Heron Update

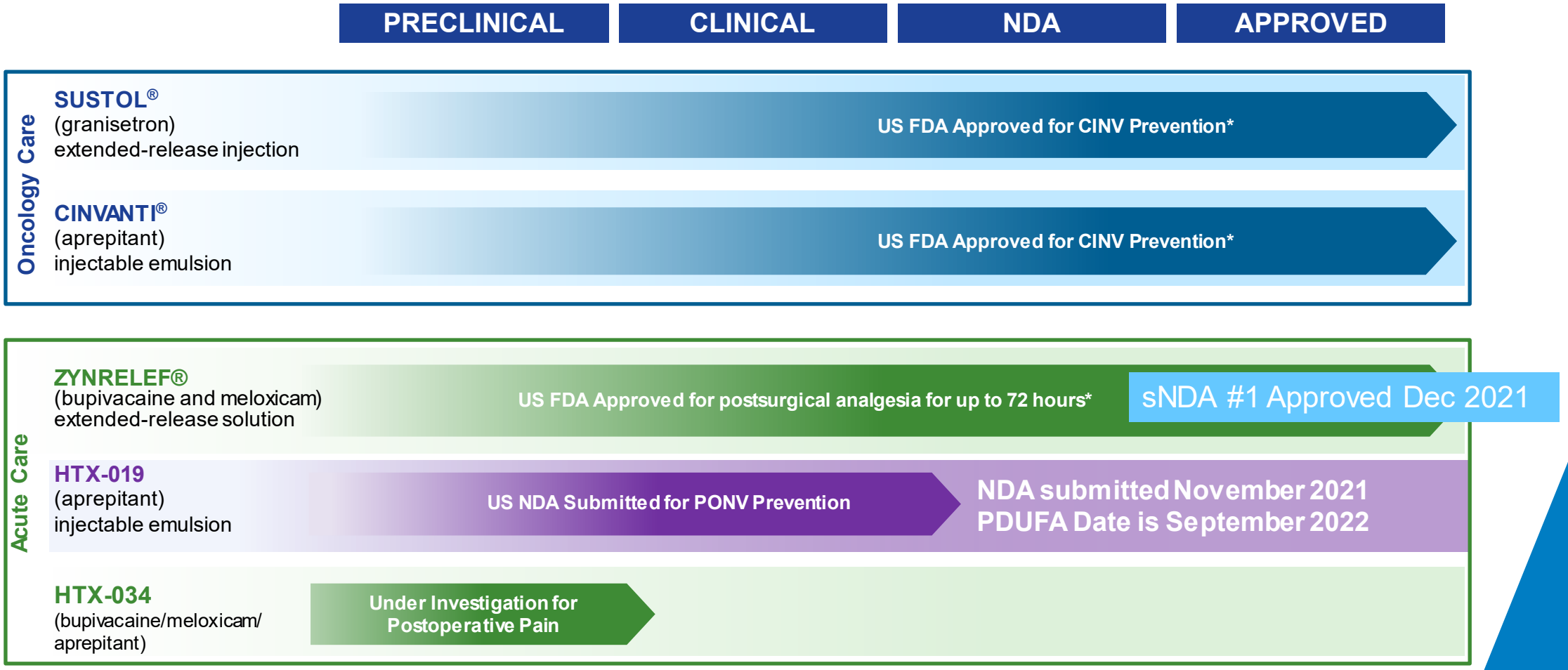
April 11, 2022

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: the timing of the commercial launch of ZYNRELEF in Europe; the potential market opportunity for ZYNRELEF in the US and Europe; the potential additional market opportunity for the expanded U.S. label; the timing and results of studies for the further expansion of the U.S. label for ZYNRELEF; the timing and results of studies for the HTX-034 development program; the timing of the FDA's review process and whether the FDA approves the NDA for HTX-019 for prevention of postoperative nausea and vomiting; the net product sales guidance for the oncology care franchise; the net cash guidance for operating activities; 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.

HERON THERAPEUTICS

Heron Pipeline



CINV: Chemotherapy-induced nausea and vomiting. **PONV:** postoperative 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 agents, is 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. **ZYNRELEF (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 foot and ankle, small-to-medium open abdominal, and lower extremity total joint arthroplasty surgical procedures. 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 (for PONV) are investigational new drugs and are not approved by the FDA

Successful FDA Interactions Resulted in Expansion of ZYNRELEF Label

- In a little over 2 months from submission, the FDA approved our supplemental NDA to significantly expand ZYNRELEF indications to include foot and ankle, small-to-medium open abdominal, and lower extremity total joint arthroplasty surgical procedures.
  - Significantly expands the commercial opportunity to ~7 million procedures
  - Significantly improves the opportunity for therapeutic substitution
- FDA has agreed to contents of a second supplemental NDA to further expand the indications to orthopedic and soft tissue surgical procedures
  - Submission targeted for 2H2022
  - Expanded broad claim structure designed to cover the full 14 million target procedures

Activities Needed for sNDA #2 to Obtain Broadest Label Underway

- Study 220 C-section: enrollment completed
- Study 221 Spine: recruiting
- AMAZE Study:
  - Abdominoplasty – enrollment completed
  - Shoulder – recruiting
- sNDA #2 on target for 2H2022

ZYNRELEF
Commercial Update

HERON
THERAPEUTICS

ZYNRELEF Launch Highlights

- CMS pass-through status in HOPD started April 1, 2022
- Continue to gain formulary approvals in targeted Hospitals and IDNs
- Building unique ordering accounts with increases in reordering rates
- Significant growth in demand units quarter over quarter
- Expanded label is already increasing our opportunity with current users
- Meaningful progress in burning through initial distribution channel inventory
- Increased separate reimbursement with commercial / Medicaid payers

The Outpatient Setting of Care Now Represents >70% of Target Surgeries With Hospital Outpatient Approaching 60%

~14M
High Value Market Procedures[1]

Hospital Inpatient 28% (3.9M procedures)

- Bundled in DRG
- 57% (2.2M) of inpatient procedures are done in 340B hospitals

Hospital Outpatient 59% (8.3M procedures)

- 17% (1.4M) have Medicare reimbursement (3-year pass-through) at ASP +6%
- 58% (4.8M) eligible for 340B discount
- Multiple SKUs – lower average costs

Ambulatory Surgical Centers 13% (1.8M procedures)

- 18% (0.33M) eligible for Medicare reimbursement at ASP + 6%
- 123 million Medicaid and commercial lives covered outside surgical bundle
- Multiple SKUs – lower average costs

72% of the opportunity lends itself to favorable reimbursement and access

OVERALL TOTAL

- **ZYNRELEF has lower acquisition cost benefit versus Exparel**
- **ZYNRELEF has HOPD reimbursement – 3-year pass-through**
- **ZYNRELEF offers 340B pricing**

SKU: stock keeping unit. **HOPD:** hospital outpatient department. 1. **Breakdown of settings of care based on** 2021 Lexis Nexis claims data

ZYNRELEF is the Only Reimbursed Local Anesthetic in Hospital Outpatient, the Largest Setting of Care

- Effective April 1, 2022 - ZYNRELEF is separately reimbursed for Medicare patients in the HOPD under 3-year transitional pass-through status
  - ZYNRELEF is the only local anesthetic with separate reimbursement in the HOPD
  - With pass-through status, the economic benefits vs Exparel in 340B and HOPD more than double
  - 72% of indicated procedures were performed in outpatient settings in 2021 (59% in HOPD, 13% in ASC)[a]
- Effective January 1, 2022 - ZYNRELEF is separately reimbursed for Medicare patients in the ASC and a product specific C-code (C9088) is assigned
- Multiple commercial payers and state Medicaid agencies covering >123 million lives have agreed to reimburse ZYNRELEF outside of the surgical packaged payment in the ASC
  - Many of these covered lives are also reimbursed separately in the HOPD
- ZYNRELEF's lower price benefits all settings of care, including those in which local anesthetics are reimbursed as part of the surgical packaged payment

HOPD: Hospital Outpatient Department; **ASC**: Ambulatory Surgical Center

[a] Based on third party claims data

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

ZYNRELEF	WAC	340B
400 mg/12 mg	$267.50	$205.36
200 mg/6 mg	$135.50	$104.14

Exparel	WAC	340B
266 mg (20 mL)	$354.53	$354.53
133 mg (10 mL)	$198.84	$198.84

ZYNRELEF Savings vs Exparel

WAC $/unit	WAC %	340B $/unit	340B %
~ $87	25%	~$149	42%
~ $63	32%	~$95	48%

Medicare NCR By Site of Care*

	NCR 340B	NCR HOPD	ASC
ZYNRELEF 400 mg/12 mg	$74.64	$12.50	$12.50
Exparel 266 mg	($354.53)	($354.53)	$1.92
ZYNRELEF 200 mg/6 mg	$35.86	$4.50	$4.50
Exparel 133 mg	($198.84)	($198.84)	($20.62)

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

ZYNRELEF Economic Benefit vs. Exparel*

- **340B accounts: ~ $429 (400 mg to 266 mg) and ~ $235 (200 mg to 133 mg)**
- **HOPD accounts: ~ $367 (400 mg to 266 mg) and ~ $203 (200 mg to 133 mg)**
- Example, 340B facility performing 250 HOPD Medicare TKAs per month save over $1 million in out-of-pocket Exparel costs and make ~ $220,000 in profit by switching to ZYNRELEF
- Research has shown all customer segments were more sensitive to and favored acquisition cost over reimbursement**

*Estimates Comparing WAC (or 340B) acquisition cost to published ASP reimbursement for Medicare patients to calculate NCR based on Q2'22 rates. Medicare reimbursement is subject to sequestration. . 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

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ZYNRELEF Continues to Gain Rapid Formulary Approvals

- ZYNRELEF formulary approvals: **260** as of February 25, 2022
  - Over 90% P&T Committee approval rate in hospitals

Formulary Approval Status	Estimated % of Approvals
Unrestricted Usage	**65%**
Restricted (Primarily for Indicated Procedures)	**35%**

- Over **100** additional P&T Committees are scheduled to review ZYNRELEF before the end of April
- Formulary approval → Medical Executive approval → CPOE → Pharmacy Orders → Patient

CPOE: computerized physician order entry

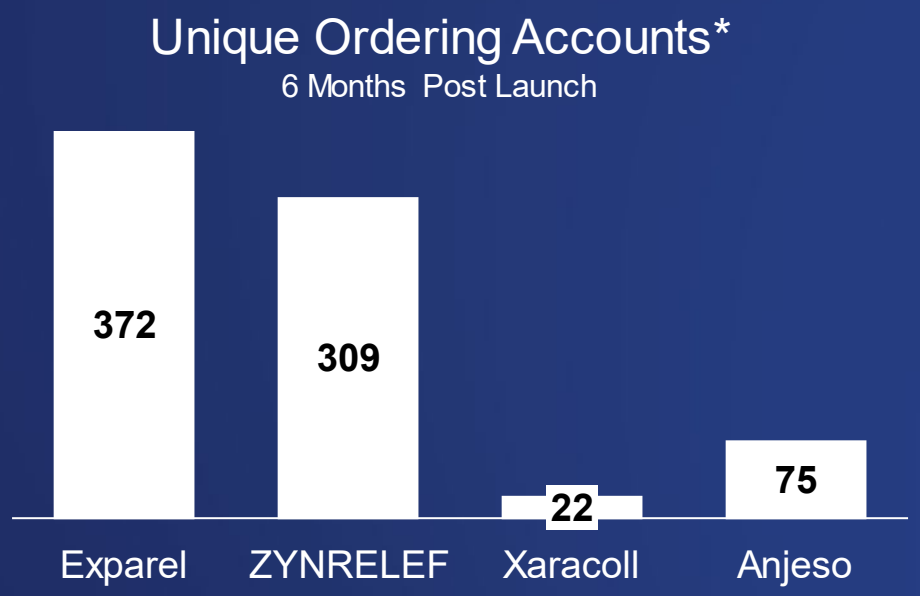
Targeting IDNs – Top Down Strategy is Creating New Opportunities for Therapeutic Interchange (through February 25, 2022)

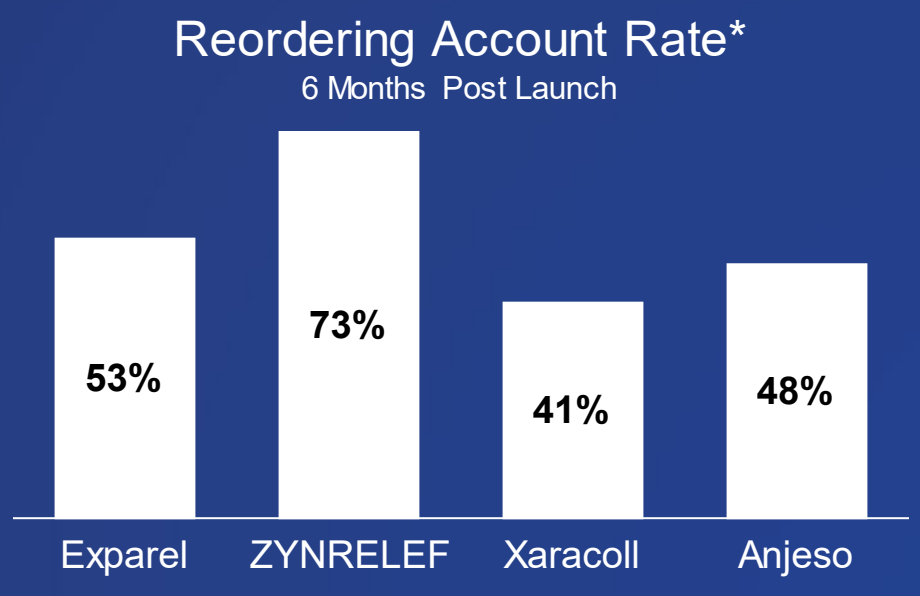
- 34 IDNs have added ZYNRELEF as formulary approved product
  - Represent 186 hospitals and 82 ASCs – many hospitals still require formulary approval
- 41% unrestricted / 59% restricted formulary approvals
- 34 IDNs represent ~ 520k of annual ZYNRELEF indicated surgical procedures
- 34 IDNs represent ~ **$61M* of Exparel** sales
- IDN's representing approximately **$40M* of Exparel** sales are currently evaluating switching to ZYNRELEF for indicated procedures

IDN: Integrated Delivery Network; **ASC:** Ambulatory Surgical Center; **WAC:** Wholesale Acquisition Cost
* Symphony DDD data for 2021 based on WAC pricing

ZYNRELEF is Gaining Significant Traction in COVID Era

- 309 unique accounts ordered ZYNRELEF (July 2021 – December 2021)
  - ZYNRELEF Reordering Account rate has grown from 50% in first 3 months



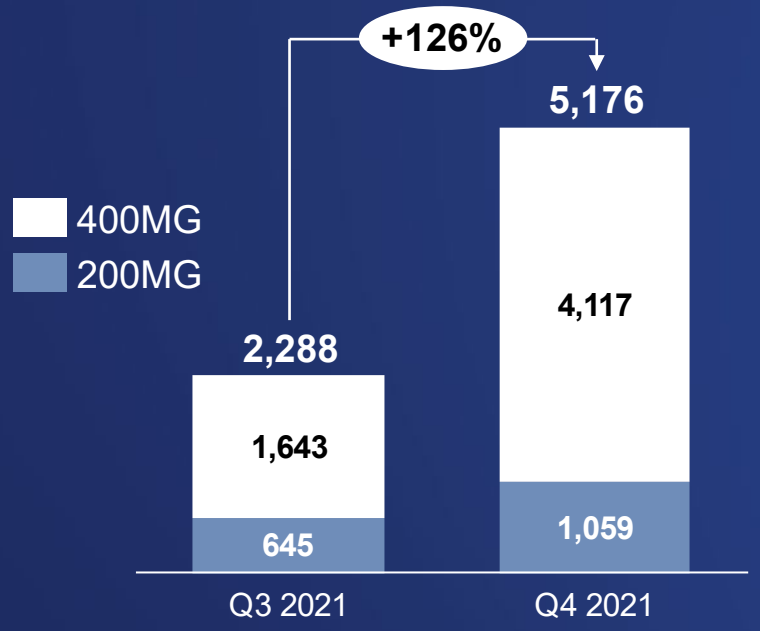


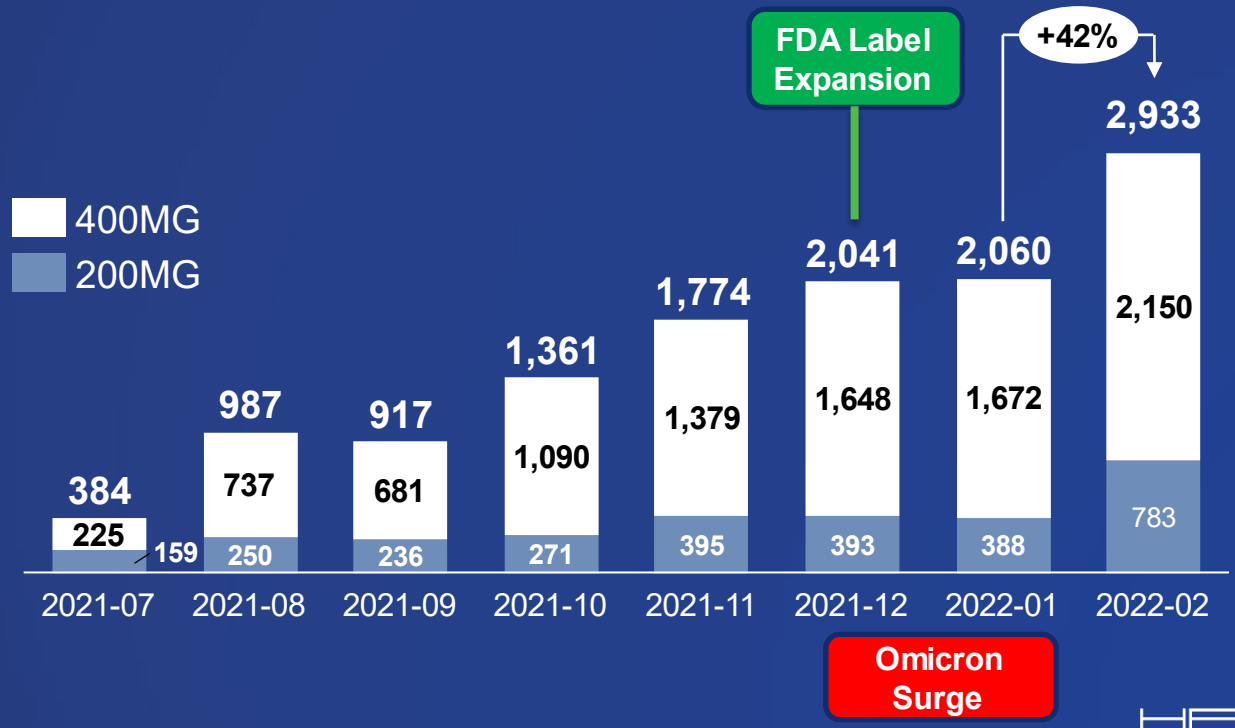
* Source: Symphony Heath SNR / ZYNRELEF EDI 867

ZYNRELEF is Rapidly Increasing Monthly Demand Volume

401 unique ordering accounts during first 8 months of launch (through February 2022)

- Grew demand unit sales **+126%** from Q3 21 to Q4 21
- 400mg SKU represents **77%** of demand since launch





ZYNRELEF EDI 867 data through 2/28/2022

Please see **IMPORTANT SAFETY INFORMATION** on pages 30 and 31 and full Prescribing Information, including **Boxed Warning**.

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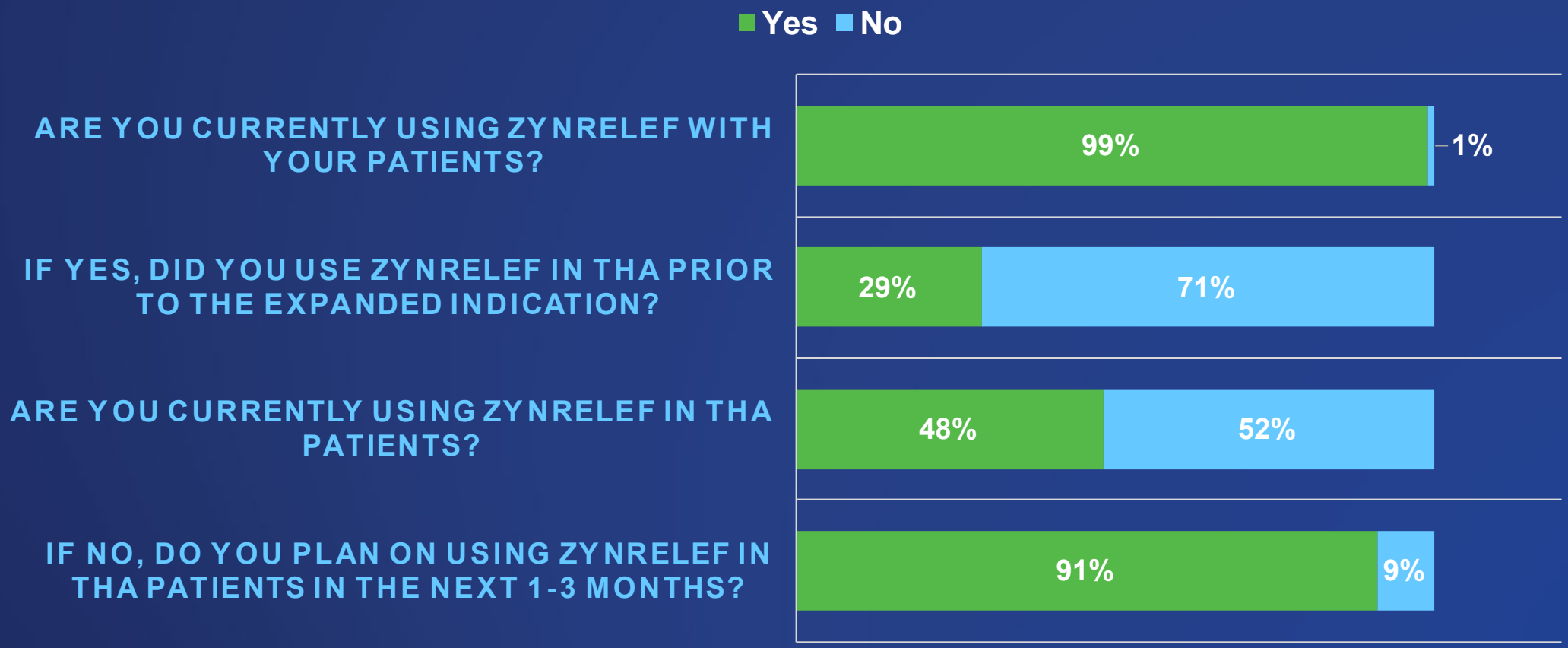
Developing Best-in-Class Medicine. Improving Lives.™

Expanded Indications Will Grow ZYNRELEF Use in THA Patients



Source: Pulse Survey of 129 Orthopedic Surgeons with prior ZYNRELEF usage experience , January 13-20, 2022

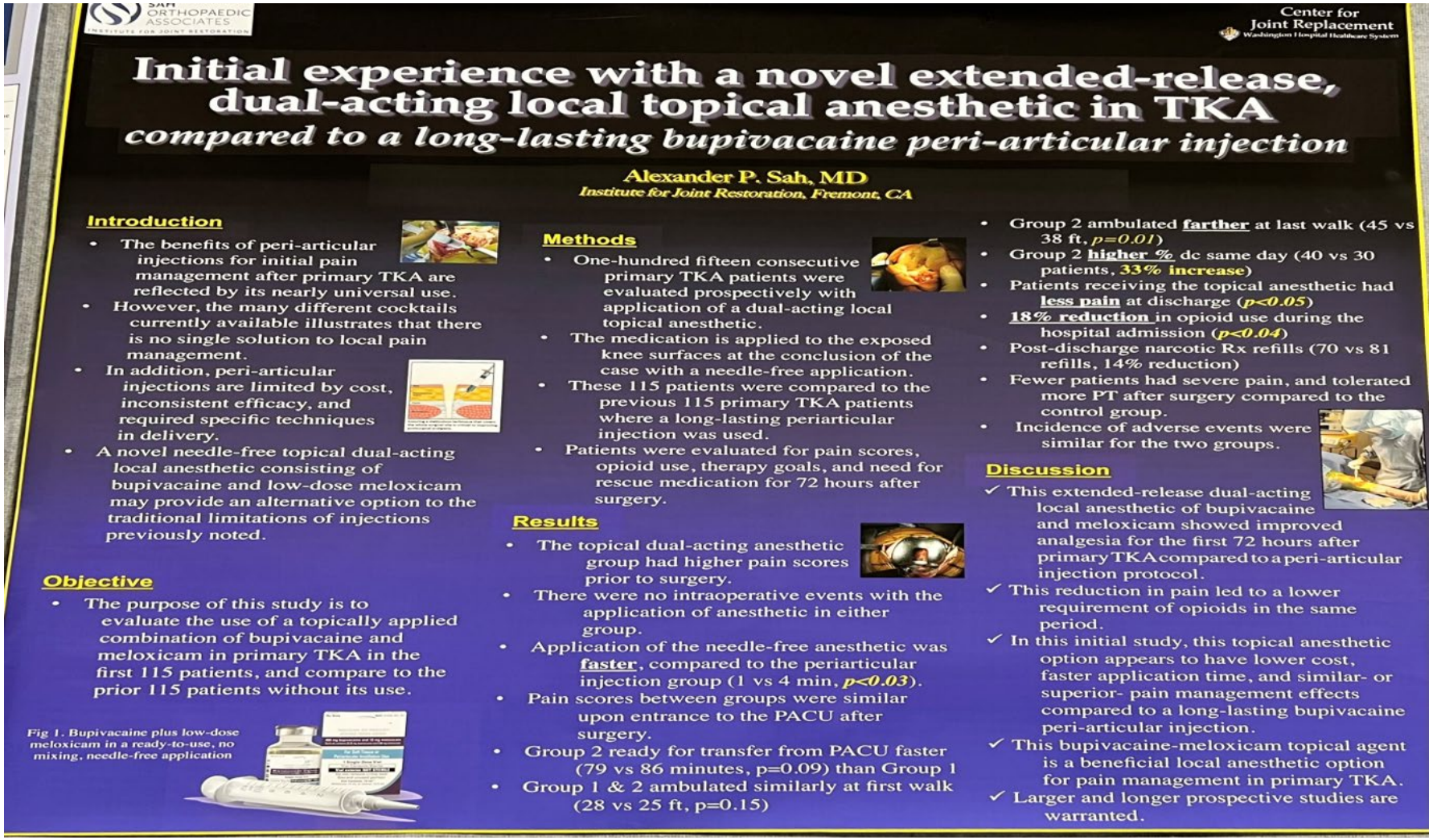
Meaningful Progress Burning through Initial DC Inventory

- Q4'21 Net Sales: **$844k**
  - Q4 Net Sales decreased vs. prior quarter of **$2.1M** as initial stocking inventory was drawn down based on demand orders
- ZYNRELEF has established nationwide access through broad distribution channel stocking
  - 85 distribution centers (DCs) have sold ZYNRELEF
- Q1'22 Ex-Factory Reorder Rate through 2/24/2022:
  - **96%** of ZYNRELEF 400mg demand units
  - **40%** of ZYNRELEF 200mg demand units

ZYNRELEF Priorities 2022

- Leverage **new label indication** for faster growth
  - Expand beyond TKA, Hernia and Bunion in unrestricted accounts
  - Expand / remove restrictions in formulary approved accounts
  - Revisit “Therapeutic Interchange” accounts with expanded label
- Build consistent usage in formulary approved ordering accounts and increase average order size – expand number of surgeons using ZYNRELEF
- Continue to gain formulary access to new IDNs and Hospitals to build pipeline
- Maximize specific C-code and Commercial/Medicaid separate reimbursement in ASCs

Why We Will Ultimately Win the Local Anesthetic Market: Independent Comparison of ZYNRELEF to Prior Exparel



SAH ORTHOPAEDIC ASSOCIATES
INSTITUTE FOR JOINT RESTORATION

Center for Joint Replacement
Washington Hospital Healthcare System

Initial experience with a novel extended-release, dual-acting local topical anesthetic in TKA
compared to a long-lasting bupivacaine peri-articular injection

Alexander P. Sah, MD
Institute for Joint Restoration, Fremont, CA

Introduction

- The benefits of peri-articular injections for initial pain management after primary TKA are reflected by its nearly universal use.
- However, the many different cocktails currently available illustrates that there is no single solution to local pain management.
- In addition, peri-articular injections are limited by cost, inconsistent efficacy, and required specific techniques in delivery.
- A novel needle-free topical dual-acting local anesthetic consisting of bupivacaine and low-dose meloxicam may provide an alternative option to the traditional limitations of injections previously noted.

Objective

- The purpose of this study is to evaluate the use of a topically applied combination of bupivacaine and meloxicam in primary TKA in the first 115 patients, and compare to the prior 115 patients without its use.

Fig 1. Bupivacaine plus low-dose meloxicam in a ready-to-use, no mixing, needle-free application

Methods

- One-hundred fifteen consecutive primary TKA patients were evaluated prospectively with application of a dual-acting local topical anesthetic.
- The medication is applied to the exposed knee surfaces at the conclusion of the case with a needle-free application.
- These 115 patients were compared to the previous 115 primary TKA patients where a long-lasting periarticular injection was used.
- Patients were evaluated for pain scores, opioid use, therapy goals, and need for rescue medication for 72 hours after surgery.

Results

- The topical dual-acting anesthetic group had higher pain scores prior to surgery.
- There were no intraoperative events with the application of anesthetic in either group.
- Application of the needle-free anesthetic was **faster**, compared to the periarticular injection group (1 vs 4 min, *p<0.03*).
- Pain scores between groups were similar upon entrance to the PACU after surgery.
- Group 2 ready for transfer from PACU faster (79 vs 86 minutes, p=0.09) than Group 1
- Group 1 & 2 ambulated similarly at first walk (28 vs 25 ft, p=0.15)
- Group 2 ambulated **farther** at last walk (45 vs 38 ft, *p=0.01*)
- Group 2 **higher %** dc same day (40 vs 30 patients, **33% increase**)
- Patients receiving the topical anesthetic had **less pain** at discharge (*p<0.05*)
- **18% reduction** in opioid use during the hospital admission (*p<0.04*)
- Post-discharge narcotic Rx refills (70 vs 81 refills, 14% reduction)
- Fewer patients had severe pain, and tolerated more PT after surgery compared to the control group.
- Incidence of adverse events were similar for the two groups.

Discussion

- ✓ This extended-release dual-acting local anesthetic of bupivacaine and meloxicam showed improved analgesia for the first 72 hours after primary TKA compared to a peri-articular injection protocol.
- ✓ This reduction in pain led to a lower requirement of opioids in the same period.
- ✓ In this initial study, this topical anesthetic option appears to have lower cost, faster application time, and similar- or superior- pain management effects compared to a long-lasting bupivacaine peri-articular injection.
- ✓ This bupivacaine-meloxicam topical agent is a beneficial local anesthetic option for pain management in primary TKA.
- ✓ Larger and longer prospective studies are warranted.

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SPAARK Study of Exparel Plus Bupivacaine vs Bupivacaine Alone in TKA Presented at AAOS and Published in JAMA Surgery

Study funded by UK National Institute for Health Research (NIHR) and Exparel provided by Pacira Biosciences

Summary

- No difference in recovery or pain
- No difference in opioid consumption
- No difference in functional outcomes
- No difference in adverse events
- Less effective in terms of QALYs as well as more costly

Compared to bupivacaine hydrochloride alone liposomal bupivacaine is not clinically or cost-effective for improving recovery or pain following knee replacement surgery.

Study of Peri-Articular Anaesthetic for Replacement of the knee (SPAARK)

Research

JAMA Surgery | Original Investigation

Efficacy of Liposomal Bupivacaine and Bupivacaine Hydrochloride vs Bupivacaine Hydrochloride Alone as a Periarticular Anesthetic for Patients Undergoing Knee Replacement
A Randomized Clinical Trial

Thomas W. Hamilton, MD, DPhil; Ruth Knight, PhD; Jamie R. Stokes, MSc; Ines Rombach, DPhil; Cushla Cooper, RN, MSc; Loretta Davies, DPhil; Susan J. Dutton, MSc; Karen L. Barker, PhD; Jonathan Cook, PhD; Sarah E. Lamb, DPhil; David W. Murray, MD; Lisa Poulton, BSc; Ariel Wang, PhD; Louise H. Strickland, RN, DPhil; Bernard H. Van Duren, DPhil; Jose Leal, DPhil; David Beard, DPhil; Hemant G. Pandit, DPhil; for the Study of Peri-Articular Anaesthetic for Replacement of the Knee (SPAARK) Study Group

IMPORTANCE More than half of patients who undergo knee replacement surgery report substantial acute postoperative pain.

OBJECTIVE To evaluate the efficacy and cost-effectiveness of periarticular liposomal bupivacaine for recovery and pain management after knee replacement.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, patient-blinded, pragmatic, randomized clinical superiority trial involved 533 participants at 11 institutions within the National Health Service in England. Adults undergoing primary unilateral knee replacement for symptomatic end-stage osteoarthritis were enrolled between March 29, 2018, and February 29, 2020, and followed up for 1 year after surgery. Follow-up was completed March 1, 2021. A per-protocol analysis for each coprimary outcome was performed in addition to the main intention-to-treat analysis.

INTERVENTIONS Two hundred sixty-six milligrams of liposomal bupivacaine admixed with 100 mg of bupivacaine hydrochloride compared with 100 mg of bupivacaine hydrochloride alone (control) administered by periarticular injection at the time of surgery.

MAIN OUTCOME AND MEASURES The coprimary outcomes were Quality of Recovery 40 (QoR-40) score at 72 hours and pain visual analog scale (VAS) score area under the curve (AUC) from 6 to 72 hours. Secondary outcomes included QoR-40 and mean pain VAS at days 0 (evening of surgery), 1, 2, and 3; cumulative opioid consumption for 72 hours; functional outcomes and quality of life at 6 weeks, 6 months, and 1 year; and cost-effectiveness for 1 year. Adverse events and serious adverse events up to 12 months after randomization were also assessed.

RESULTS Among the 533 participants included in the analysis, the mean (SD) age was 69.0 (9.7) years; 287 patients were women (53.8%) and 246 were men (46.2%). Baseline characteristics were balanced between study groups. There was no difference between the liposomal bupivacaine and control groups in QoR-40 score at 72 hours (adjusted mean difference, 0.54 [97.5% CI, −2.05 to 3.13]; $P = .64$) or the pain VAS score AUC at 6 to 72 hours (−21.5 [97.5% CI, −46.8 to 3.8]; $P = .06$). Analyses of pain VAS and QoR-40 scores demonstrated only 1 statistically significant difference, with the liposomal bupivacaine arm having lower pain scores the evening of surgery (adjusted difference −0.54 [97.5% CI, −1.07 to −0.02]; $P = .02$). No difference in cumulative opioid consumption and functional outcomes was detected. Liposomal bupivacaine was not cost-effective compared with the control treatment. No difference in adverse or serious adverse events was found between the liposomal bupivacaine and control groups.

CONCLUSIONS AND RELEVANCE This study found no difference in postoperative recovery or pain associated with the use of periarticular liposomal bupivacaine compared with bupivacaine hydrochloride alone in patients who underwent knee replacement surgery.

TRIAL REGISTRATION isrctn.com Identifier: ISRCTN54191675

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Supplemental content

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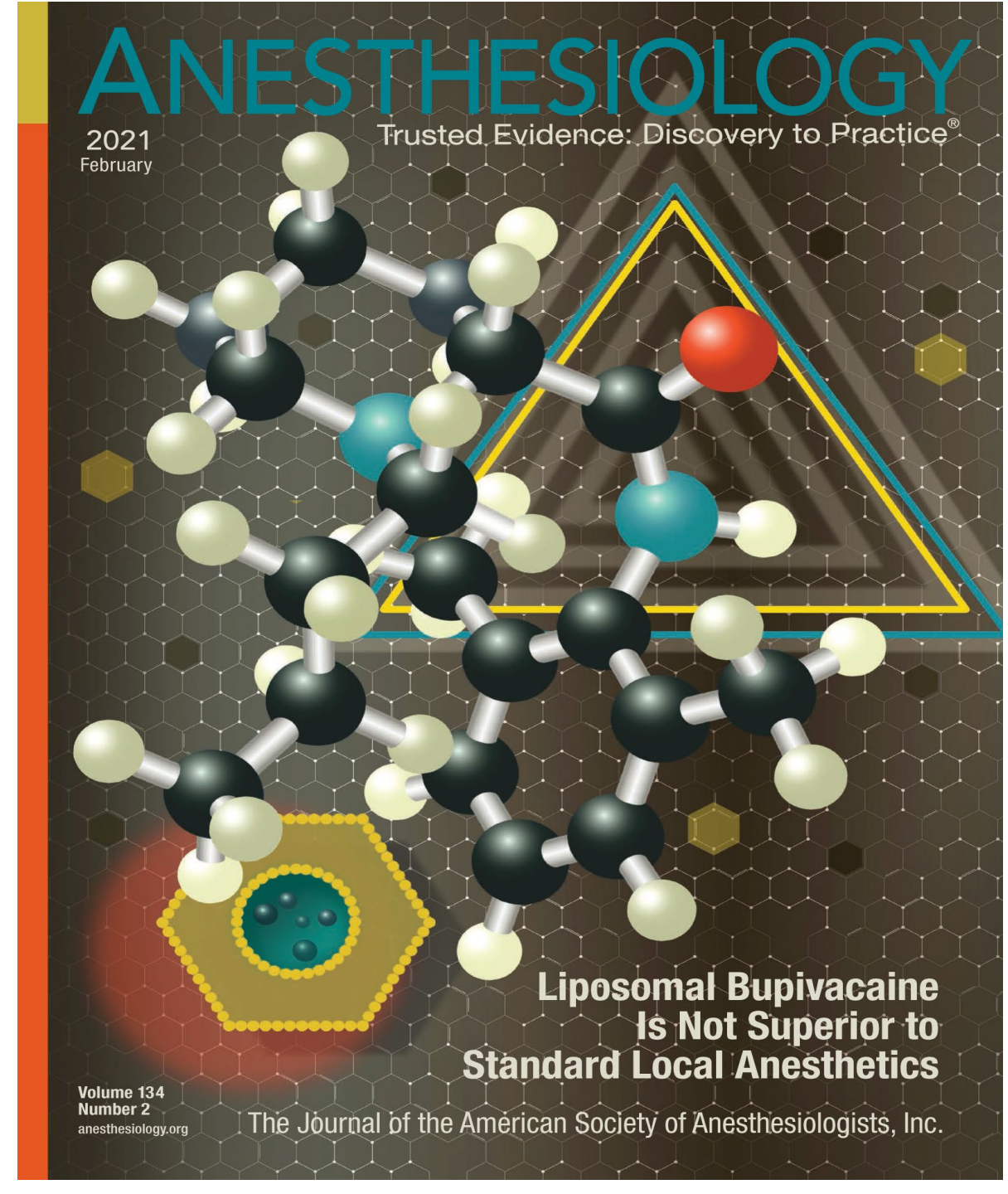


ANESTHESIOLOGY

Perineural Liposomal Bupivacaine Is Not Superior to Nonliposomal Bupivacaine for Peripheral Nerve Block Analgesia

A Systematic Review and Meta-analysis

Nasir Hussain, M.D., M.Sc., Richard Brull, M.D., Brendan Sheehy, M.D., Michael K. Essandoh, M.D., David L. Stahl, M.D., Tristan E. Weaver, M.D., Faraj W. Abdallah, M.D., M.Sc.

Anesthesiology 2021; 134:147–64

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Liposomal bupivacaine was developed in an effort to extend the duration of local analgesia
- Despite the availability of many studies, it remains unclear whether and when liposomal bupivacaine offers significant advantages over the standard formulation

What This Article Tells Us That Is New

- Nine trials were included in a meta-analysis examining the difference in 24- to 72-h rest pain severity scores for liposomal and nonliposomal bupivacaine
- The area under the curve pain scores for the 24- to 72-h period were statistically but probably not clinically significant
- Secondary outcome analysis likewise failed to uncover benefits for liposomal bupivacaine regarding analgesic consumption, length of stay, and functional recovery

ABSTRACT

Background: Liposomal bupivacaine is purported to extend analgesia of peripheral nerve blocks when administered perineurally. However, evidence of the clinical effectiveness of perineural liposomal bupivacaine is mixed. This meta-analysis seeks to evaluate the effectiveness of perineural liposomal bupivacaine in improving peripheral nerve block analgesia as compared with nonliposomal local anesthetics.

Methods: The authors identified randomized trials evaluating the effectiveness of peripheral nerve block analgesic that compared liposomal bupivacaine with nonliposomal local anesthetics. The primary outcome was the difference in area under the receiver operating characteristics curve (AUC) of the pooled 24- to 72-h rest pain severity scores. Secondary outcomes included postoperative analgesic consumption, time to first analgesic request, incidence of opioid-related side effects, patient satisfaction, length of hospital stay, liposomal bupivacaine side effects, and functional recovery. AUC pain scores were interpreted in light of a minimal clinically important difference of 2.0 cm · h.

Results: Nine trials (619 patients) were analyzed. When all trials were pooled, AUC pain scores ± SD at 24 to 72 h were 7.6 ± 4.9 cm · h and 6.6 ± 4.6 cm · h for nonliposomal and liposomal bupivacaine, respectively. As such, perineural liposomal bupivacaine provided a clinically unimportant benefit by improving the AUC (95% CI) of 24- to 72-h pain scores by 1.0 cm · h (0.5 to 1.6; $P = 0.003$) compared with nonliposomal bupivacaine. Excluding an industry-sponsored trial rendered the difference between the groups nonsignificant (0.7 cm · h [−0.1 to 1.5]; $P = 0.100$). Secondary outcome analysis did not uncover any additional benefits to liposomal bupivacaine in pain severity at individual timepoints up to 72 h, analgesic consumption, time to first analgesic request, opioid-related side effects, patient satisfaction, length of hospital stay, and functional recovery. No liposomal bupivacaine side effects were reported.

Conclusions: Perineural liposomal bupivacaine provided a statistically significant but clinically unimportant improvement in the AUC of postoperative pain scores compared with plain local anesthetic. Furthermore, this benefit was rendered nonsignificant after excluding an industry-sponsored trial, and liposomal bupivacaine was found to be not different from plain local anesthetics for postoperative pain and all other analgesic and functional outcomes. High-quality evidence does not support the use of perineural liposomal bupivacaine over nonliposomal bupivacaine for peripheral nerve blocks.

(Anesthesiology 2021; 134:147–64)

Liposomal bupivacaine used for infiltration[1–18] and field blocks[19–25] is proposed to provide extended postoperative analgesia up to 72 h[26,27] after various surgical procedures. Recently, the U.S. Food and Drug Administration (Silver Spring, Maryland) approved liposomal bupivacaine for perineural use in interscalene block of the brachial plexus.[28] However, evidence of the clinical effectiveness of perineurally applied liposomal bupivacaine in extending

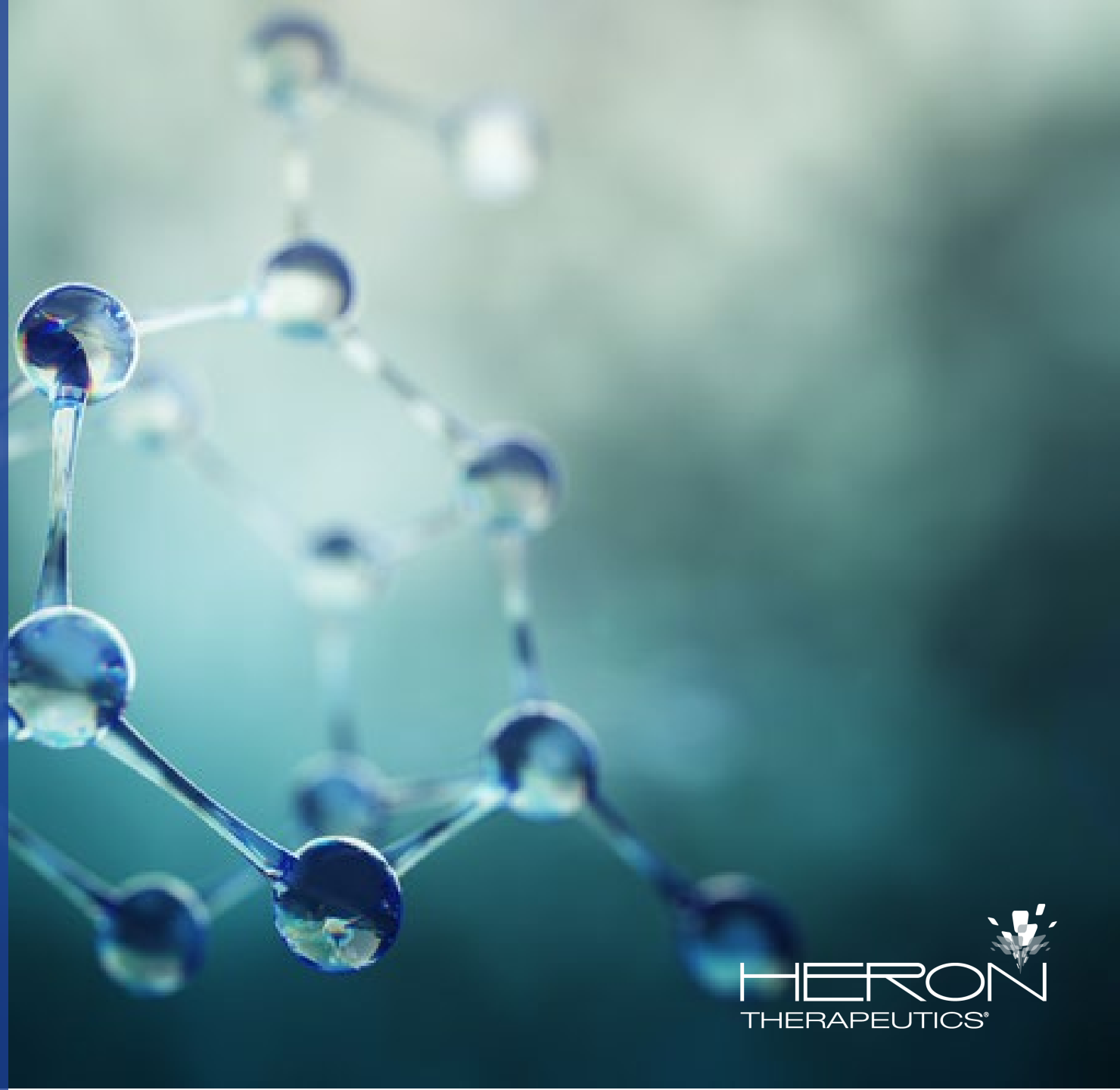
This article has been selected for the Anesthesiology CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue. This article is featured in "This Month in Anesthesiology," page 1A. This article is accompanied by an editorial on p. 139 and a review article on p. 293. This article has a related Infographic on p. 17A. This article has an audio podcast. This article has a visual abstract available in the online version.

Submitted for publication July 27, 2020. Accepted for publication November 19, 2020. From the Department of Anesthesiology, The Ohio State University, Wexner Medical Center, Columbus, Ohio (N.H., B.S., M.K.E., D.L.S., T.E.W.); Department of Anesthesiology and Pain Medicine, University of Toronto, Canada (R.B., F.W.A.); Women's College Research Institute, Toronto, Canada (R.B., F.W.A.); and the Department of Anesthesiology and Pain Medicine, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Canada (F.W.A.).

 Anesthesiology 2021; 134:147–64. DOI: 10.1097/ALN.0000000000003651

Oncology Care Franchise

Q4’21 Review



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CINV Franchise 2021 Results

- Q4'21 CINV Franchise net product sales were **$19.9 million**

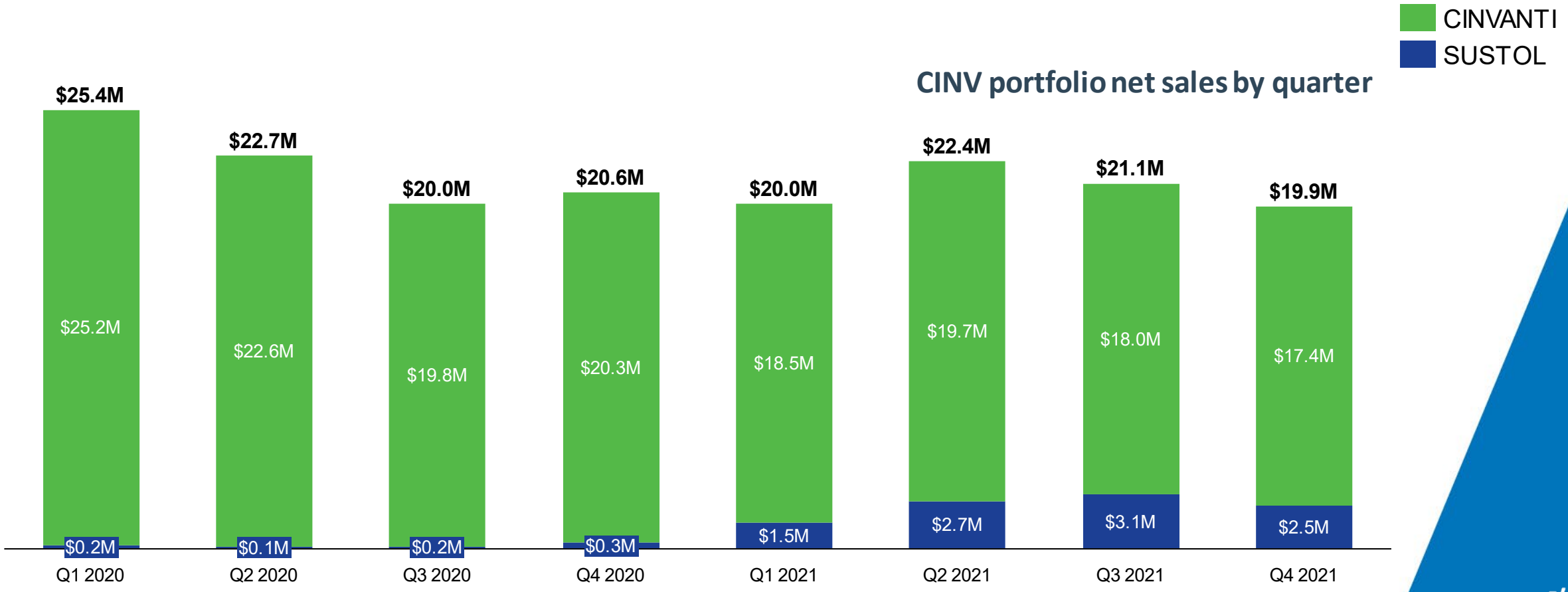
- Solid 2021 performance despite headwinds remaining in the CINV market
  - Reduction in the clinic anti-emetic market was due to COVID-related decreases in cancer screening and patient visits
  - OCM and value-based contracting reimbursement continues to drive generics market share
  - Continued aggressive competition
    - Generic fosaprepitant
    - IV Akynzeo

OCM: Oncology Care Model

HERON THERAPEUTICS

Heron's CINV Portfolio Net Sales Stabilized in Markets Dominated by Generics during 2021, Poised for Growth in 2022

- CINVANTI demand unit sales stabilized in 2021 maintaining 98% of 2020 levels
- SUSTOL sales rebounded in 2021 following the Refresh Program



CINV Franchise 2022 Outlook

- Sales for CINVANTI and SUSTOL are poised for moderate growth in 2022 based on improving reimbursement tailwinds
  - Generic fosaprepitant ASP reimbursement decreased to **$28.50** in Q1'22 (44% ↓ from Q2'21)
  - Generic fosaprepitant separate reimbursement in HOPD ended effective January 1, 2022.
  - IV Akynzeo ASP reimbursement decreased to **$503.98** in Q1'22 (>$190 ↓ vs. Q1'21)
  - CINVANTI ASP reimbursement increased to **$223.86** in Q1'22 (19% ↑ from Q2'21)

- **CINV Franchise net sales guidance: Q1'22 expected in the range of $20M to $22M**
  - Infusion bag shortages: CINVANTI – only NK_1 that does not need IV infusion bag
  - Virtually all HEC and majority of MEC regimens utilize 5-HT_3 + NK_1, thus the backlog of patients coming into treatment creates opportunities for both products

ASP: Average Sales Price; **HOPD:** Hospital Outpatient Department

HERON THERAPEUTICS

Heron's Commercial Strategy

Establish Heron as a leading company in Acute Care

- ZYNRELEF is off to a fast start and growing rapidly
- Growth is accelerating with ZYNRELEF's label expansion
- Expand Acute Care footprint with HTX-019 for PONV in Q4'22, if approved

Return Growth and Maximize Profitability of Oncology Care

- Net sales stabilized in 2021 and poised for moderate growth in 2022
- Reduce COGS through larger scale manufacturing in 2022
- Aligned resources to support the strategy

HTX-019 for Postoperative Nausea and Vomiting (PONV)

NDA Submitted November 2021

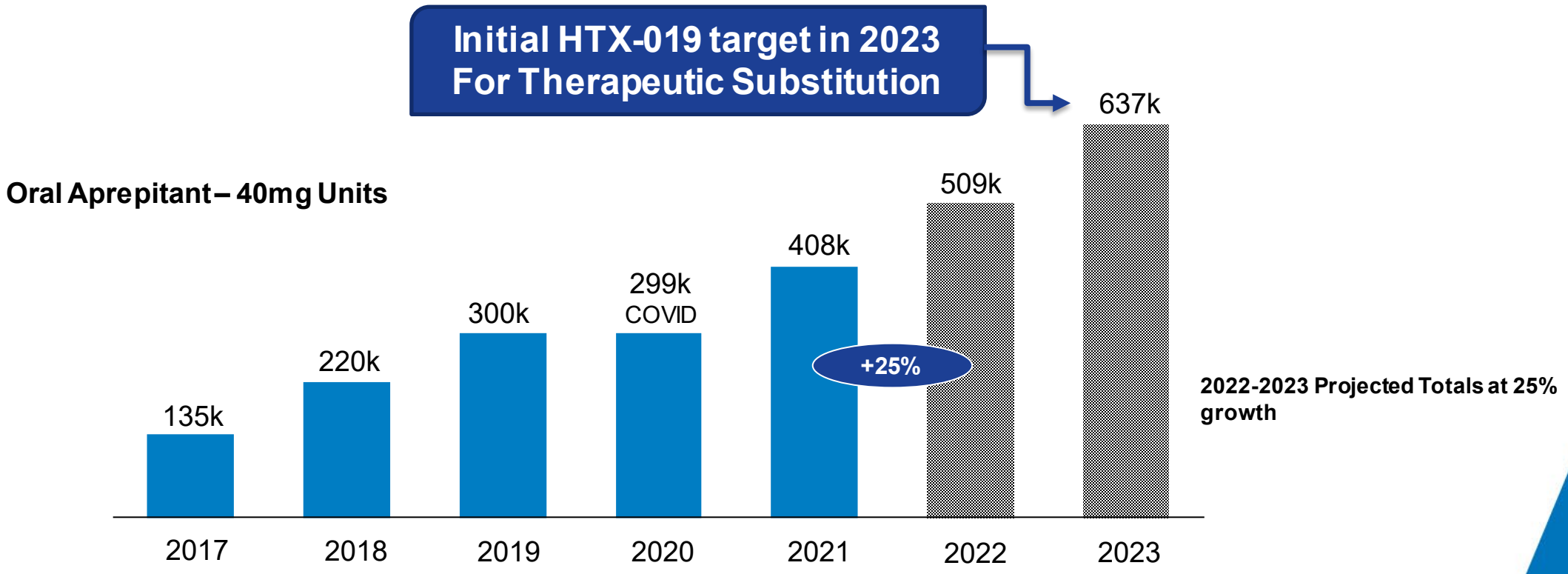
HTX-019 is an investigational new drug for PONV and not approved by the FDA

HTX-019 for PONV

- PONV is a large market ~25x the size of CINV
- HTX-019 has significant potential advantages over oral aprepitant and IV fosaprepitant:
  - Therapeutic plasma concentrations where ≥97% receptor occupancy in the brain would be predicted are achieved in minutes versus >1 hour for oral aprepitant
  - 30-second administration of HTX-019 versus 20-30 minutes for fosaprepitant
  - IV fosaprepitant can be very painful when administered into a peripheral vein (In prior BE comparison HTX-019 was better tolerated than EMEND IV, with 65% fewer AEs at least possibly related to treatment and no AEs of greater than mild severity)
- NDA for prevention of PONV in adults submitted November 2021. The FDA set a Prescription Drug User Fee Act (PDUFA) goal date of September 17, 2022
- Conversion of over 500,000 oral pills projected for 2022 will be initial target for IV product
- 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

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
  - Q2'21 WAC ~ $88/capsule
- **~ 1,100** current ordering accounts[1]

[1] Source IQVIA DDD Non-Retail data 2017 -2021

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

Financial Summary

Heron had cash, cash equivalents and short-term investments of $157.6 million as of December 31, 2021. We expect net cash used for operating activities of $44 million to $48 million in the first quarter of 2022, and we anticipate that our net cash usage will continue to moderate lower in 2022.

Summary Statement of Operations and Net Cash Used in Operations (In thousands, except per share amounts)	Three Months Ended December 31, 2021	Twelve Months Ended December 31, 2021
Net product sales	$ 20,655	$ 86,346
Operating expenses[1]	74,192	304,174
Other income (expense), net	(1,109)	(2,855)
Net loss[1]	$ (54,646)	$ (220,683)
Net loss per share[2]	$ (0.54)	$ (2.24)
Net cash used in operations	$ (45,258)	$ (203,354)
Condensed Balance Sheet Data (in thousands)		**December 31, 2021**
Cash, cash equivalents and short-term investments		$ 157,580
Accounts receivable, net		$ 35,499
Inventory[3]		$ 48,382
Total assets		$ 305,706
Total stockholders' equity		$ 77,570

Common shares outstanding as of December 31, 2021 totaled 102.0 million.

[1] Includes $12.9 million and $46.9 million of non-cash, stock-based compensation expense for the three and twelve months ended December 31, 2021, respectively.
[2] Based on 102.0 million and 98.5 million weighted-average common shares outstanding for the three and twelve months ended December 31, 2021, respectively.
[3] Includes $23.6 million for ZYNRELEF, $23.1 million for CINVANTI and $1.7 million for SUSTOL.

HERON THERAPEUTICS

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, similar local anesthetics, 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.

HERON THERAPEUTICS

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 adverse effects on cartilage; 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

HERON THERAPEUTICS