-Analysis Concluded That Aprepitant is the Most Effective Drug for PONV*

Out-comes	Effects and confidence in the estimate of effects (network meta-analysis)											
	Aprepitant*		**Ramosetron***		**Granisetron***		**Dexamethasone***		**Ondansetron***		**Fosaprepi-tant***	**Droperidol***
Vomiting (or dry retching) within 24 hours postoperatively												
Total studies: 282; total participants: 50,812; number of treatments: 65 (36 drug combinations, 28 single drugs, placebo)												
Place-bo (com-para-tor) 300 per 1000[a] (30%)	**RR 0.26** (0.18 to 0.38) Net-work esti-mate	222 few-er per 1000 (246 fewer to 186 fewer)	**RR 0.44** (0.32 to 0.59) Network estimate	168 fewer per 1000 (204 few-er to 123 fewer)	**RR 0.45** (0.38 to 0.54) Network estimate	165 fewer per 1000 (186 few-er to 138 fewer)	**RR 0.51** (0.44 to 0.57) Network estimate	147 fewer per 1000 (168 few-er to 471 fewer)	**RR 0.55** (0.51 to 0.60) Net-work esti-mate	135 few-er per 1000 (147 fewer to 120 fewer)	**RR 0.06** (0.02 to 0.21) Net-work esti-mate	282 fewer per 1000 (294 few-er to 237 few-er)	**RR 0.61** (0.54 to 0.69) Network estimate	117 few-er per 1000 (138 few-er to 93 fewer)
	⊕⊕⊕⊕ **High** Confidence in network estimate		⊕⊕⊕⊕ **High** Confidence in network estimate		⊕⊕⊕⊕ **High** Confidence in network estimate[1]		⊕⊕⊕⊕ **High** Confidence in network estimate[1]		⊕⊕⊕⊕ **High** Confidence in network esti-mate[1]		⊕⊕⊕⊖ **Moder-ate** Confidence in network esti-mate due to incoherence		⊕⊕⊖⊖ **Moderate** Confidence in net-work estimate due to publication bias and heterogeneity[1,2]	

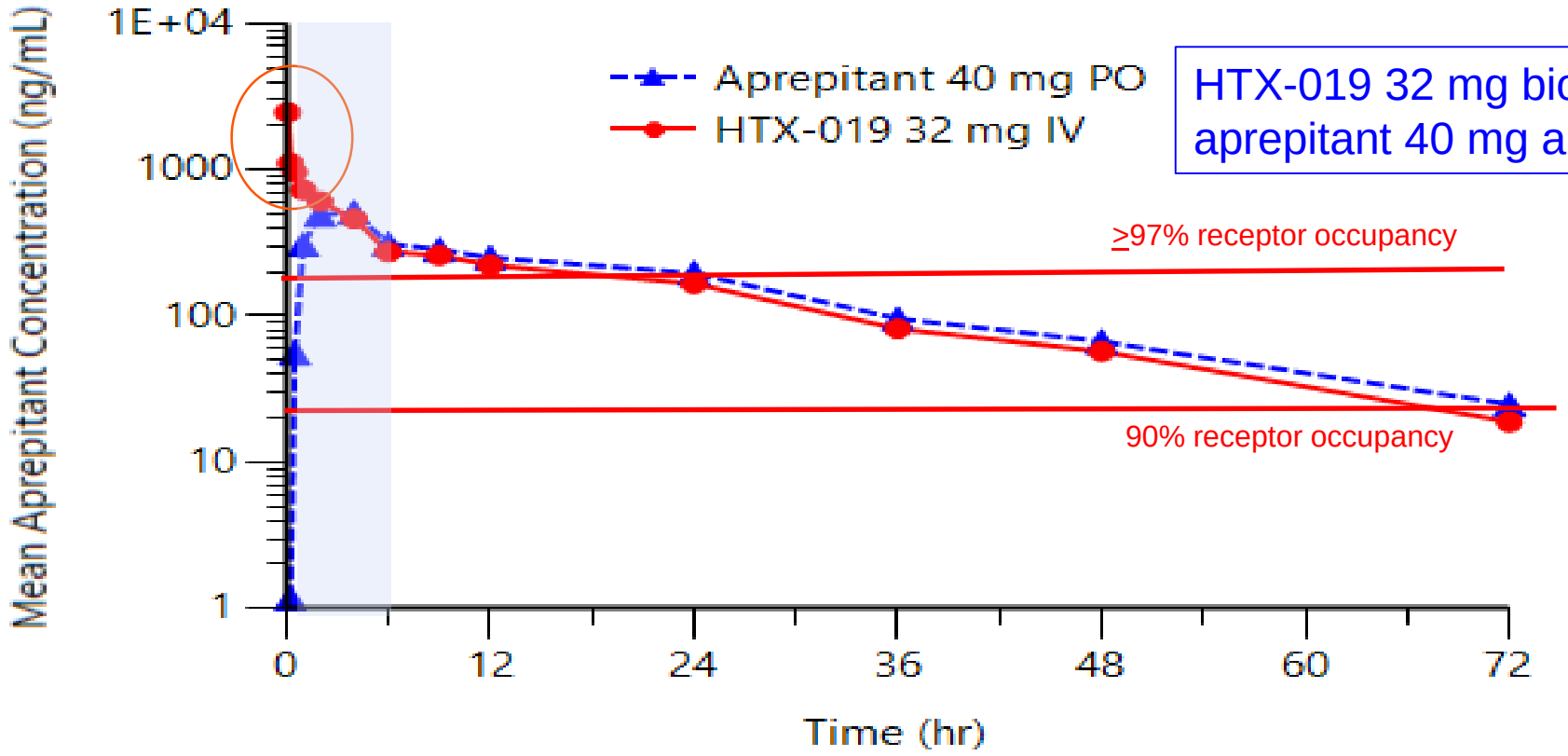
Approximately 100 fewer patients vomiting per 1000

*Weibel S, Rücker G, Eberhart LHJ, Pace NL, Hartl HM, Jordan OL, et al. *Cochrane Database of Systematic Reviews*. 2020

HTX-019 is an investigational new drug for PONV and not approved by the FDA

100% Receptor Occupancy Should Occur Much Faster With HTX-019 IV Push Than Aprepitant Oral

Very high peak levels should quickly drive drug into the brain with 100% receptor occupancy during high risk period



HTX-019 32 mg bioequivalent to oral aprepitant 40 mg approved for PONV

HTX-019 is an investigational new drug for PONV and not approved by the FDA

PONV Market is >20X the size of the CINV Market

PONV ~53M Treatments vs. ~2.5M CINV Treatments

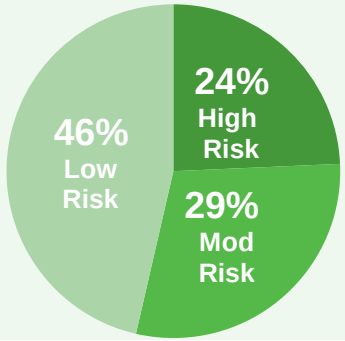
Patient Population & Market Size

Diagnostics

~26M

US Diagnostic Procedures at Risk of PONV in 2020

Patients by PONV Risk



Surgeries

~39M

US Surgical Procedures at Risk of PONV in 2020

- **Approximately 65M diagnostic and surgical procedures are at risk of resulting in PONV in the US**
- **More than half of these patients are at moderate to high risk of PONV**

Prophylaxis Patients

~35M

PONV Prophylaxis Patients in 2020

PONV Rescue Patients

~13M

PONV Rescue Patients in 2020

~5M

2nd Line Rescue in 2020

Source: *PONV quantitative survey DRG June 2020*

HTX-019 is an investigational new drug for PONV and not approved by the FDA

Target ~ 14M Surgical Procedures Where PONV is High Clinical Concern

~39M Surgical Procedures that Could Result in PONV

Key Surgical Types where Postoperative Emesis could be Clinically Concerning

Abdominal (GI and OB)

As vomiting directly involves the gastrointestinal tract, emesis can directly injure surgical sites that involve this organ system

CV / CT

Retching and vomiting can lead to transient increases in blood pressure which can result in damage/disruption of arterial surgical sites

Cranial

Intracranial pressure increases during emesis, cranial surgeries, such as craniotomy, are at elevated risk of poor outcomes due to PONV

~14M

"High Clinical Concern" Procedures in 2020

(36% of all Surgical Procedures)

~5M Clinically Concerning Cases of PONV

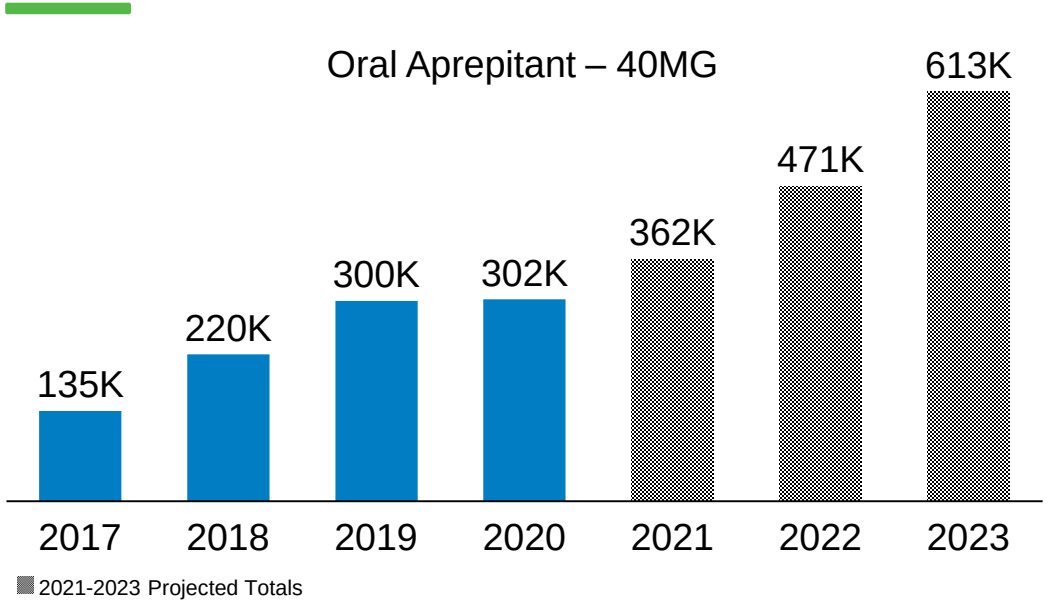
(35% of patients undergoing these procedures may develop PONV despite prophylaxis)

HCPs are more likely to take an aggressive approach managing PONV in cases where postoperative emesis could have a negative impact on the patient's clinical outcomes

Source: *PONV quantitative survey DRG June 2020*

HTX-019 is an investigational new drug for PONV and not approved by the FDA

Oral Aprepitant is Already Rapidly Growing with No Promotion, Product Limitations and High Acquisition Cost



- Oral Aprepitant volume is growing rapidly at premium price despite no promotion

Q2'20 WAC ~ $88/capsule

Acquisition cost: $43 - $64 per capsule[1]

- ~ **1,100** current ordering accounts[2]

- **HTX-019 advantages vs. Oral Aprepitant**
  - Flexible 30-second IVP vs. oral administration
  - Onset of action – 5 minutes vs. 1 to 3 hours
  - Heron product promotion efforts
- **Strategic fit with HTX-011**
  - Same commercial organization
  - Same Hospital & ASC targets
  - Same surgeon, anesthesiology & pharmacy targets
- **More convenient formulations of NK-1 class are needed based on existing PONV guidelines**

Source: 1 Banner Health, 2 IQVIA DDD Non-Retail data Q4'20

HTX-019 is an investigational new drug for PONV and not approved by the FDA

HTX-019 for PONV is Ideal Strategic Fit for Heron

- Large market ~ 14M target surgical procedures with significant unmet need for more convenient formulations of NK-1 class drugs
- Potential Significant Advantages of HTX-019
  - 30-second IV Push injection with immediate onset of action
  - Aprepitant is the most effective therapeutic agent for emesis
  - 505(b)(2) regulatory pathway for existing asset
  - Existing contract manufacturers
- Synergies with HTX-011 commercial organization
  - Same target accounts and target audiences
  - Capacity & access advantages of adding a 2nd product to promote
  - Minimal incremental investment will improve ROI

HTX-019 is an investigational new drug for PONV and not approved by the FDA

Financial Summary

Proforma cash, cash equivalents and short-term investments of $316.5 million, which includes our cash, cash equivalents and short-term investments as of March 31, 2021 and our recent financing

Summary Statement of Operations and Net Cash Used in Operations (In thousands, except per share amounts)	Three Months Ended March 31, 2021
Net product sales	$ 20,018
Operating expenses[1]	72,132
Other income (expense)	(500)
Net loss[1]	$ (52,614)
Net loss per share[2]	$ (0.58)
Net cash used in operations	$ (41,938)
Condensed Balance Sheet Data (In thousands)	**March 31, 2021**
Cash, cash equivalents and short-term investments	$ 166,466
Accounts receivable, net	$ 38,525
Total assets	$ 310,932
Total stockholders' equity	$ 196,225

Common shares outstanding as of March 31, 2021 totaled 91.4 million.

[1] Includes $11.5 million of non-cash, stock-based compensation expense for the three months ended March 31, 2021.
[2] Based on 91.4 million weighted-average common shares outstanding for the three months ended March 31, 2021.

HERON THERAPEUTICS