

Company Update

October 1, 2018

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 2018 net product sales guidance for the CINV franchise; the potential market opportunity for HTX-011 and the CINV franchise; the timing of the HTX-011 NDA filing and review process; 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.

Status of Product Portfolio

	Preclinical	Clinical	NDA	Approved
SUSTOL® (granisetron) extended-release injection		Approved by U.S. FDA for CINV Prevention		
CINVANTI® (aprepitant) injectable emulsion		Approved by U.S. FDA for CINV Prevention		
HTX-011 bupivacaine + meloxicam ER Local Administration		Postoperative Pain with Local Administration	• Fast Track and Breakthrough Therapy designations granted • Positive Phase 2, 2b and 3 results	
HTX-011 bupivacaine + meloxicam ER Nerve Block		Postoperative Pain with Nerve Block	Positive Phase 2b results in breast augmentation	

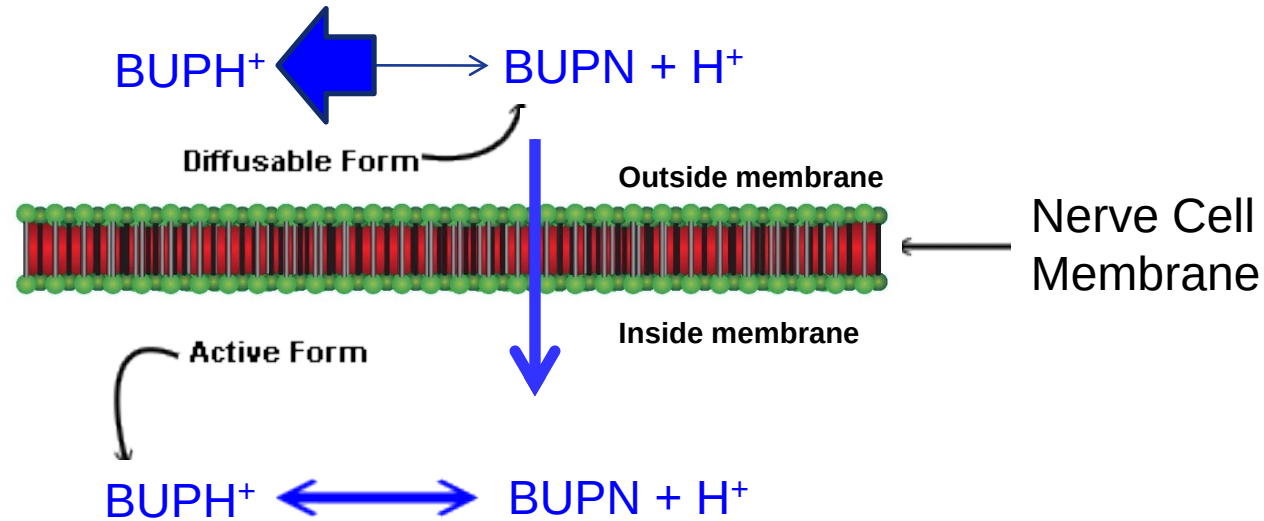
HTX-011 for Postoperative Pain Management Has Received FDA Breakthrough Therapy Designation

- Breakthrough Therapy designation (BTD) designed to expedite development and review of drugs:
 - Intended to treat serious conditions; and
 - **For which preliminary clinical evidence indicates substantial improvement over available therapies on clinically significant endpoint(s)**
- Designation granted by FDA based on results of completed Phase 2 studies and Phase 3 studies
 - HTX-011 produced significant reductions in both pain intensity through 72 hours and need for opioids post-surgery compared to placebo and bupivacaine solution, the standard of care
- Based on BTD, FDA also granted a Rolling Review of HTX-011 new drug application (NDA) to facilitate their timely review
 - initial components of NDA submitted in September

HTX-011 is an investigational new drug and not approved by the FDA

HTX-011's Unique Mechanism of Action

Inflammation Can Reduce the Activity of Local Anesthetics



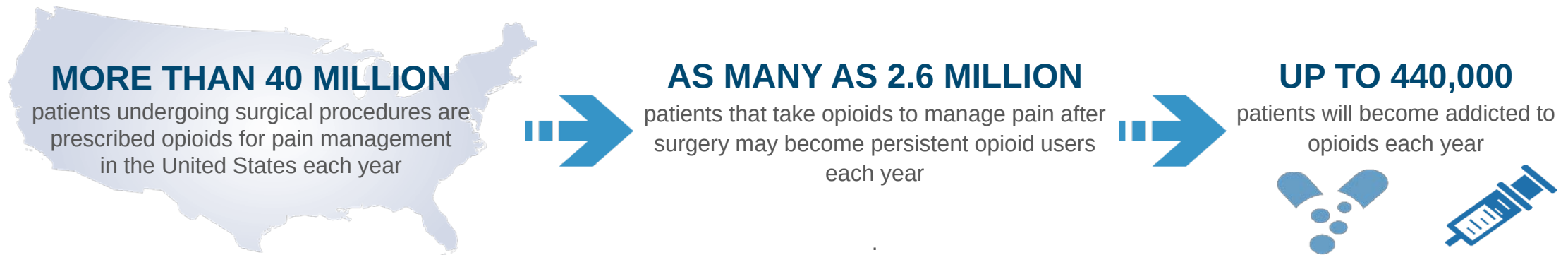
- Surgical insult produces an immediate drop in pH
- As inflammatory cytokines are released and inflammation sets in, the acidic environment is maintained for many days
- The acidic environment shifts the balance to the ionized form, which is unable to enter the nerve

- Acidic environment associated with inflammation results in far less drug penetrating the nerve membrane and reduced anesthetic effects^{1,2}
- Bupivacaine is very sensitive to reduced pH
- Addition of meloxicam is designed to help reduce local inflammation and allow bupivacaine to work better in the first several days after surgery

1. Ueno, et al. J of Inflammation Research 1:41-48 2008.

2. Local anesthetic nerve penetration model adapted from Becker and Reed, Anesth Prog 53:98–109 2006

Postoperative Opioids Are a Gateway to Addiction



In addition

>1 BILLION OPIOID PILLS

are taken home from the hospital after surgery each year

70% of all these opioid pills go unused

90% of these pills remain inside the home in unsecured locations

32% of all opioid addicts report first opioid exposure through leftover pills

>\$15 BILLION

of the annual healthcare costs associated with addiction can be attributed to postoperative pain management



**HTX-011 ACHIEVED STATISTICALLY SIGNIFICANT
REDUCTIONS IN PAIN AND THE NEED FOR
OPIOIDS VS. BUPIVACAINE IN EVERY PHASE 2
STUDY AND BOTH PHASE 3 STUDIES**

Seven Active-Controlled Studies to Be Included in HTX-011 NDA

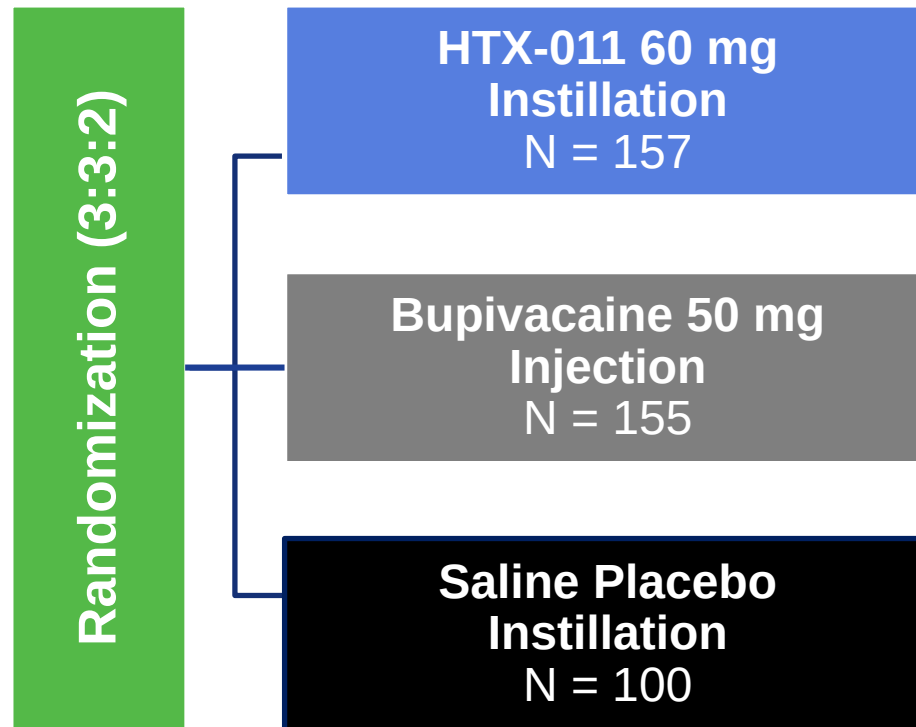
NDA, planned in 2018, will request broad label for reduction of postoperative pain for 72 hours and the use of opioid analgesics after surgery

Study	Phase	Surgical Model	Tissue Type	Significant for Pain Reduction vs. PBO	Significant for Pain Reduction vs. BPV	Significant Reduction in Opioid Use	PK – PD Relationship
202	2	Hernia Repair	Soft	✓	✓	✓	✓
203	2	Abdominoplasty	Soft	✓	✓	✓	✓
208	2	Bunionectomy	Bony	✓	✓	✓	✓
209	2b	TKA	Bony	✓	✓	✓	✓
211	2b	Breast Augmentation	Soft	✓	✓	✓	✓
301	3	Bunionectomy	Bony	✓	✓	✓	✓
302	3	Hernia Repair	Soft	✓	✓	✓	✓

PHASE 3

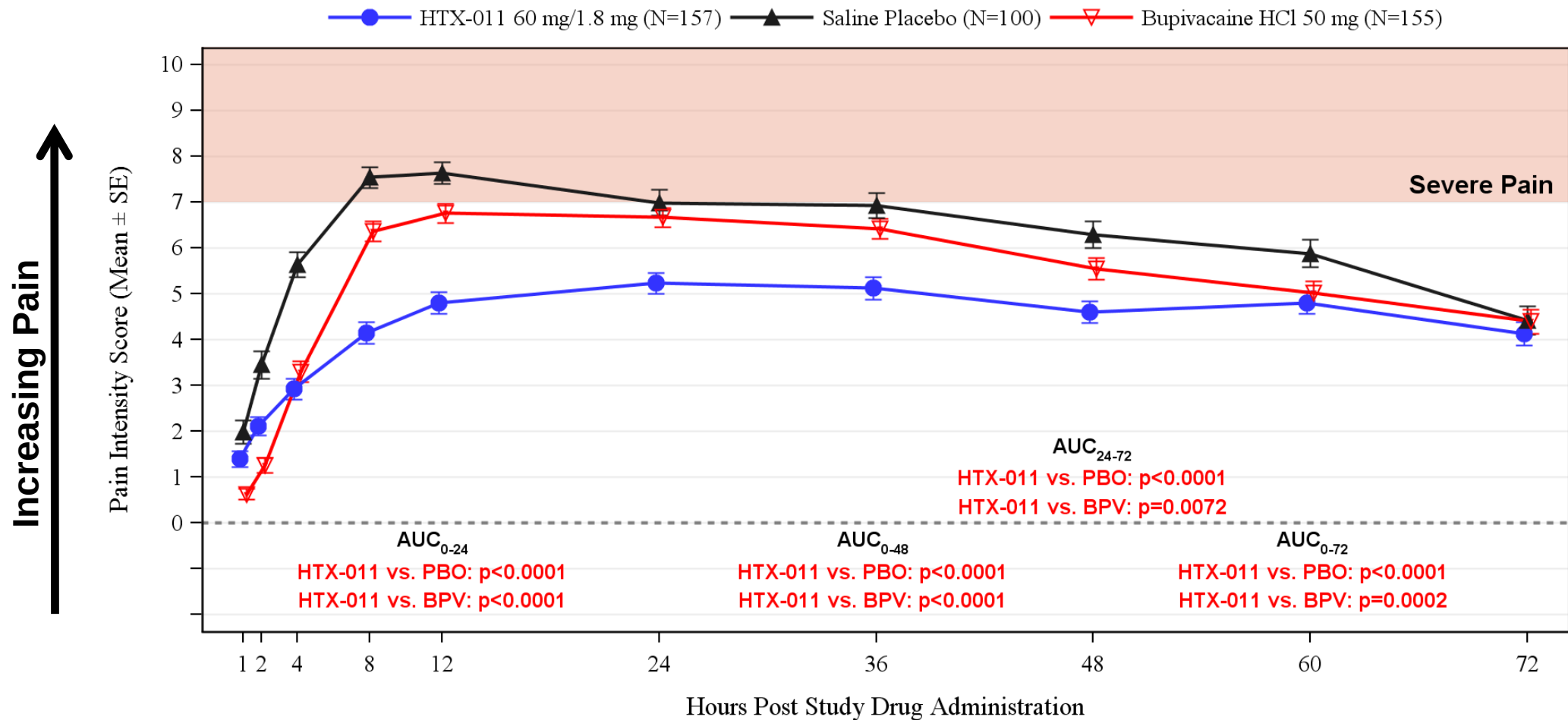
Study 301/EPOCH1: Phase 3 Bunionectomy

Study Design



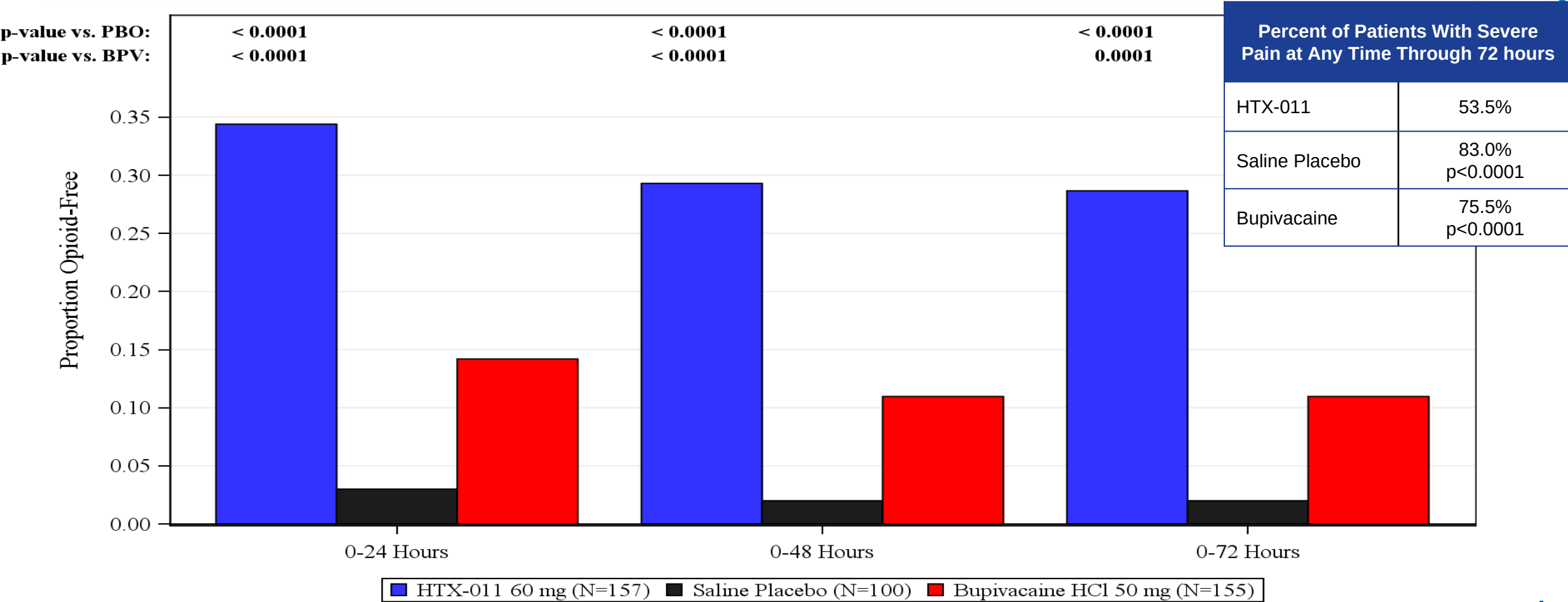
Study 301 Endpoints
Primary: Pain Intensity AUC ₀₋₇₂ vs. placebo
1 st Key Secondary: Pain Intensity AUC ₀₋₇₂ vs. bupivacaine
2 nd Key Secondary: Opioid use vs. placebo
3 rd Key Secondary: Opioid-free vs. bupivacaine
4 th Key Secondary: Opioid use vs. bupivacaine

Study 301: HTX-011 Reduces Pain After Bunionectomy Significantly Better Than Placebo or Bupivacaine (Standard-of-Care)



HTX-011 significantly better than placebo and bupivacaine through 72 hours even without adjustment for opioid use

Study 301: HTX-011 Significantly Increases Proportion of Opioid-Free Subjects vs Bupivacaine and Placebo



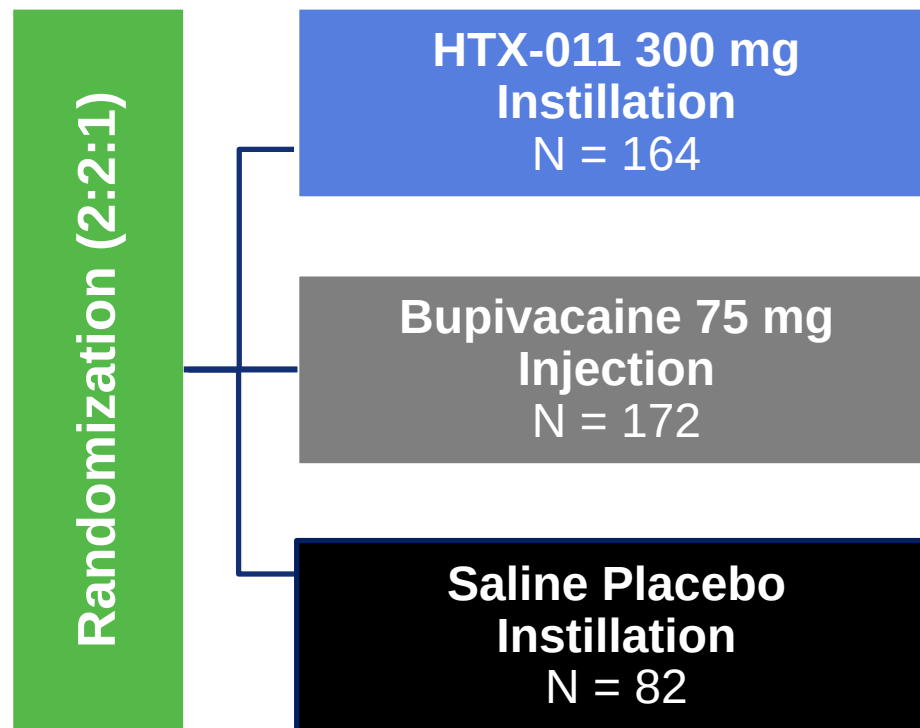
Source: Figure 14.2.3

Study 301: Incidence of Treatment Emergent Adverse Events Occurring in $\geq 5\%$ in the HTX-011 Group

Preferred Term	HTX-011 60 mg (N=157)	Saline Placebo (N=101)	Bupivacaine HCl 50 mg (N=154)
Any TEAE	83.4%	78.2%	85.1%
Nausea	37.6%	43.6%	45.5%
Dizziness	21.7%	17.8%	23.4%
Incision site oedema	17.2%	12.9%	14.3%
Vomiting	14.6%	18.8%	21.4%
Headache	14.0%	9.9%	13.0%
Incision site erythema	12.7%	7.9%	11.7%
Post procedural contusion	12.1%	12.9%	11.7%
Bradycardia	7.6%	5.9%	7.8%
Impaired healing	6.4%	1.0%	3.9%
Constipation	5.7%	6.9%	11.7%
Muscle twitching	5.7%	5.0%	5.2%
Pruritus	5.1%	5.9%	0.6%

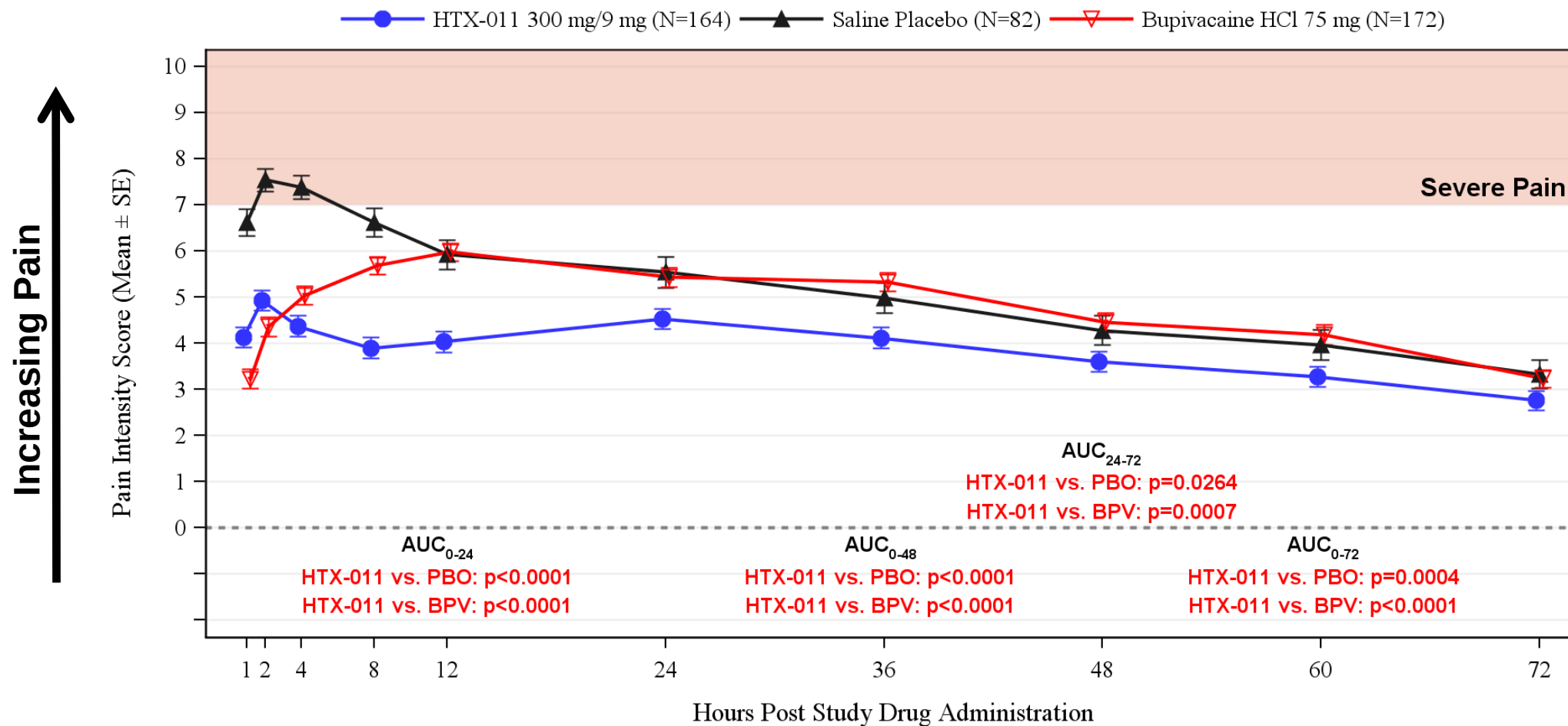
Study 302/EPOCH2: Phase 3 Herniorrhaphy

Study Design



Study 302 Endpoints
Primary: Pain Intensity AUC ₀₋₇₂ vs. placebo
1 st Key Secondary: Pain Intensity AUC ₀₋₇₂ vs. bupivacaine
2 nd Key Secondary: Opioid use vs. placebo
3 rd Key Secondary: Opioid-free vs. bupivacaine
4 th Key Secondary: Opioid use vs. bupivacaine

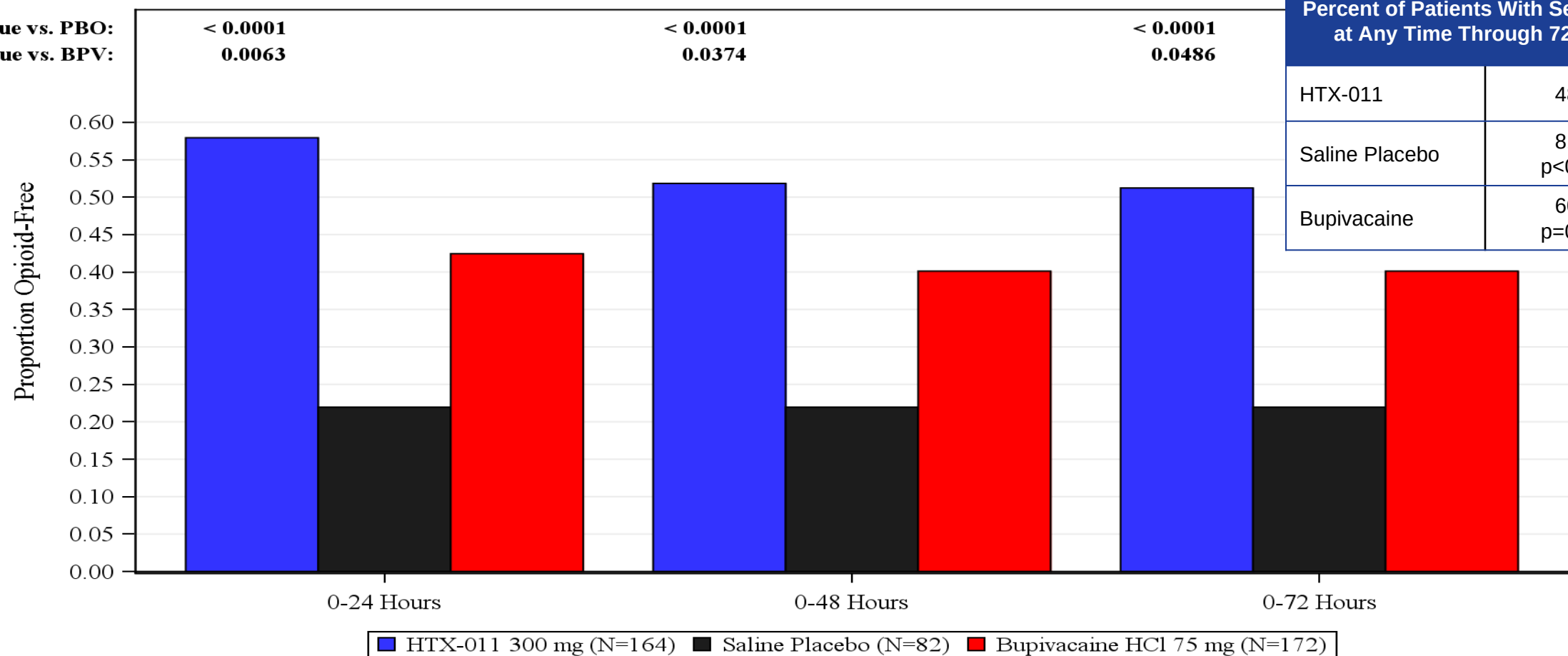
Study 302: HTX-011 Reduces Pain After Herniorrhaphy Significantly Better Than Placebo or Bupivacaine (Standard-of-Care)



HTX-011 significantly better than placebo and bupivacaine through 72 hours even without adjustment for opioid use

Study 302: HTX-011 Significantly Increases Proportion of Opioid-Free Subjects vs Bupivacaine and Placebo

p-value vs. PBO:
p-value vs. BPV:



Percent of Patients With Severe Pain at Any Time Through 72 hours

HTX-011	48.8%
Saline Placebo	81.7% p<0.0001
Bupivacaine	60.5% p=0.0372

Source: Figure 14.2.3

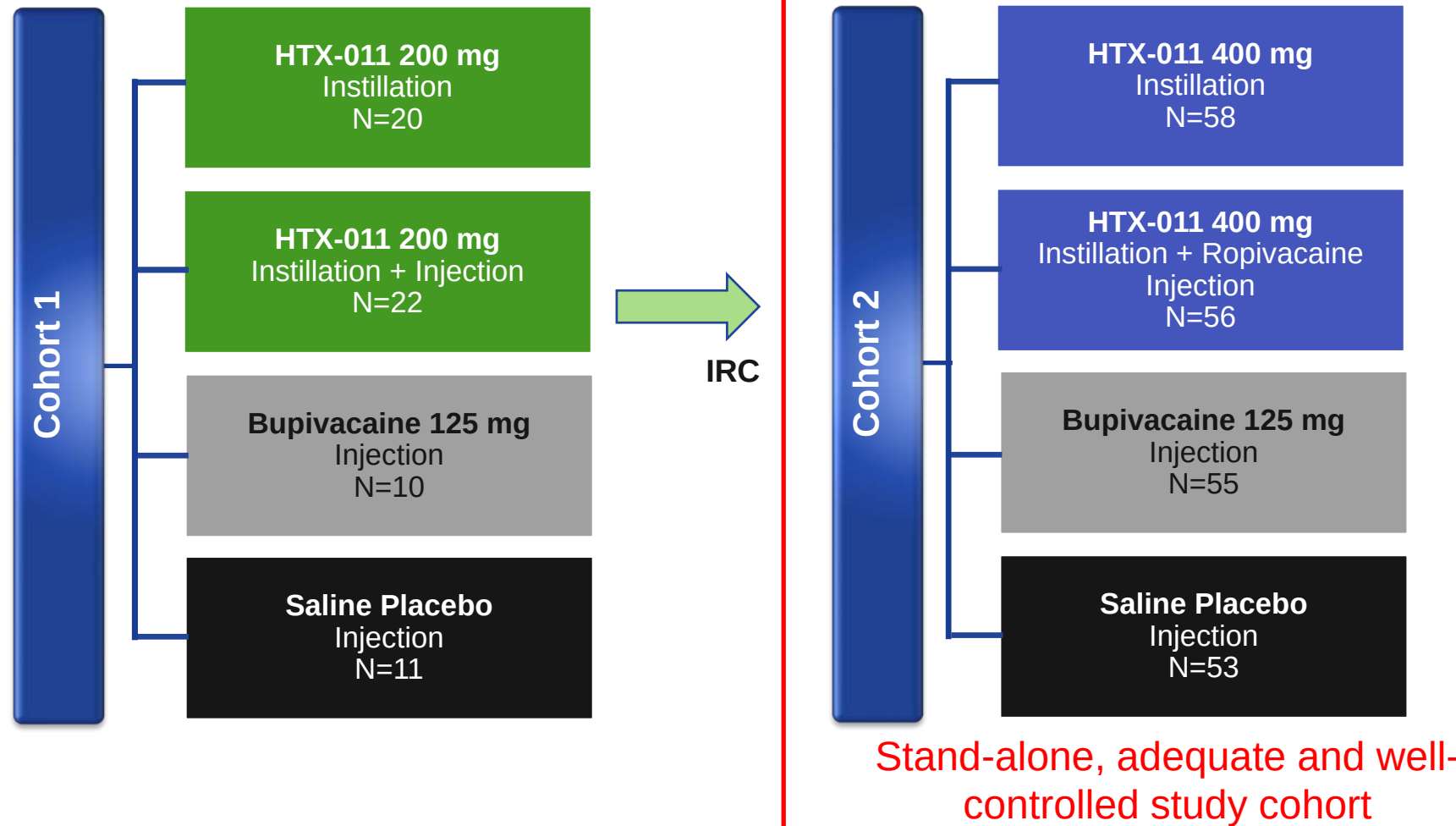
Study 302: Incidence of Treatment Emergent Adverse Events Occurring in $\geq 5\%$ in the HTX-011 Group

Preferred Term	HTX-011 300 mg (N=163)	Saline Placebo (N=82)	Bupivacaine HCl 75 mg (N=173)
Any TEAE	73.0%	74.4%	73.4%
Nausea	18.4%	34.1%	21.4%
Constipation	17.2%	18.3%	23.7%
Dizziness	14.7%	15.9%	24.3%
Headache	12.9%	12.2%	13.9%
Bradycardia	9.2%	7.3%	9.2%
Dysgeusia	9.2%	3.7%	12.1%
Skin odor abnormal	8.0%	1.2%	0.6%

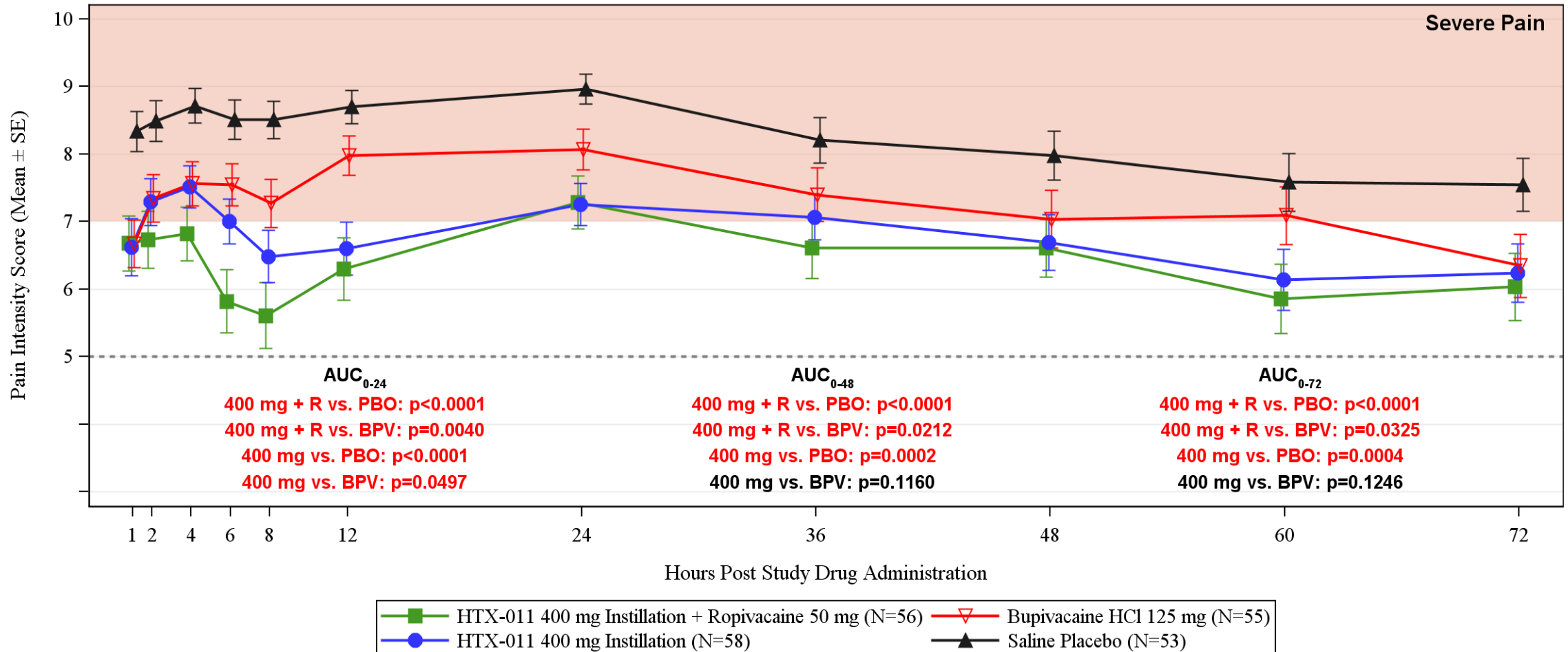
RECENTLY COMPLETED PHASE 2B STUDIES

Study 209: Phase 2b Total Knee Arthroplasty (TKA)

Study Design



Study 209: Significant Separation between HTX-011 Arms and Placebo through 72 Hours for Pain at Rest

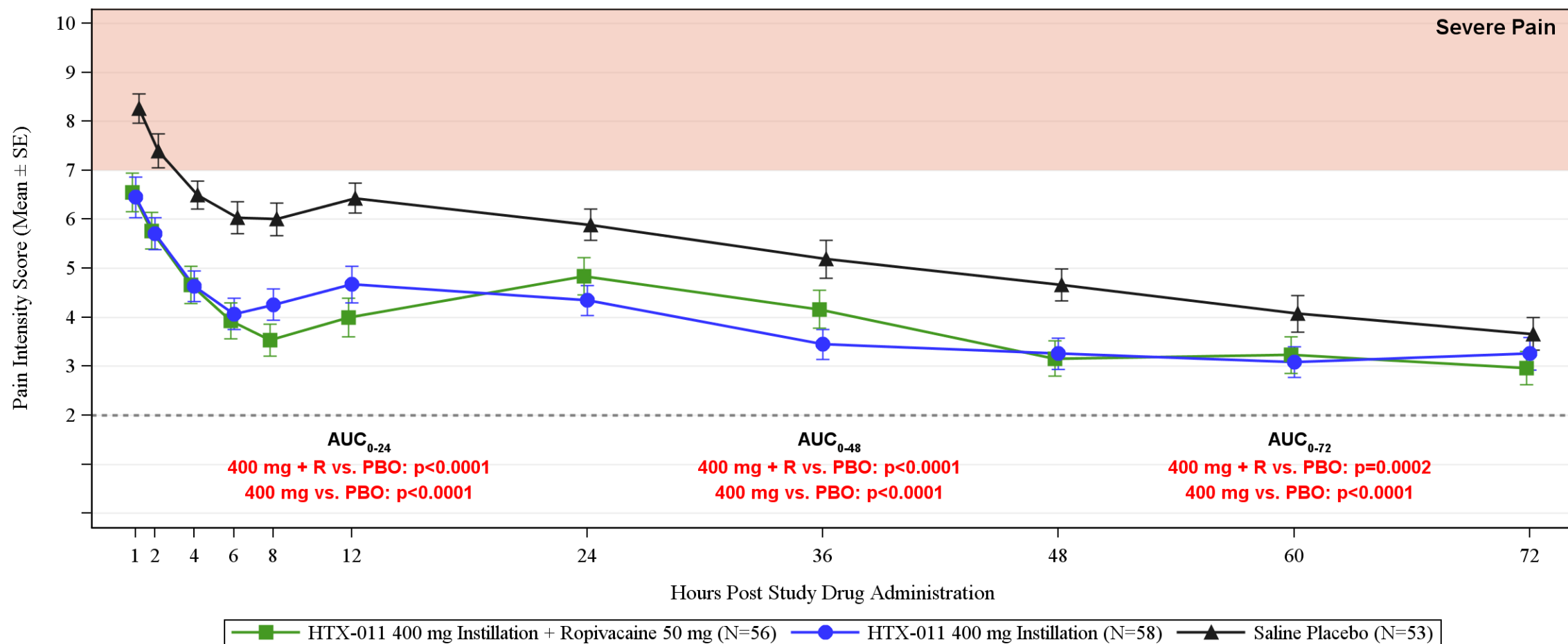


Notes:

Pain intensity collected at rest

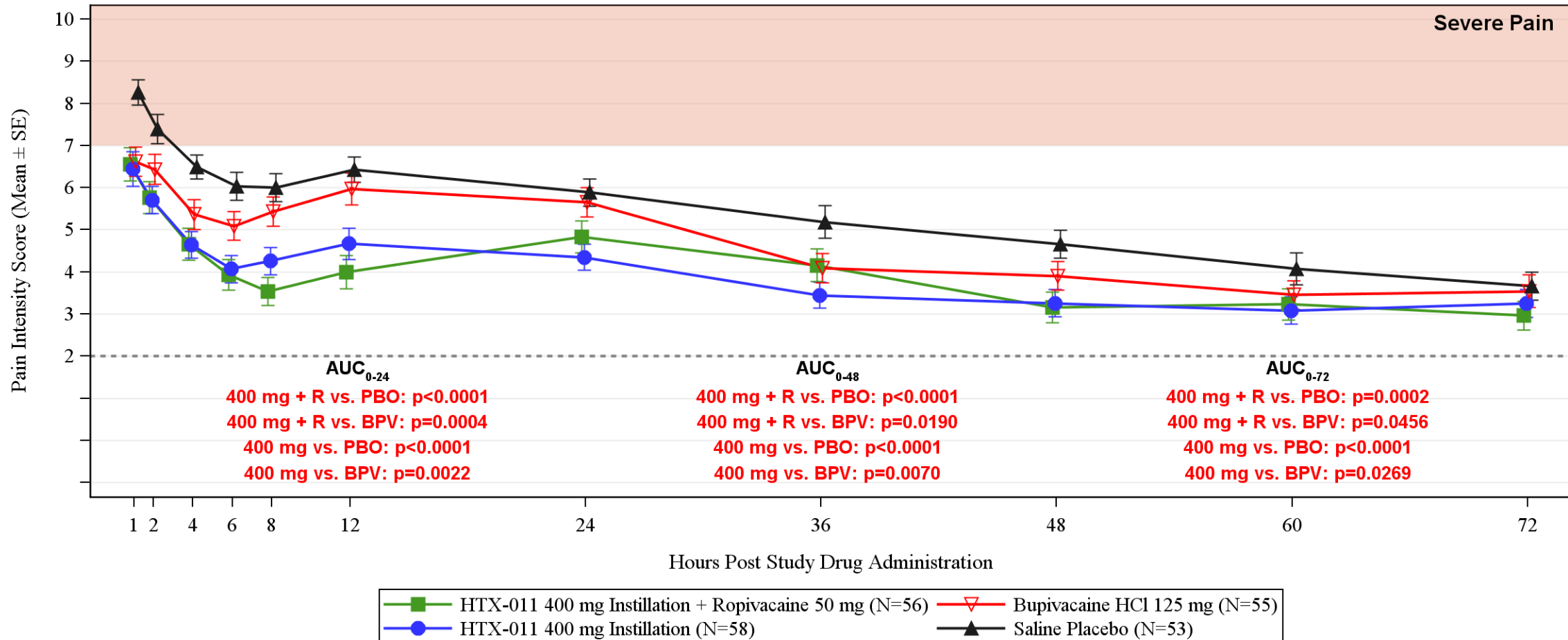
wWOCF for use of opioid rescue medication and LOCF for missing pain data

Study 209: Significant Separation Between HTX-011 Arms and Placebo Through 72 Hours Without Adjustment for Opioid Use – Conservative Comparison



Pain intensity collected at rest
 LOCF for missing data and no adjustment for use of opioid rescue medication

Study 209: HTX-011 Significantly Superior to Both Placebo and Bupivacaine Through 72 Hours With Conservative Analysis Not Adjusting for Opioid Use

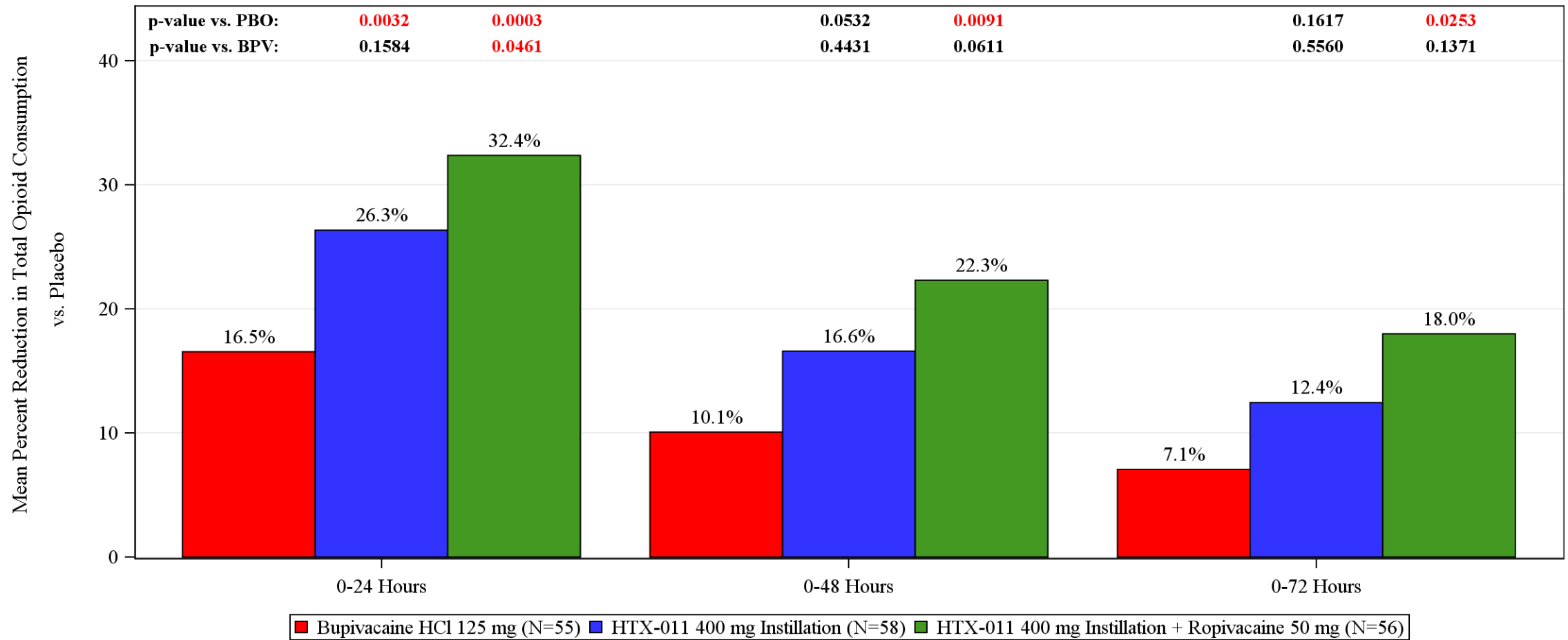


Notes:

Pain intensity collected at rest

LOCF for missing data and no adjustment for use of opioid rescue medication

Study 209: HTX-011 plus Ropivacaine Significantly Reduces Opioid Use vs. Placebo through 72 Hours



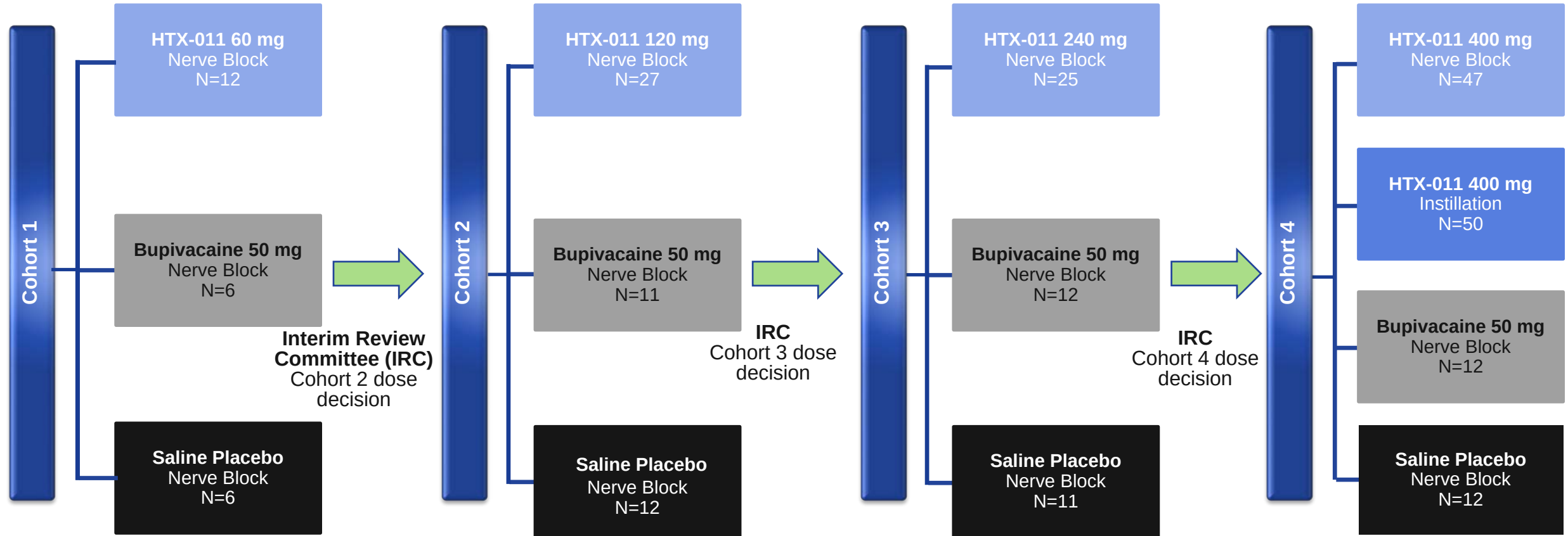
Opioid consumption is presented in mean milligrams of morphine equivalents

Can HTX-011 Study 209 and the Exparel PILLAR* TKA Study be Compared?

- Cross-study comparison between these 2 studies is more difficult than other cross-study comparisons due to several factors including different anesthesia and background analgesics:
 - PILLAR Study used spinal anesthesia and scheduled postoperative acetaminophen and celecoxib mandated until discharge plus opioids permitted as rescue medication. Since mean pain data for 0-12 hours from the study not shown, we don't know how long the spinal anesthesia used in that study provided a pain benefit postoperatively (if patients start with lower pain, they have less pain later using wWOCF). Both placebo and Exparel arms received the same background dose of bupivacaine 100 mg
 - Study 209 used general anesthesia and pain medications not permitted after surgery except for opioid rescue medication. Placebo and bupivacaine HCl active-control (125 mg) arms included
- Data from Pillar don't make sense:
 - Pain AUC12-48 in PILLAR-BPV control group was 30% lower than BPV group in Study 209, yet the PILLAR patients took 70% more opioid, even with background scheduled non-opioid analgesics
 - While the mean opioid use in the PILLAR-control arm of 84.9 MME is excessively high (equal to 17 doses of morphine 5 mg in 48 hours), the doses >220 MME used by 2.9% of Exparel patients and 8.7% of control patients are almost twice allowed by the protocol (maximum opioid rescue in the protocol was 120 MME in 48 hours); these patients took the equivalent of almost 5 mg of morphine every hour for 48 hours
 - Considerable statistical issues with the analysis of the data as detailed by Stanford Professor Steven Shafer in a letter to the editor**
- PILLAR Investigators asked to publish the actual pain data (both wWOCF and LOCF) to better understand magnitude and duration of efficacy of Exparel in TKA

*Mont MA, et al. *The Journal of Arthroplasty* (2017) doi: 10.1016/j.arth.2017.07.024 **Shafer S. Letter to the Editor (2018) doi.org/10.1016/j.arth.2018.03.032

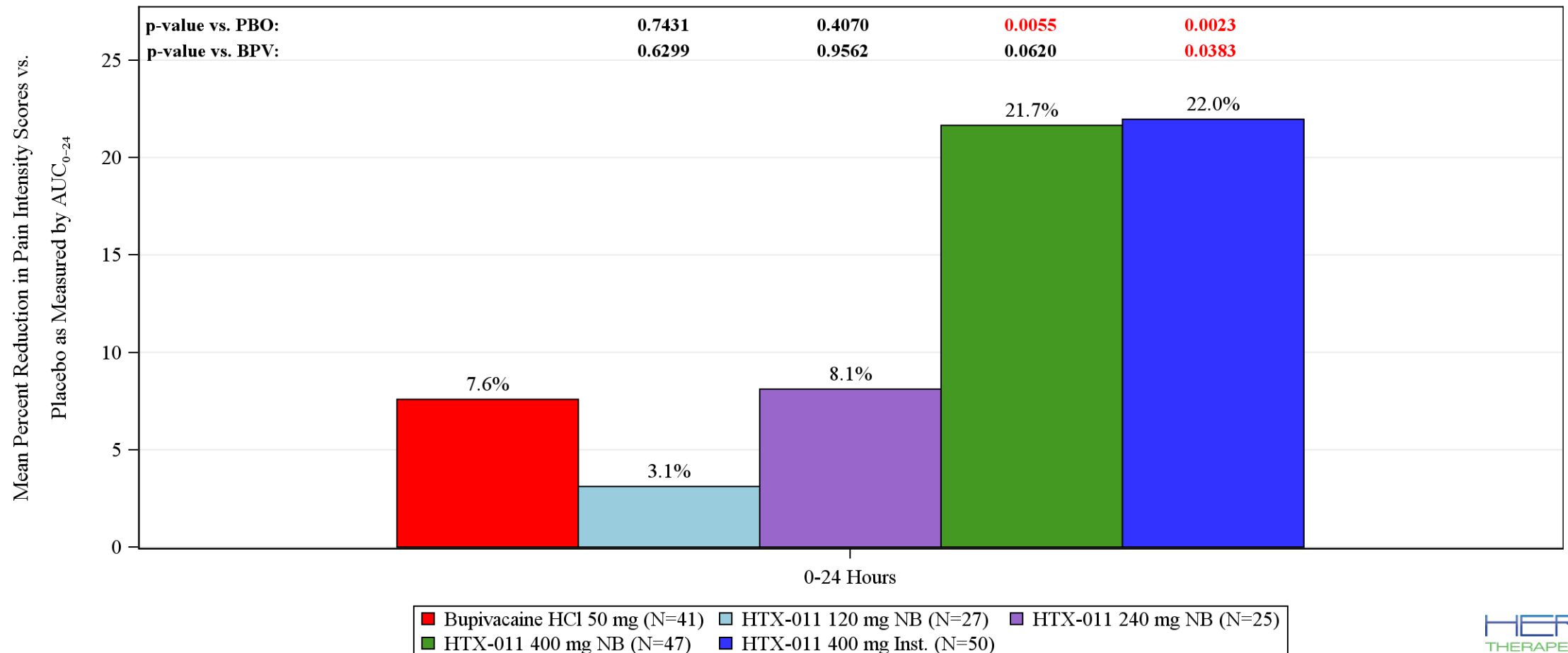
Study 211: Phase 2b Breast Augmentation Study Design



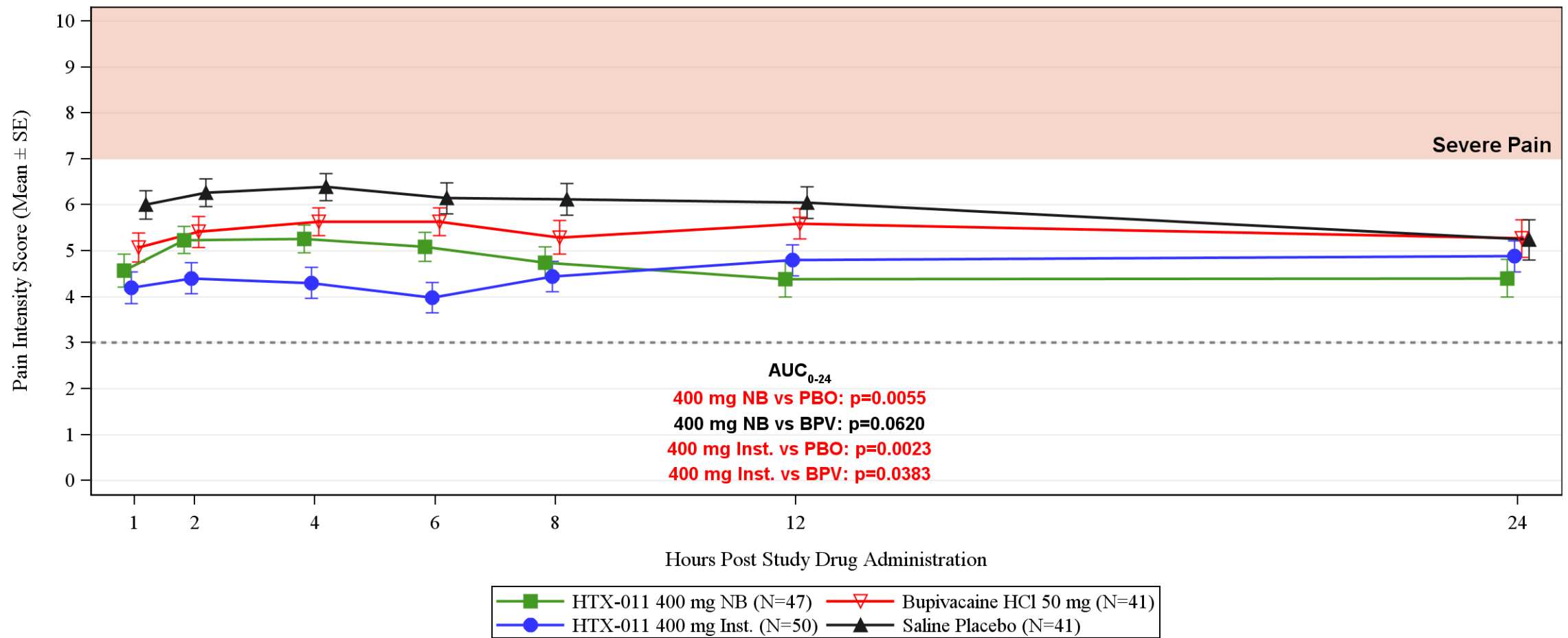
Protocol includes additional optional cohorts to evaluate other doses and administration techniques

Study 211: Pain Reduction from HTX-011 at Rest Approximately Triple that of Bupivacaine

HTX-011 achieved primary endpoint for AUC_{0-24} with activity and at rest



Study 211: HTX-011 Instillation Shows Superior Reduction in Pain at Rest Intensity Early and HTX-011 Nerve Block Shows Durable Response

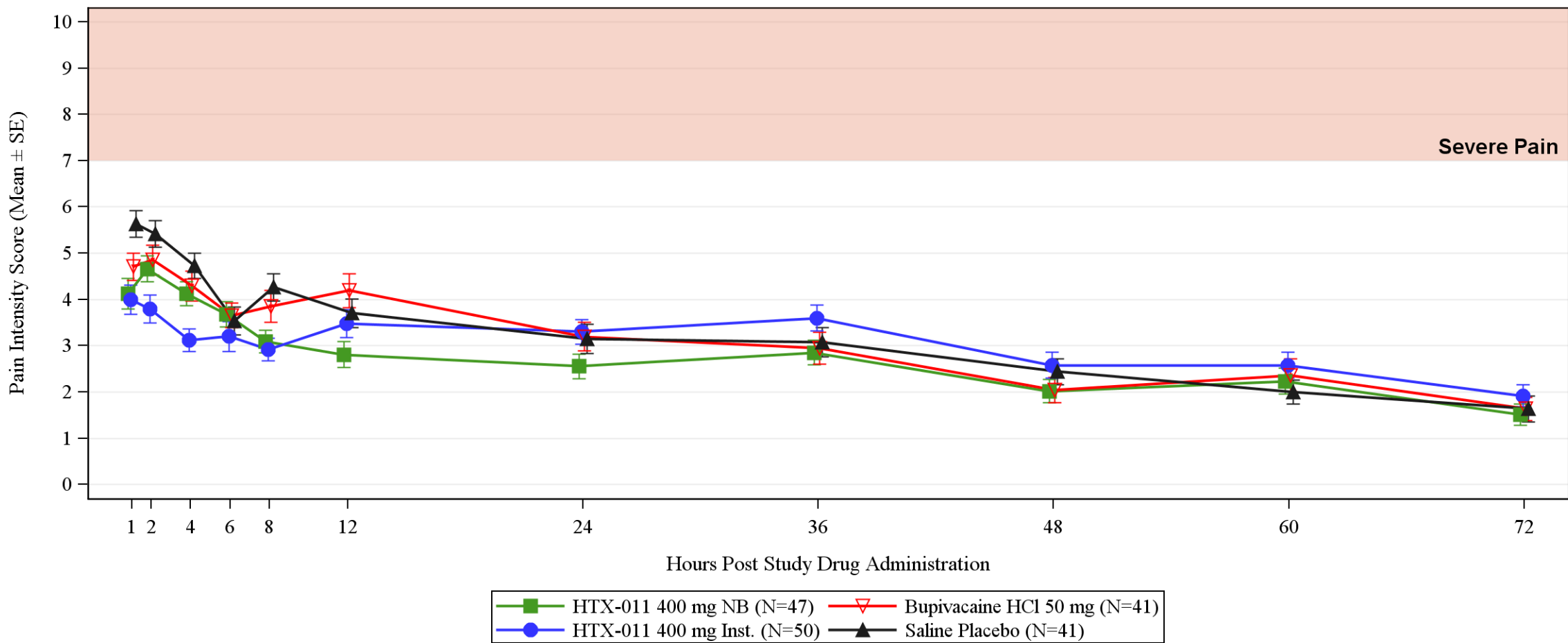


Notes:

Pain intensity collected at rest

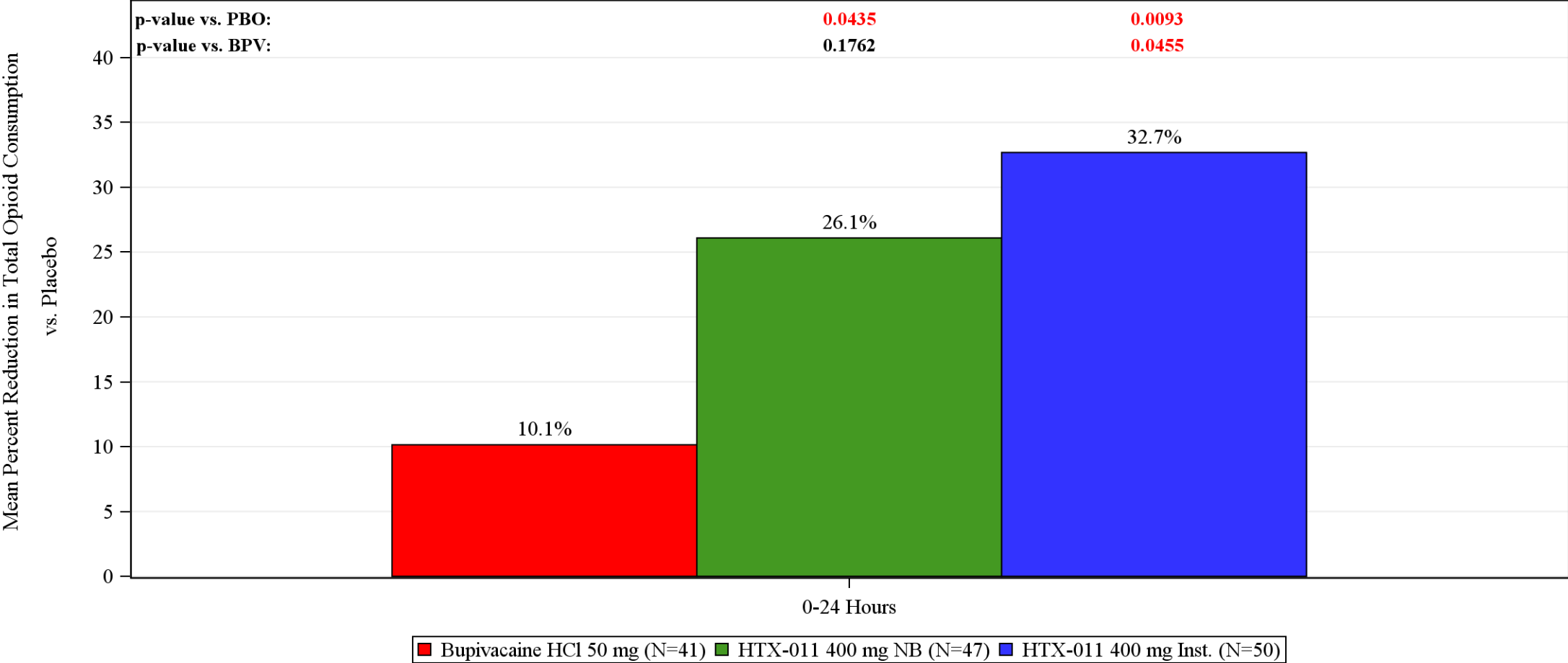
wWOCF, windowed-worst observation carried-forward for use of opioid rescue medication and LOCF for missing pain data

Study 211: Raw Pain Scores in All Arms Drop Quickly; Difficult to Discriminate between Arms after 24 Hours



Notes:
Raw pain intensity collected at rest
Scores not adjusted for opioid use

Study 211: Both HTX-011 Arms Significantly Reduce Opioid Use vs. Placebo through 24 Hours



Opioid consumption is presented in mean milligrams of morphine equivalents

Safety Summary

HTX-011 was generally well tolerated across all Phase 2 and Phase 3 studies with no clinically meaningful differences in:

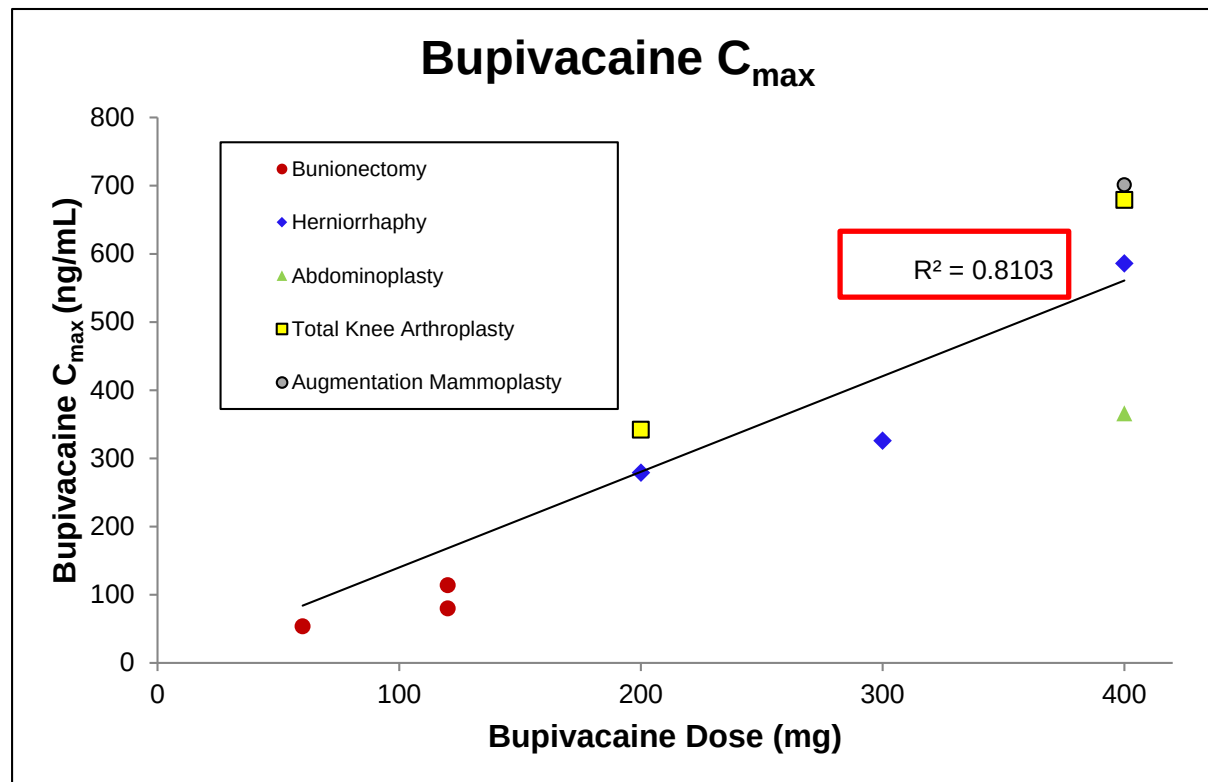
- Overall adverse events
- The incidence of serious adverse events
- Premature discontinuations due to adverse events
- Potential local anesthetic systemic toxicity (LAST) adverse events
- Potential wound healing related adverse events in 4 of 5 surgical models
 - Small imbalance in wound healing events in bunionectomy likely due to the vasodilatory effects of bupivacaine with superficial surgery; incidence higher for bupivacaine HCl and HTX-011 compared with the saline placebo. No wound healing imbalances in the other 4 surgical models
- No deaths on HTX-011 (one on bupivacaine)



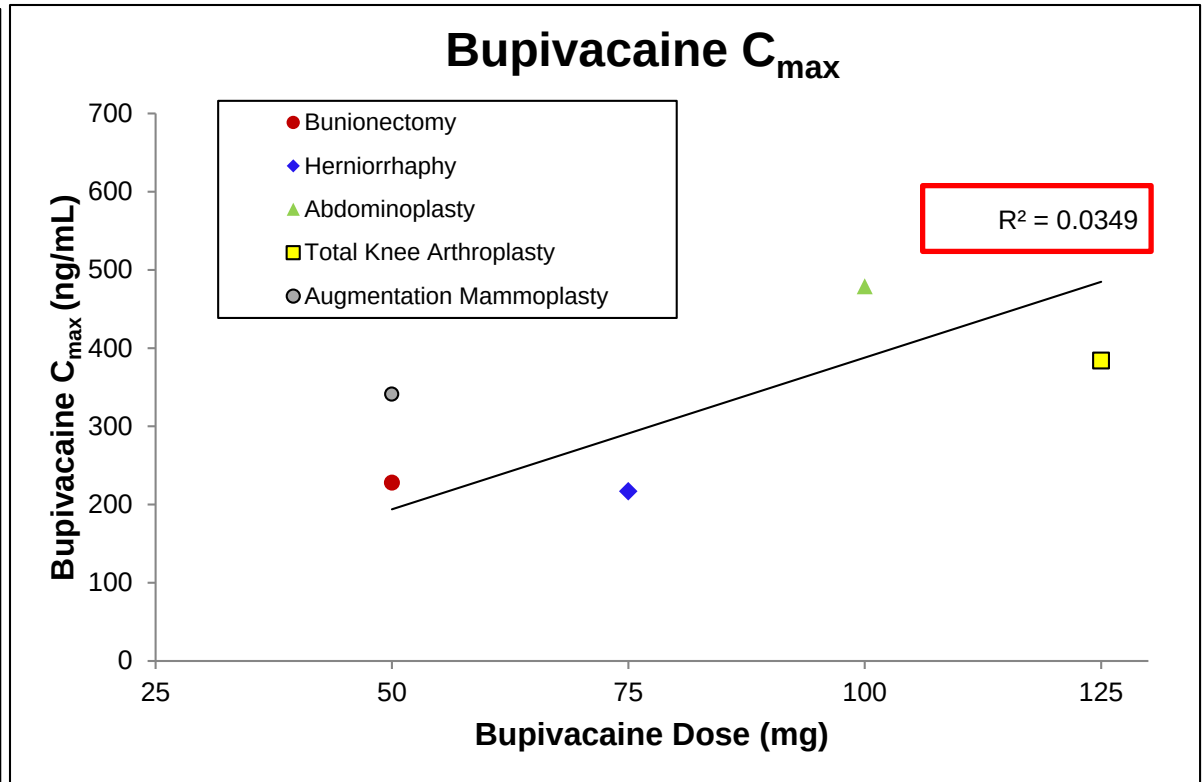
CONSISTENT PHARMACOKINETICS AND STRONG CORRELATION BETWEEN PK – PD ACROSS SURGICAL MODELS

HTX-011 Pharmacokinetics Across 5 Diverse Surgical Models Are Dose-Linear Versus Bupivacaine Solution

HTX-011

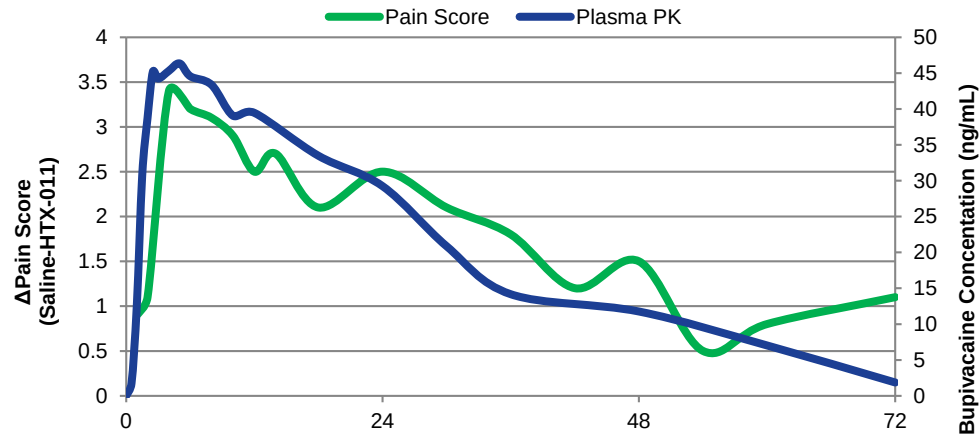


Bupivacaine HCl

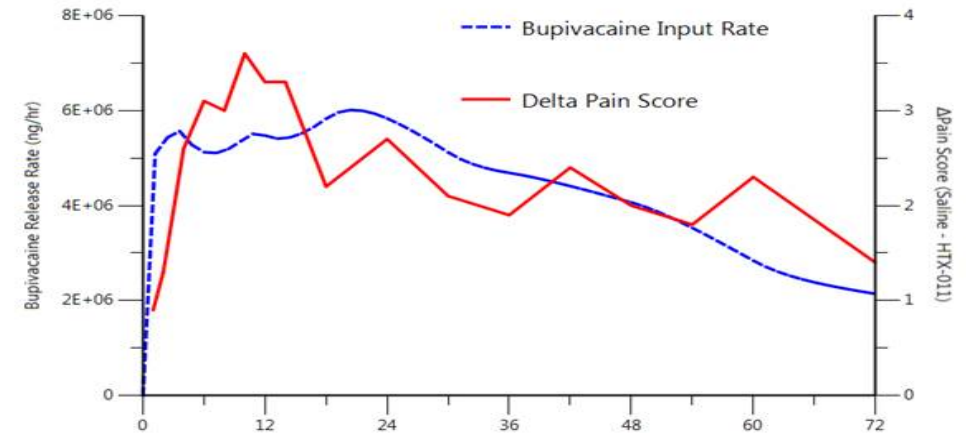


Correlation Between Pain Reduction and Pharmacokinetics of HTX-011 Across Surgical Models

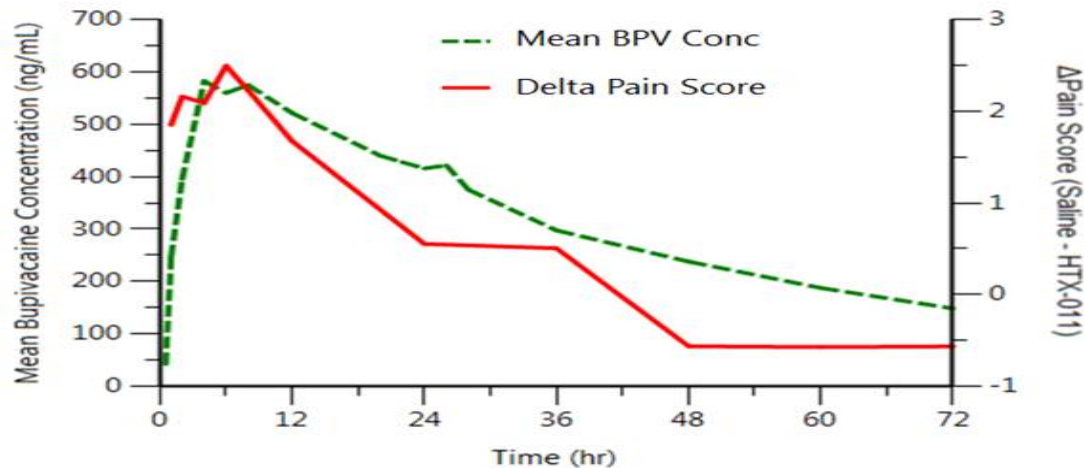
Bunionectomy



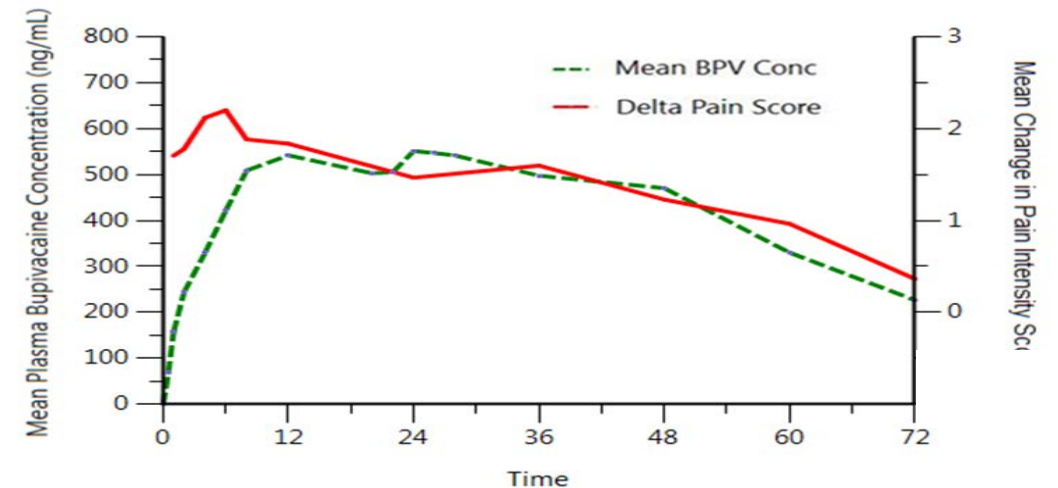
Hernia Repair



Breast Augmentation



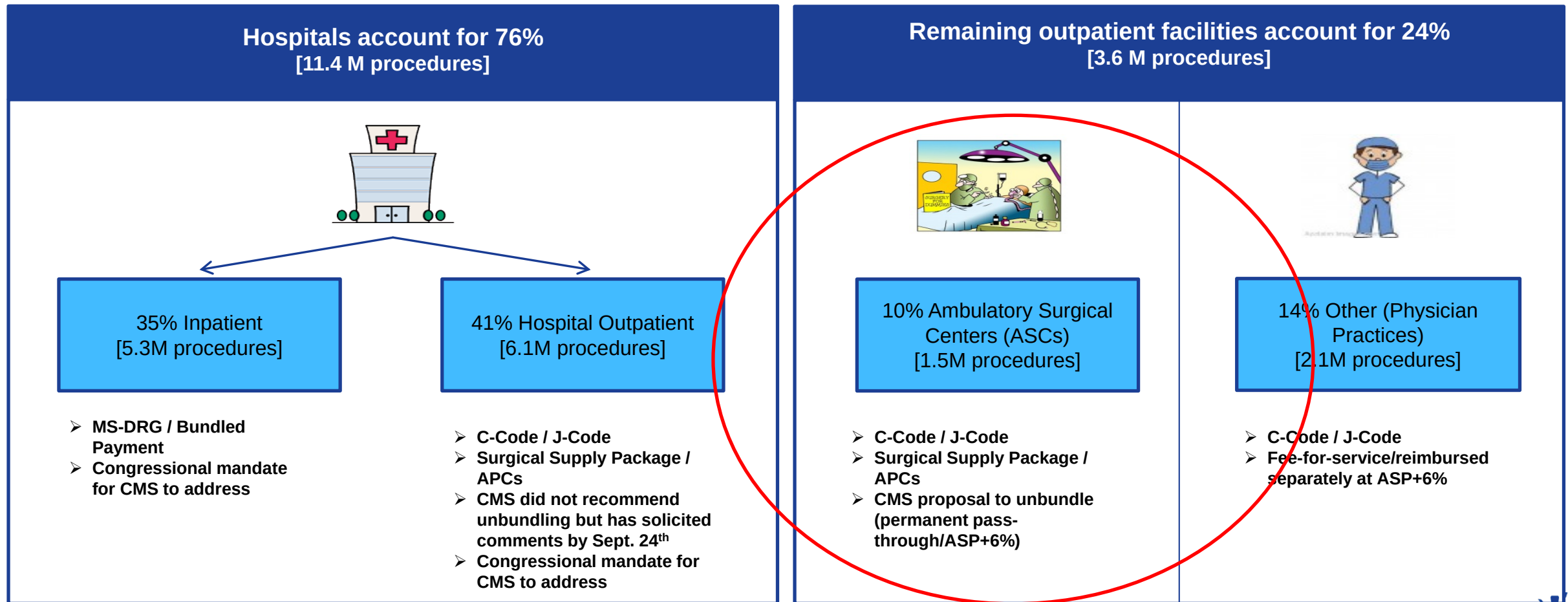
Total Knee Arthroplasty



HTX-011 NDA Filing Plans

- Goal is to file an NDA in 2018 requesting a broad label for reduction of postoperative pain for 72 hours and use of opioid analgesics after surgery
- HTX-011 produced significant reductions in both pain intensity and need for opioids through 72 hours post-surgery compared to placebo and bupivacaine solution, the standard of care, in both Phase 3 studies
- NDA will contain PK, efficacy and safety data from 5 surgical models with HTX-011 doses from 60 mg to 400 mg to support a broad label:
 - Bunionectomy (Phase 2 & 3 data)
 - Herniorrhaphy (Phase 2 & 3 data)
 - Abdominoplasty (Phase 2 data)
 - Total Knee Arthroplasty (Phase 2b data)
 - Breast augmentation (Phase 2b data)

9.7 Million Out of the 15 Million Initial Target Procedures (65%) Will Have ASP+6% Reimbursement At Launch*



*Based on obtaining a C-Code within 90 days of approval

340b Hospital Summary

- ~2258 hospitals (excluding children's & psych)
 - Perform 8.4M outpatient surgeries
 - 4.4M inpatient surgeries/year
- Manufacturers required to provide 23.1% discount off ASP/WAC
- Effective January 1, 2018, CMS reimbursement to hospitals for 340B drugs changed significantly from ASP+6% to ASP-22.5%
- Change enables CMS to capture most of the discounts manufacturers provide eligible hospitals
- **Products with pass-through status are exempt from this reimbursement change**

340B Drug Reimbursement

Without C-Code	With C-Code
ASP – 22.5%	ASP + 6%

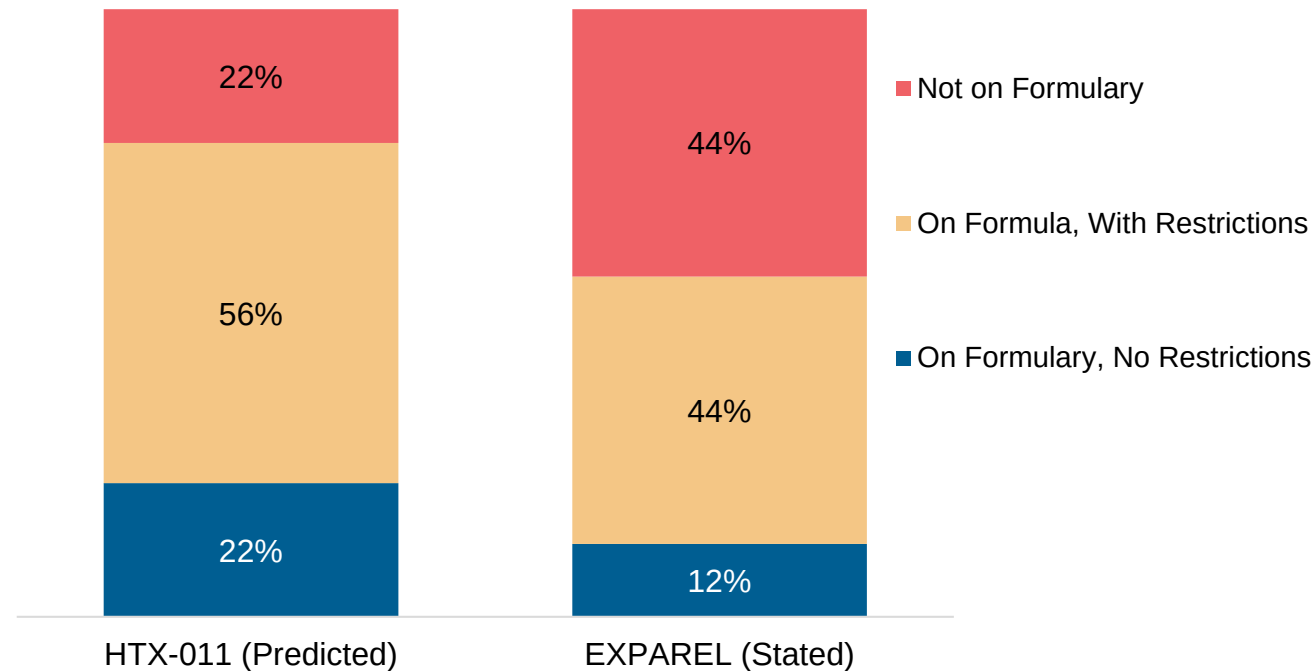
Being Second to Market is NOT a Significant Obstacle to Commercial Success

- First to market is not a guarantee of being the largest seller – Lipitor, Crestor, Eliquis, and Naropin for nerve block are good examples
- Penetration of Exparel is low (<6% of the addressable market) providing a significant unmet need and diminishing the obstacle to the acceptance of HTX-011
 - Across most product attributes, surveyed surgeons and pharmacy directors consistently prefer HTX-011 over Exparel based on their view of:
 - Unique mechanism of action
 - Superior efficacy profile of HTX-011, with significant benefit over bupivacaine HCl
 - Significant reduction in severe pain resulting in significant increase in opioid-free patients
 - Simple route of administration eliminating the need for up to 120 injections, with no need for extensive training
 - Surveyed pharmacy directors state that they would be provide better access to HTX-011 than the access currently enjoyed by EXPAREL

Sources: DRG Pharmacy Director Surveys

Pharmacy Directors State That They Would Provide Better Access to HTX-011 Than Currently Available to EXPAREL

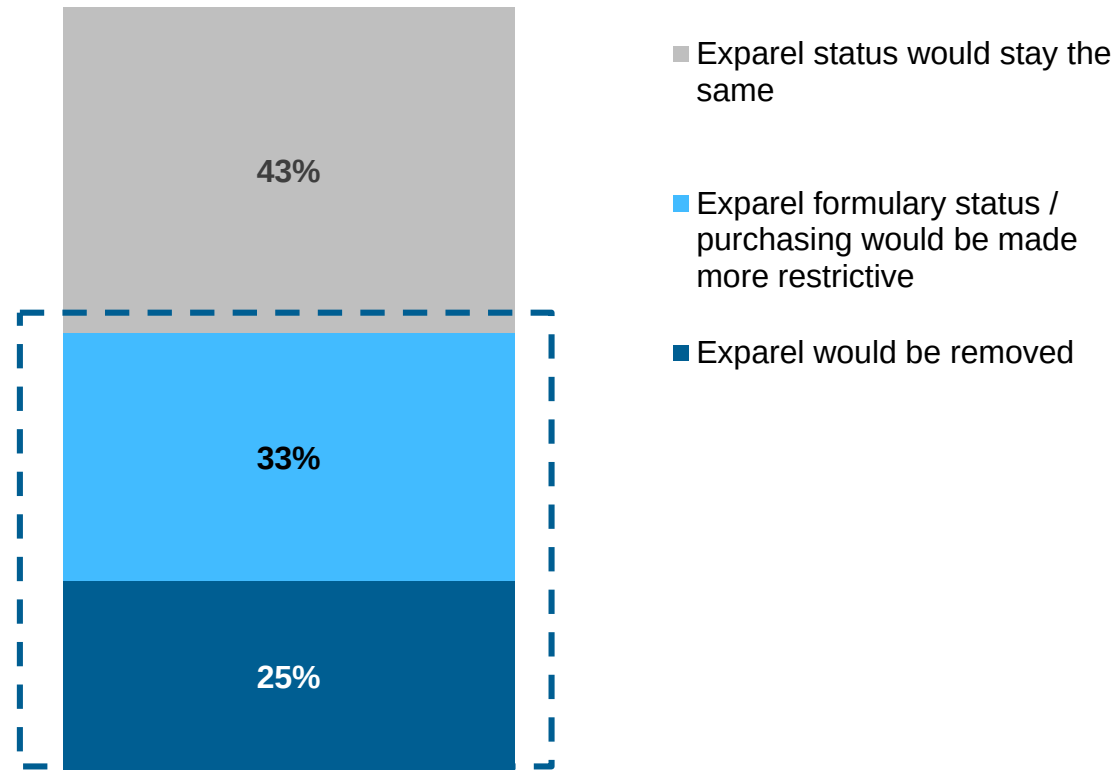
Formulary Status of Exparel vs. Expected HTX-011 Status



Sources: DRG Pharmacy Director Surveys

Up to 25% of Pharmacy Directors Report That Exparel Would be Removed From Formulary When HTX-011 Becomes Available

Impact of HTX-011 Launch on Exparel Formulary Status



% of Pharmacy Directors
(DRG Survey, 2018)

N = 40 Pharmacy Directors

Most pharmacy directors indicate HTX-011 would displace Exparel on formulary

- Over 50% of pharmacy directors report that if HTX-011 became available on their institution's formulary, Exparel would be subject to greater restrictions or would be entirely removed from formulary
- For institution's with less formulary consolidation, Exparel may continue to be stocked to accommodate a small segment of patients not using HTX-011

*"We can **encourage use of [HTX-011]** by making use of **standing order sets** and our EMR system, so if we continued to carry Exparel, we would make it restricted to only patients contraindicated to Product X."*
– Pharmacy Director

Large US Market Opportunity

Theoretical and Target Market

~28M Annual US Surgical Procedures Requiring Postoperative Pain Management That Were Considered Potentially Suited For HTX-011



*Based on the current WAC of Exparel

High-Value Procedures in Initial Target Market

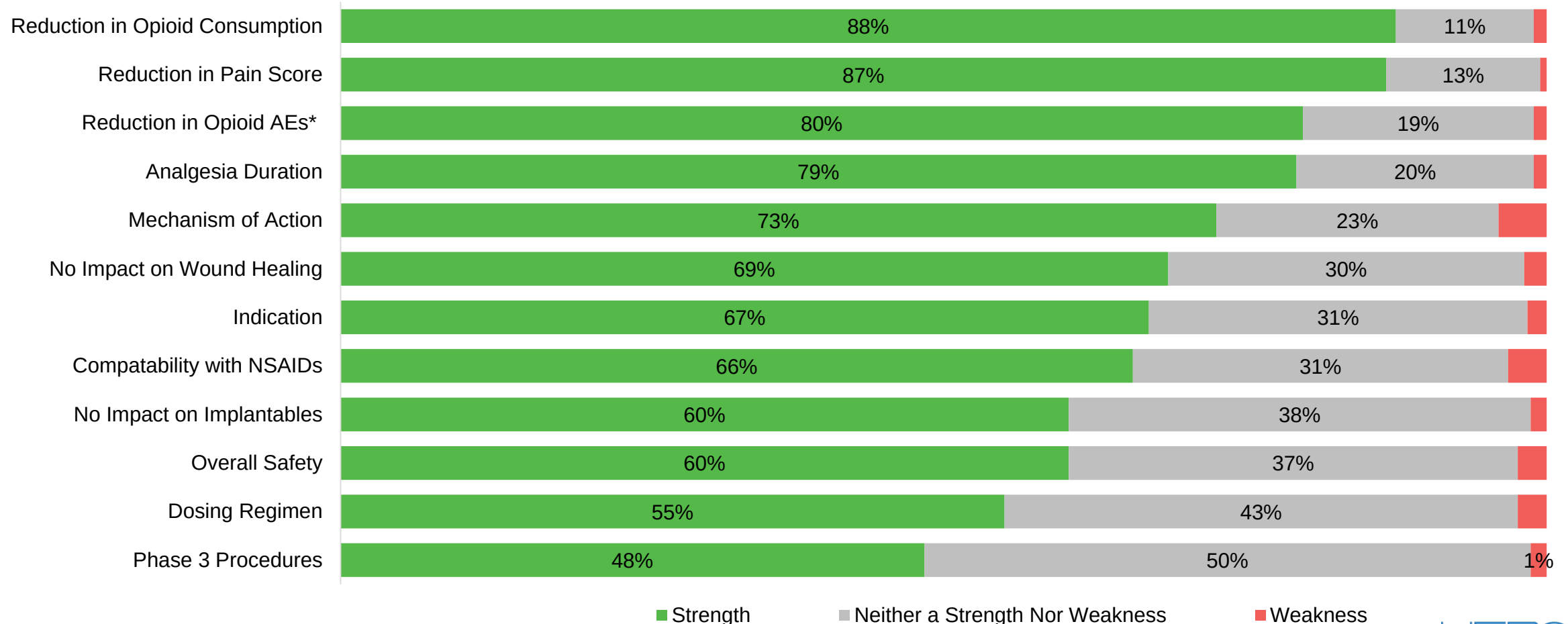
	Procedure	Annual Volume ('000s, US, 2015)						Overall % Local Anesthetic Use
		Total Procedures	Inpatient	Outpatient (C-code)	ASC (C-Code)	Medicare	Non-Medicare	Survey
Ortho Surgery	Knee arthroplasty	815	721	65	28	41%	59%*	87%
	Hip arthroplasty	337	325	7	5	43%	57%*	81%
	Shoulder arthroplasty	107	96	8	2	47%	52%*	89%
	Rotator cuff repair	550	11	343	192	27%	73%*	86%
	Spine procedures	750	463	249	36	35%	65%*	95%
General Surgery	Hernia repair	1,096	200	777	106	25%	74%	77%
	Hemorrhoidectomy	504	10	147	73	9%	37%*	88%
	Colon and small bowel resection	483	461	18	0.7	33%	66%*	82%
Plastic Surgery	Abdominoplasty	160	29	118	11	16%	83%	72%
	Mammoplasty	>300	10	92	19	6%	34%	85%
OB/GYN	C-Section	1,285	1273	6.1	0	2%	98%*	32%

*Note: For settings in which procedure-specific breakdown of Medicare vs. non-Medicare was not available, the overall Medicare vs. non-Medicare breakdown was applied to the total volume of procedures occurring in the given setting

Completed studies

Overwhelmingly Positive Response by Physicians and Pharmacists to HTX-011's Target Product Profile

HTX-011 Target Product Profile: Strengths



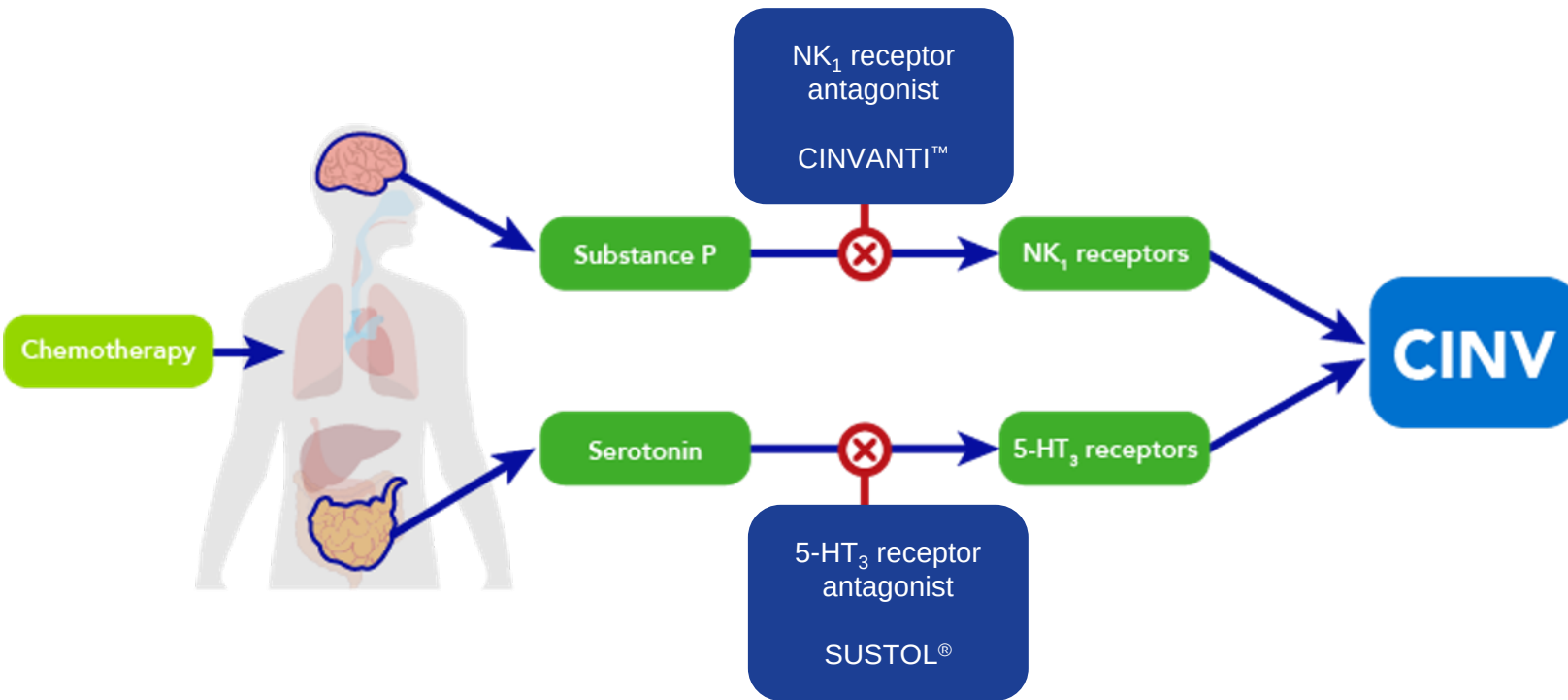
n = 376 total (101 anesthesiologists, 51 general surgeons, 122 orthopedic surgeons, 50 plastic surgeons, 52 pharmacy directors)

*Opioid AE's are assumed to be reduced with significant reduction in use



CINV Commercial Products

CINV Prophylaxis Typically Requires Two Complimentary Mechanisms of Action



NK₁ receptor antagonists

- Substance P is primary driver of delayed CINV, but related to ~15% of acute failures
- EMEND® IV (fosaprepitant), which has 90% share of the US NK₁ market, contains the synthetic surfactant polysorbate 80 that has been associated with **serious** hypersensitivity and infusion site reactions

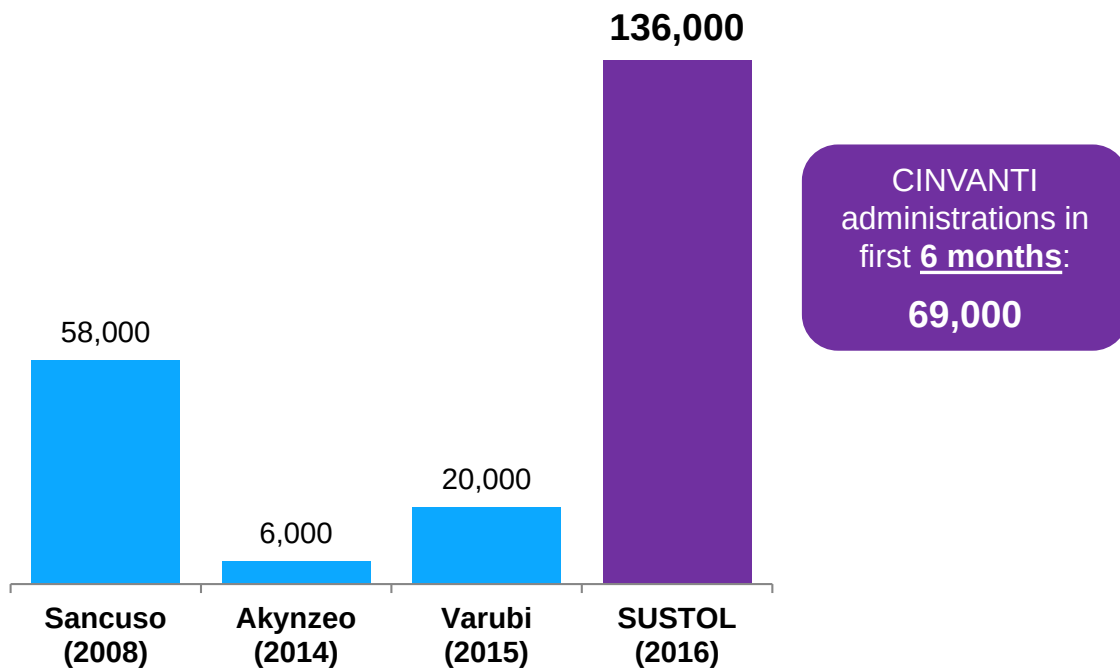
5-HT₃ receptor antagonists

- These are the backbone of CINV prophylaxis
- Excessive serotonin release is the primary driver for CINV in the acute phase and secondary driver in the delayed phase

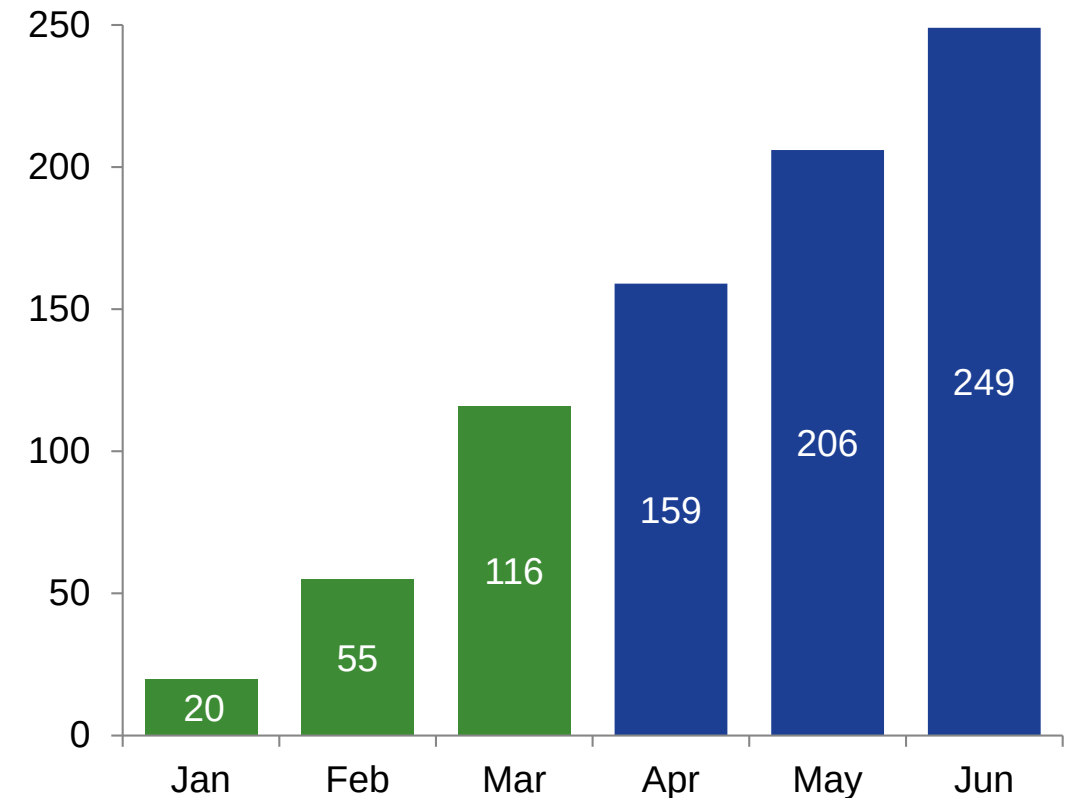
Heron's CINV Portfolio Continues to Outperform All Recent CINV Branded Launches

CINV Brand Launches Since 2008

Approximate administrations in
First 18 Months (launch aligned)

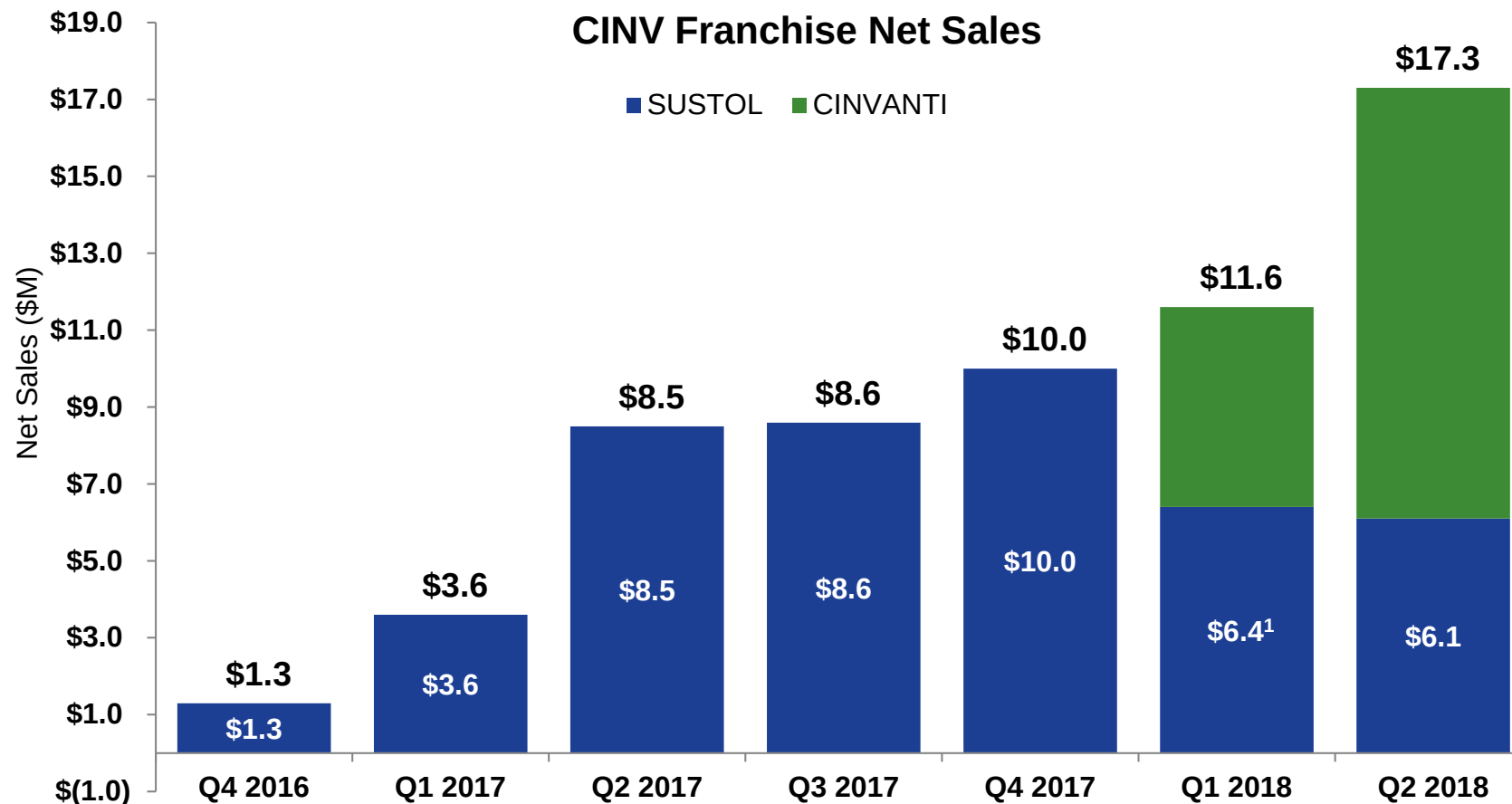


CINVANTI Ordering Accounts Since Launch



Sources: IMS DDD; Heron actuals (distributor 867 reports); due to data availability, Sancuso data includes actuals for launch months 3-12 and estimates for months 1-2; Varubi includes actuals for launch months 1-15 and estimates for months 16-18

Heron CINV Portfolio achieved \$17.3M Q2 2018 Net Sales



¹If it were not for the fact that the Company adopted the required revenue recognition rules (Topic 606) on January 1, net sales would have been \$7.7M

2018 CINV Franchise Outlook

✓ **SUSTOL®:** We continue to expect core SUSTOL business to be weak during the palonosetron arbitrage with growth thereafter

✓ **CINVANTI®**

- We believe it has the best overall profile compared to the other available NK₁ antagonists
- Offers strong strategic and operational fit with existing commercial organization
- We continue to see steady growth in the marketplace

✓ **CINV Franchise**

- **2018 guidance: full-year CINV net product sales at the upper end of our prior \$60 million to \$70 million guidance**

Financial Summary

Summary Statement of Operations and Net Cash Used in Operations (In thousands, except per share data)	Three Months Ended June 30, 2018	Six Months Ended June 30, 2018
Net product sales	\$ 17,277	\$ 28,844
Operating expenses ¹	56,130	119,687
Other income (expense), net	183	(92)
Net loss ¹	\$ (38,670)	\$ (90,935)
Net loss per share ²	\$ (0.54)	\$ (1.33)
Net cash used in operations	\$ (60,729)	\$ (122,442)

Condensed Balance Sheet Data (In thousands)	June 30, 2018
Cash, cash equivalents and short-term investments	\$ 422,964
Accounts receivable, net	\$ 45,886
Total assets	\$ 510,556
Promissory note payable	\$ 25,000
Total stockholders' equity	\$ 431,891

Common shares outstanding at June 30, 2018 totaled 77.6 million.

¹ Includes \$7.8 million and \$15.5 million of non-cash, stock-based compensation expense for the three and six months ended June 30, 2018, respectively.

² Based on 72.0 million and 68.4 million weighted-average common shares outstanding for the three and six months ended June 30, 2018, respectively.

Key Catalysts in Pain Management & CINV

Franchises

HTX-011 for Postoperative Pain	CINVANTI [®] and SUSTOL [®] for CINV
✓ Fast Track designation granted	2018 net sales guidance for CINV franchise: upper end of \$60M - \$70M
✓ Completed enrollment in Phase 3 pivotal trials	
✓ Top-line Pivotal Phase 3 results 1H 2018	
✓ Topline results from breast augmentation and TKA studies late 1H 2018	
✓ Breakthrough Therapy designation received from FDA	
NDA filing 2018	