

Supplemental NDA (sNDA) for EXPAREL[®] (bupivacaine liposome injectable suspension) as a Nerve Block for Regional Analgesia



February 14-15, 2018

Pacira Pharmaceuticals, Inc.

Anesthetic and Analgesic Drugs Advisory Committee

Introduction

Michael Rozycki, PhD

Vice President, Regulatory Affairs

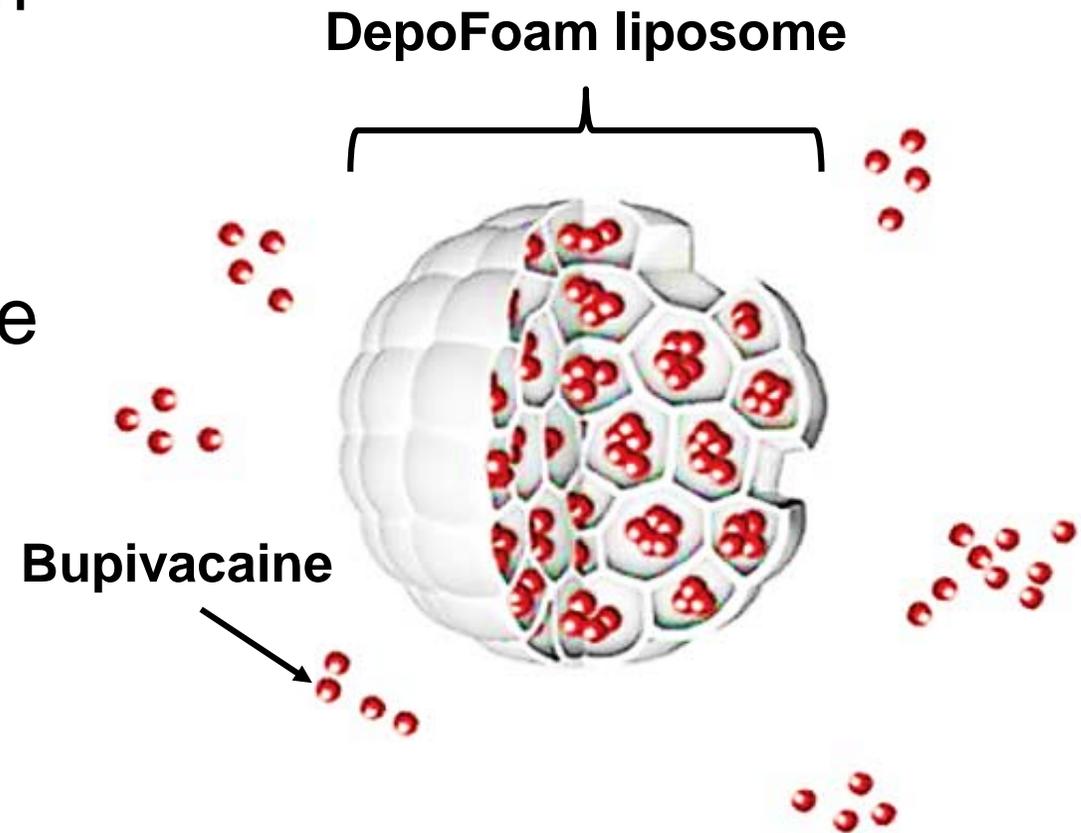
Pacira Pharmaceuticals, Inc.

EXPAREL Overview

- FDA approved, opioid-free, bupivacaine-based, long-acting local anesthetic
- Bupivacaine used for nearly 50 years
 - WHO essential medication
- EXPAREL used more than 3,000x per day via infiltration / field block for safe and effective, long-lasting analgesia
- EXPAREL can reduce postsurgical use of opioids
- Data support broad nerve block indication

EXPAREL: DepoFoam[®] Encapsulated Bupivacaine

- DepoFoam drug delivery system composed of multivesicular liposomes
- Extended release of bupivacaine for long-acting pain relief
- Analgesic effect localized to injection site



EXPAREL Approved in 2011 for Infiltration/Field Block

- Based on 2 positive Phase 3, randomized, double-blind, placebo-controlled trials
- Demonstrated efficacy in 2 representative acute pain models
 - Hemorrhoidectomy
 - Bunionectomy

Initial Clinical Studies of EXPAREL as Nerve Block

Study	Region	Nerve Block	Clinical Setting
Study 322	Thoracic	Intercostal	Thoracotomy
Study 323	Lower	Femoral	Total knee arthroplasty [TKA]

Supplemental NDA (sNDA) for Nerve Block

- May 2014: sNDA for nerve block for regional analgesia
- February 2015: Complete Response Letter
 - Demonstration of efficacy in at least 1 additional setting
 - Additional PK data through T_{max} and characterization of onset and duration of femoral block
 - Analyses of existing cardiac safety data
- October 2017: sNDA resubmitted

Two Additional Phase 3 Studies to Support Efficacy and Safety of EXPAREL for Nerve Block

Study	Region	Nerve Block	Clinical Setting
Study 326	Lower	Femoral	TKA
Study 327	Upper	Brachial plexus	Total shoulder arthroplasty [TSA] or rotator cuff repair [RCR]

Data Addresses CRL Approvability Requirements

- Demonstration of efficacy in at least 1 additional setting
 - ✓ Study 327 met all primary and secondary endpoints
- Additional PK data through T_{max} and characterization of onset and duration of femoral block
 - ✓ Study 326 characterized PK and sensory/motor data
- Analyses of existing cardiac safety data
 - ✓ No evidence of cardiac toxicity

Our Presentation Will Address Key FDA Briefing Book Concerns

FDA Concern	Key Conclusions
Pharmacokinetic (PK) Variability	Lower maximum concentrations with EXPAREL vs. bupivacaine HCl
Applicability of Data to Other Nerve Blocks	Clinical data support broad nerve block indication
Comparator Group	Initial EXPAREL approval (and nerve block program) based on placebo-controlled trials
Local Anesthetic Systemic Toxicity	Data suggest lower risk vs. bupivacaine HCl

Current EXPAREL Indication for Infiltration

EXPAREL is a liposome injection of bupivacaine, an amide local anesthetic, indicated for single-dose infiltration into the surgical site to produce postsurgical analgesia

- Written FDA correspondence in 2015
 - Statements in EXPAREL label created ambiguity regarding scope of approved indication
 - Indication encompasses field blocks (e.g. TAP)

Proposed Integrated Indication

EXPAREL is a liposome injection of bupivacaine, an amide local anesthetic, indicated for single-dose infiltration to produce local analgesia and as a nerve block to produce regional analgesia

Agenda

**Rationale for Use of
EXPAREL as a Nerve Block**

Anoushka Afonso, MD
Memorial Sloan Kettering Cancer Center

Efficacy

Roy Winston, MD
Pacira Pharmaceuticals, Inc.

Safety

Richard Scranton, MD, MPH
Pacira Pharmaceuticals, Inc.

Clinical Perspective

Jeffrey Gadsden, MD
Duke University School of Medicine

Conclusion and Q&A

Richard Scranton, MD, MPH
Pacira Pharmaceuticals, Inc.

Additional Responders

- **Statistics**
Jason Connor, PhD
Lead Statistical Scientist
ConfluenceStat, LLC
- **Pharmacovigilance**
Judith Jones, MD, PhD
President and CEO
The Degge Group, Ltd, a PharmaLex Company
- **Anesthesiology**
Margaret Holtz, MD
Director, Orthopedic Anesthesia & Acute Pain
WellStar Kennestone Regional Medical Center
- **Anesthesiology and Neuroscience**
Susanna Byram, MD, PhD
Assistant Professor
Anesthesiology and Critical Care Medicine
Loyola University Health Systems
- **Cardiology and Cardiac Electrophysiology**
Robert Kleiman, MD
Chief Medical Officer and Vice President
Global Cardiology
eResearch Technology (ERT)
- **Cardiothoracic Surgery**
David Rice, MB, BCh, BAO, FRCSI
Professor, Thoracic and Cardiovascular Surgery
The University of Texas
MD Anderson Cancer Center
- **Pharmacokinetics**
Neal Davies, BSc(Pharm), PhD, RPh
Dean and Professor
Pharmacy and Pharmaceutical Sciences
University of Alberta

Rationale for Use of EXPAREL as a Nerve Block

Anoushka Afonso, MD

Director, Enhanced Recovery after Surgery (ERAS)

Memorial Sloan Kettering Cancer Center

Multimodal Management Recommended to Manage Acute Postsurgical Pain

- Combines ≥ 2 analgesic agents or techniques that act by different mechanisms to provide better pain relief with fewer opioids
- Usually includes systemic analgesics with local anesthetics

	RESEARCH EDUCATION TREATMENT ADVOCACY		The Journal of Pain, Vol 17, No 2 (February), 2016: pp 131-157 Available online at www.jpain.org and www.sciencedirect.com
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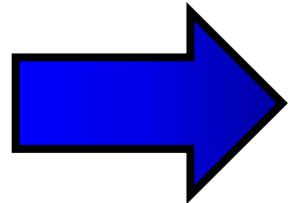
Guidelines on the Management of Postoperative Pain

Management of Postoperative Pain: A Clinical Practice Guideline
From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council

Memorial Sloan Kettering Cancer Center Enhanced Recovery After Surgery (ERAS) Programs

- Ovarian
- Colorectal
- Breast reconstruction
- Cystectomy
- Thoracic
- Pediatric
- Ambulatory (< 23 hour stays)

ERAS

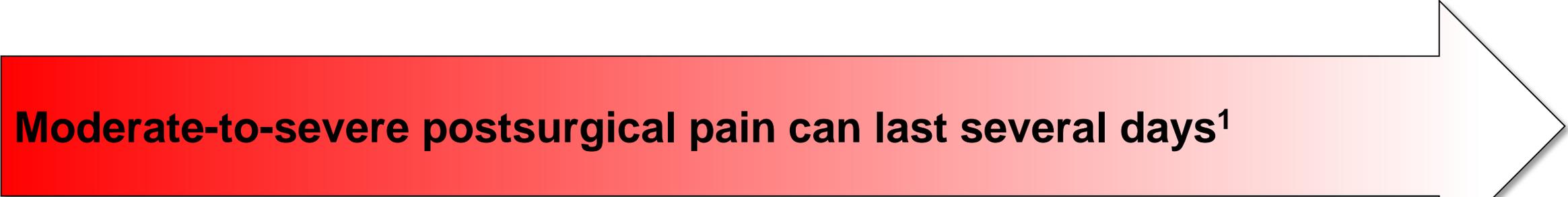


- Reduction in opioid consumption
- Reduction in length of stay

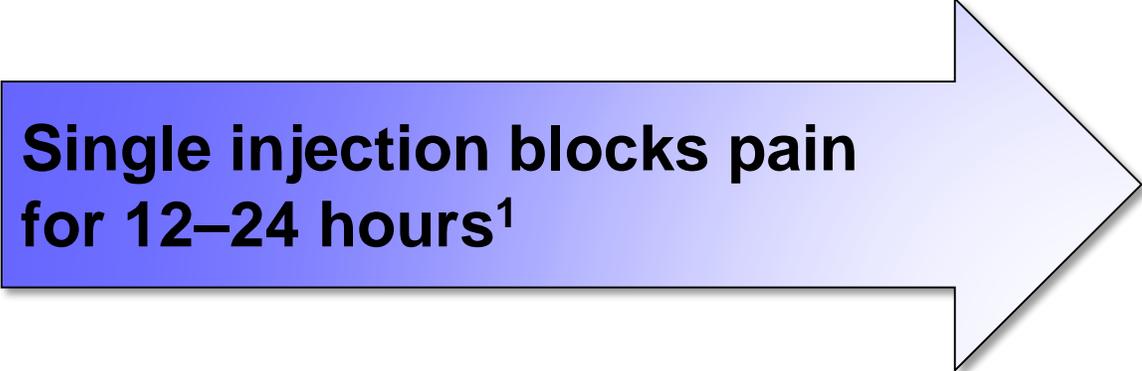
Local Anesthetics Can be Administered for Infiltration or as Nerve Block

Characteristic	Infiltration / Field Block	Nerve Block
Type of analgesia	Local	Regional
Number of injection(s)	Multiple	Single
Injection site(s)	Surgical site; peripheral nerve / plane	Near nerve or nerve bundle
Technique	Direct visualization	Ultrasound guidance
Nerve(s) targeted	Nerve endings	Large nerves
EXPAREL indicated?	Yes	No

Conventional Local Anesthetics Limited by Short Duration of Effect



Moderate-to-severe postsurgical pain can last several days¹



Single injection blocks pain for 12–24 hours¹

- **Untreated acute pain can lead to chronic pain²**

Current Options for Controlling Moderate-to-Severe Postsurgical Pain After Nerve Block

Continuous peripheral nerve block with catheter



Opioids



Limitations of Continuous Peripheral Nerve Block with Catheter and Pump

- Technically challenging and can take additional time
- Common clinical concerns¹⁻³
 - Catheter migration or dislodgment
 - Infection
 - Mechanical pump failure
 - Patient dissatisfaction
- Local anesthetic exposure commonly exceeds 400 mg/day^{4,5}

1. Jeng et al. *Br J Anaesth* 2010;105:i97-i107.

2. Joshi et al. *J Pain Res* 2015;8:781-9.

3. FDA. Infusion pump improvement initiative. 2010.

4. Rosenberg et al. *Br J Anaesth* 1991;66:25-30.

5. Esteve et al. *Ann Fr Anesth Reanim* 1990;9:322-5.

Opioids Associated with Common Adverse Events Leading to Increased Morbidity

- Opioid analgesics have negative adverse effects^{1,2}
 - Nausea
 - Vomiting
 - Constipation
 - Ileus
 - Confusion
 - Somnolence
 - Pruritus
 - Urinary retention
 - Dysphoria
 - Delirium
- Most serious risk: respiratory depression
 - 1 in 83 using PCA after surgery require naloxone rescue³

Postsurgical Opioid Use Linked to Long-term Opioid Use

1 in 16 opioid-naïve surgical patients become chronic users



1 year later

6.0% still on opioids

Longer initial exposure increases risk of long-term use



1 year later

13.5% still on opioids

Summary of Rationale for Using EXPAREL as Nerve Block

- EXPAREL is an extended-release form of bupivacaine
 - Bupivacaine: local anesthetic used for decades
- FDA-approved for infiltration and field block since 2011
- Advantages of expanding indication
 - Provide long-acting, single-shot nerve block
 - Reduce patients' exposure to opioids

Efficacy

Roy Winston, MD

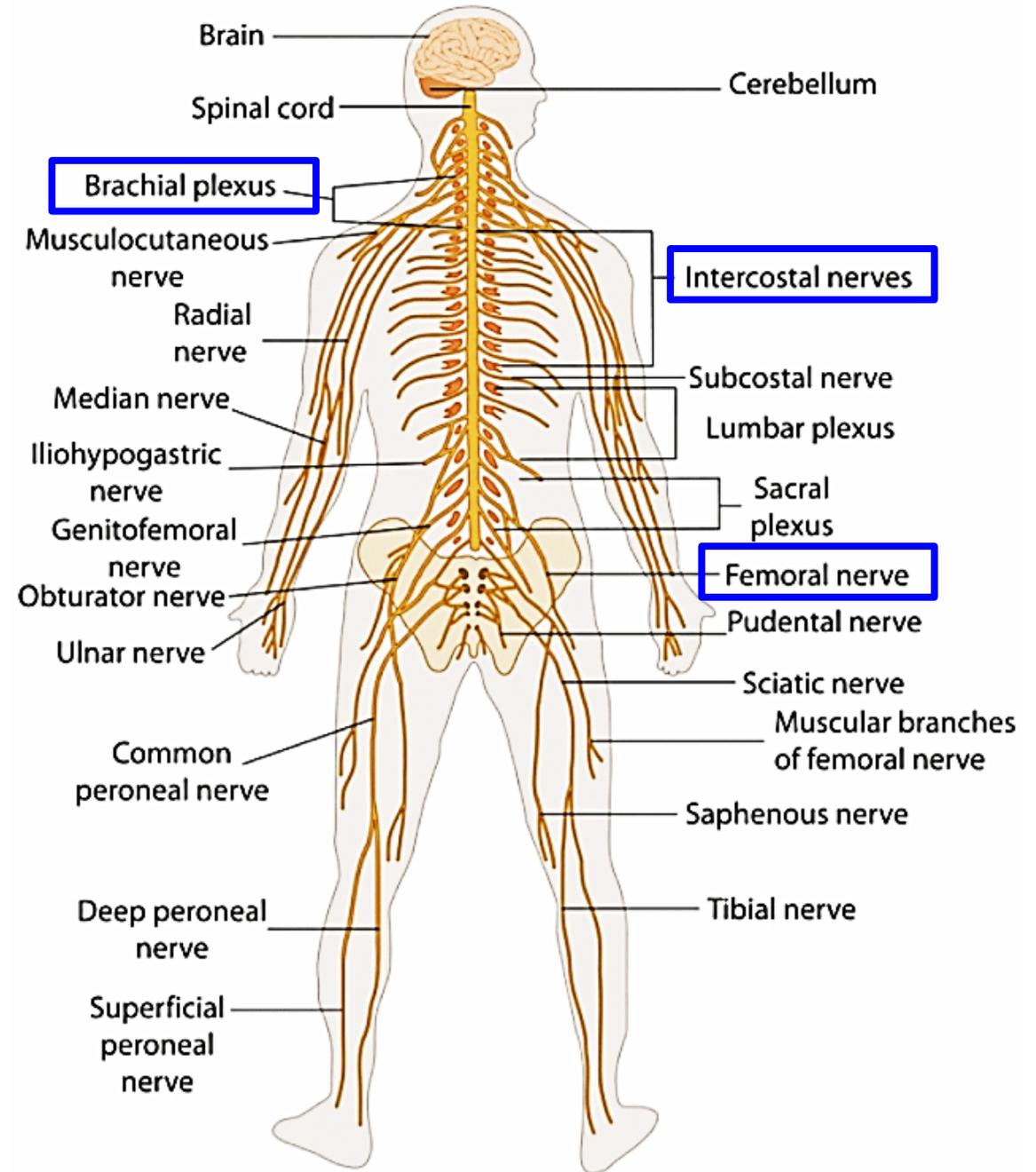
Sr. Vice President

Anesthesia, Surgery, and Medical Affairs

Pacira Pharmaceuticals, Inc.

EXPAREL Nerve Block Program Evaluated Representative Nerves

- Representative nerve block models chosen
 - Upper and lower extremities
 - Major single nerve and nerve plexus
- Two positive Phase 3 studies support approval



Four Phase 3 Randomized, Placebo-Controlled, Double-Blind, Multicenter Nerve Block Studies

Study	Region	Nerve Block	N	Surgery Type	Doses
327	Upper	Brachial Plexus	140	TSA/RCR	133 mg
322	Thoracic	Intercostal	185	Thoracotomy	266 mg
323 (Part 2)	Lower	Femoral	184	TKA	266 mg
326	Lower	Femoral	230	TKA	133 and 266 mg

Key Inclusion / Exclusion Criteria

- Adults (≥ 18 years of age)
- Scheduled to undergo corresponding procedure in trial
- Normal motor function
- No planned concurrent surgical procedure
- No long-acting opioids or NSAID (except for aspirin) within 3 days of surgery
- No opioids within 24 hours of surgery

Perioperative Analgesic Medications

Time Period	Medication
Preoperative	<ul style="list-style-type: none">▪ Low-dose aspirin and acetaminophen / paracetamol (3000 mg daily max) before study drug administration
Intraoperative	<ul style="list-style-type: none">▪ Short-acting opioids
Postoperative	<ul style="list-style-type: none">▪ Protocol-specified rescue medications

Rescue Medication

- Studies 327 (TSA/RCR) and 326 (TKA)
 - Immediate-release oxycodone PRN (5–10 mg q4h)
 - IV morphine or hydromorphone if oral meds could not be tolerated
- Study 322 (intercostal)
 - First rescue: IV fentanyl 100 mcg
 - Second rescue: PCA morphine or hydromorphone or IM morphine
- Study 323 (TKA)
 - First rescue: hydromorphone 0.5 mg IV bolus
 - Second rescue: PCA (morphine or hydromorphone)
 - Third rescue: femoral nerve block with bupivacaine HCl (1.25 mg/mL)

Primary and Secondary Efficacy Endpoints

Efficacy Endpoints	Study 327	Study 322	Study 323 (Part 2)	Study 326
Primary	VAS AUC through 48 hrs	NRS-R AUC through 72 hrs	NRS-R AUC through 72 hrs	VAS AUC through 72 hrs
Secondary (ranked)				
Total opioid use	1	1	1	1
% Opioid-free	2	not ranked	2	not ranked
Time to first opioid	3	2	3	2

Statistical Methods

- Efficacy analyses included all patients who received study drug and underwent planned surgery
- Windowed worst observation carried forward (wWOCF) procedure to account for rescue medication
- Missing data imputed using pre-specified method
 - LOCF or multiple imputation

Patient Characteristics

Characteristic	Study 327		Study 322		Study 323 (Part 2)		Study 326	
	EXPAREL N=69	Placebo N=71	EXPAREL N=94	Placebo N=91	EXPAREL N=92	Placebo N=92	EXPAREL N=151*	Placebo N=79
Age (yrs), mean	61	59	58	59	66	64	65	65
Caucasian	77%	76%	100%	100%	82%	84%	89%	85%
Hispanic/Latino	4%	7%	4%	3%	9%	10%	3%	3%
Female	36%	32%	32%	34%	57%	62%	52%	67%
US	75%	75%	2%	3%	100%	100%	50%	51%

*Two doses 133 mg and 266 mg

Patient Disposition

	Study 327		Study 322		Study 323 (Part 2)		Study 326	
	EXPAREL	Placebo	EXPAREL	Placebo	EXPAREL	Placebo	EXPAREL	Placebo
Randomized	69	72	96	95	99	97	153*	79
Analyzed	69	71	94	91	92	92	151*	79
% Completed	99%	99%	85%	78%	83%	85%	97%	94%
Reason for discontinuation (n)								
Lack of efficacy	-	-	8	10	2	2	-	-
AE	-	-	2	4	-	-	1	1
Withdrawal	-	-	-	2	3	3	3	4
Lost to follow-up	-	-	-	-	2	-	-	-
Death	-	-	2	4	-	-	-	-
Other	1	-	2	1	10	10	1	-

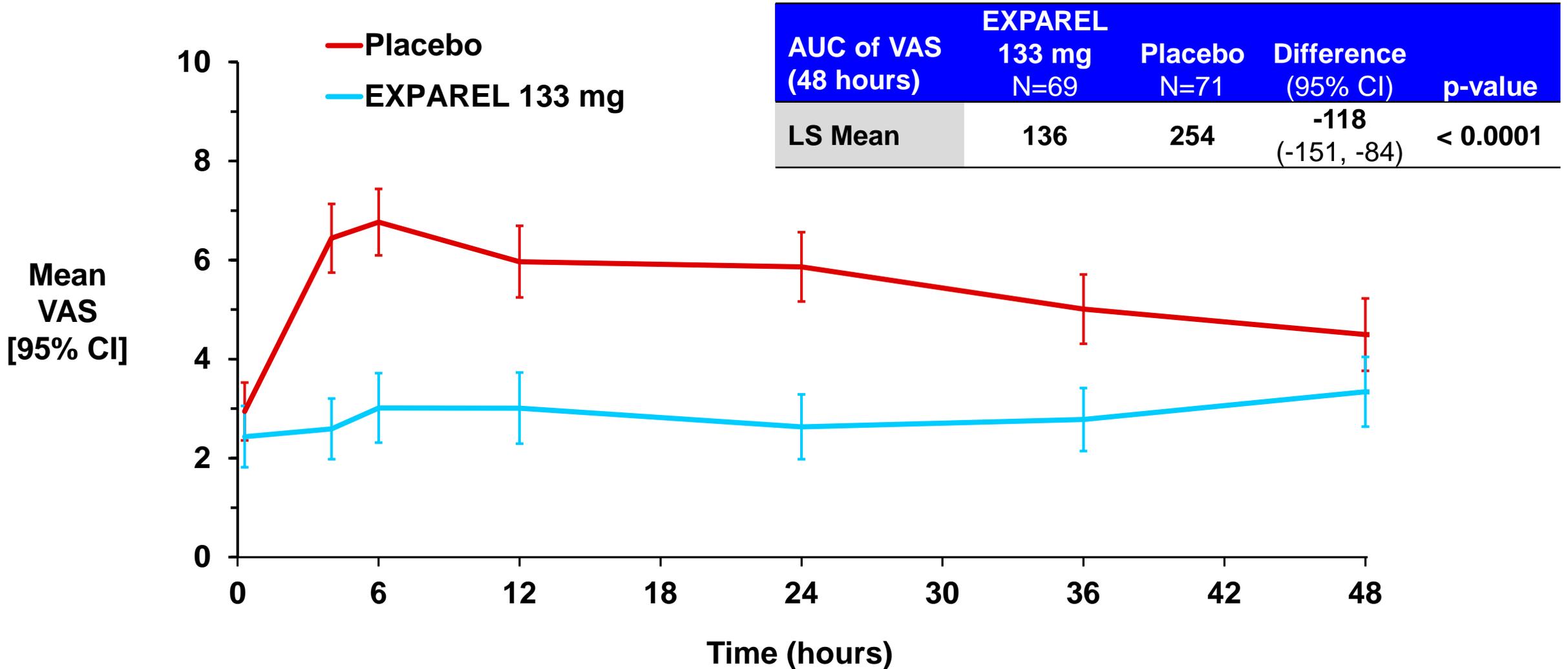
*Two doses 133 mg and 266 mg

Study 327

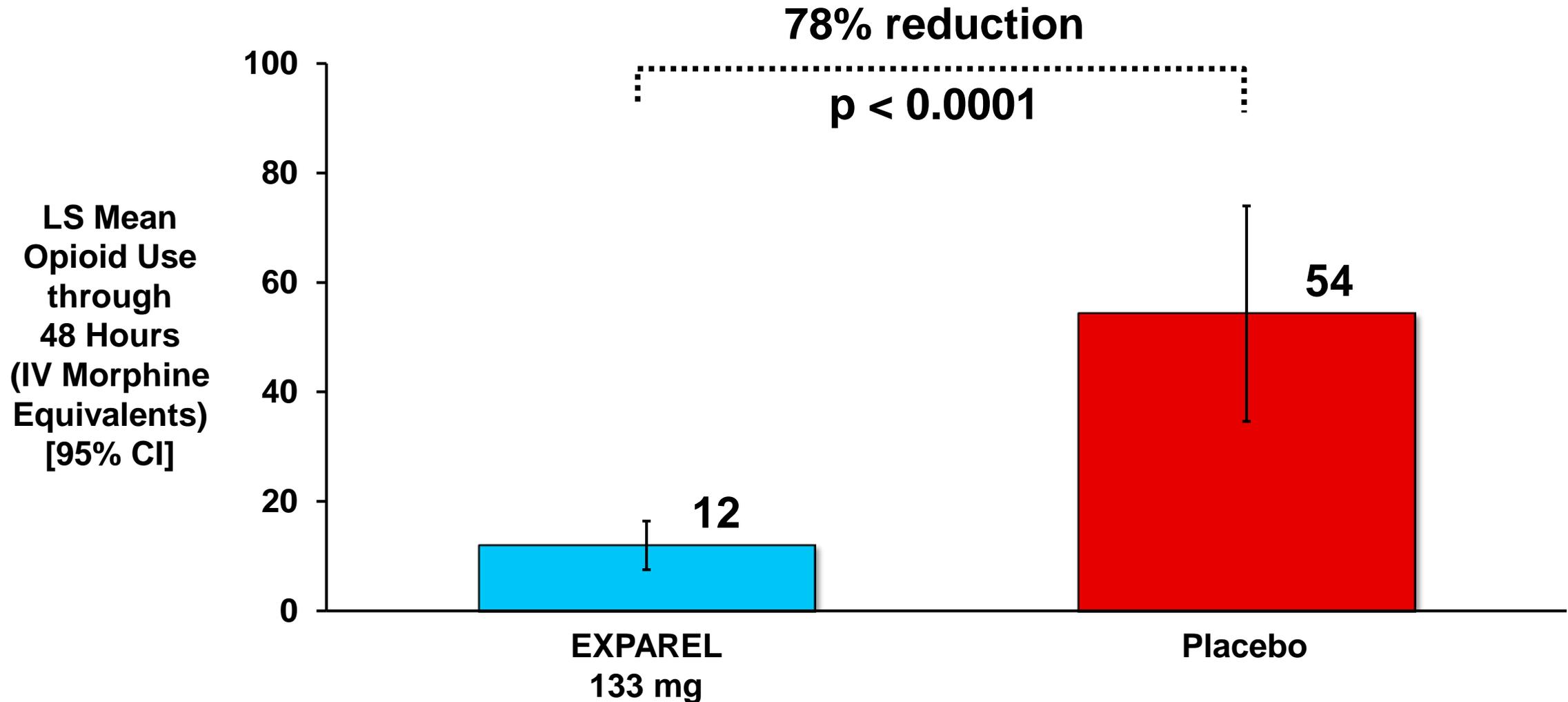
Brachial plexus nerve block in TSA/RCR

- EXPAREL 133 mg

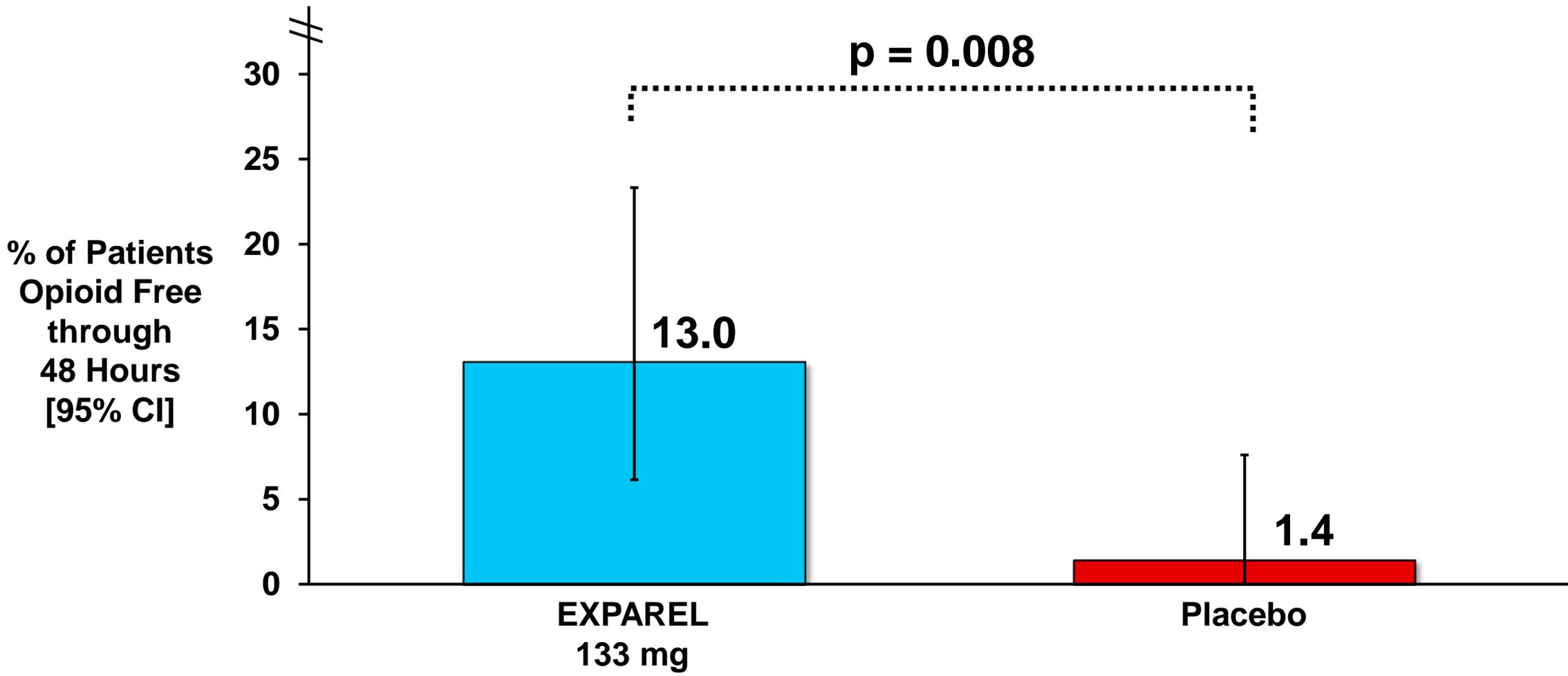
Study 327: Primary Endpoint Met



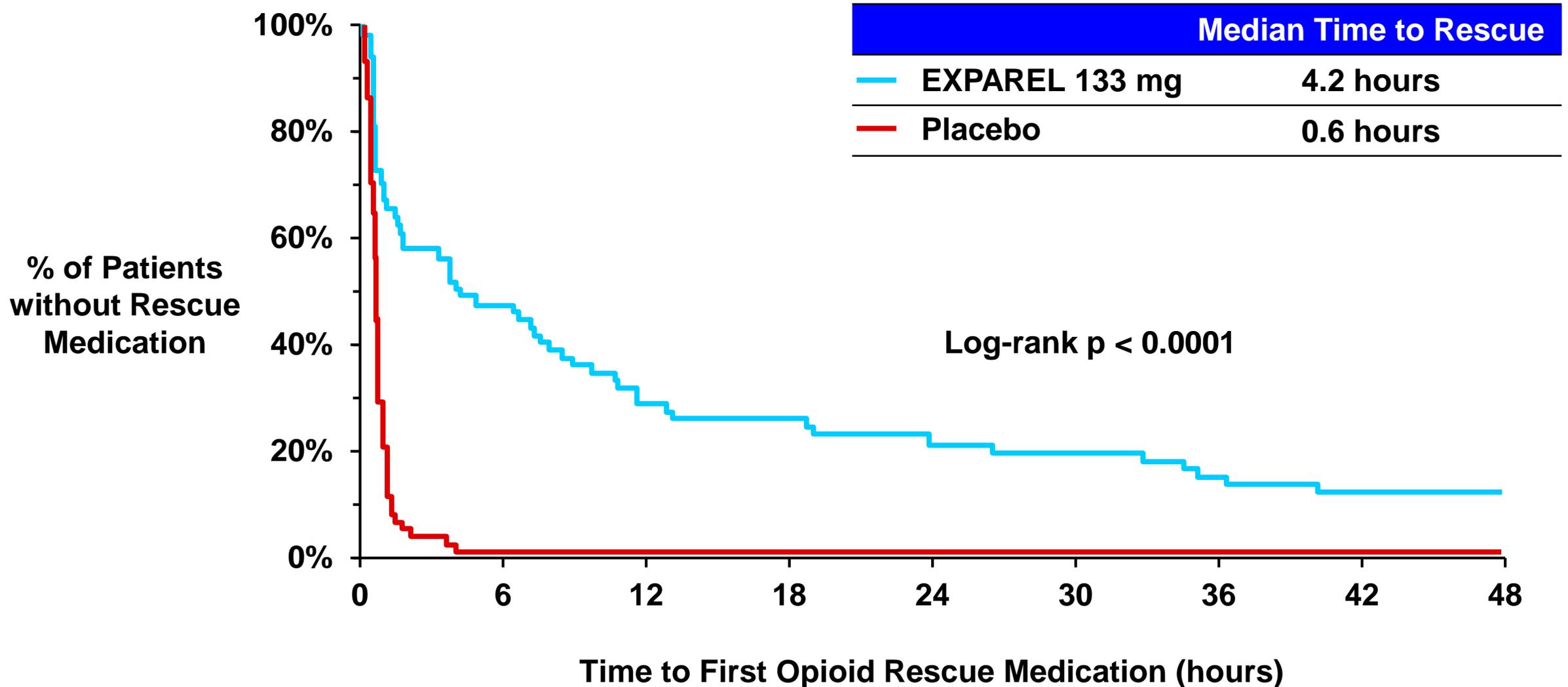
Study 327: Less Opioid Consumption with EXPAREL through 48 Hours



Study 327: More EXPAREL Patients Opioid-Free through 48 Hours



Study 327: Longer Time To Opioid Rescue Medication with EXPAREL

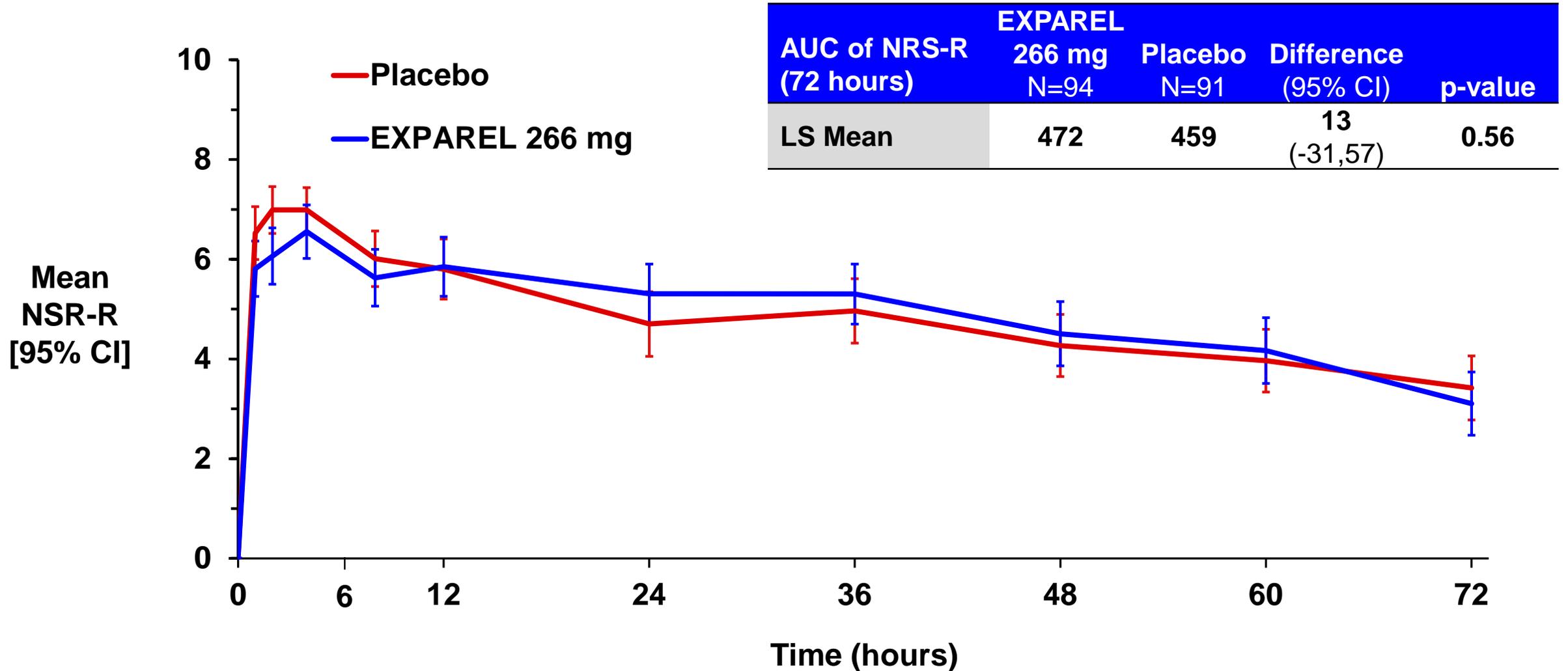


Study 322

Intercostal nerve block in thoracotomy

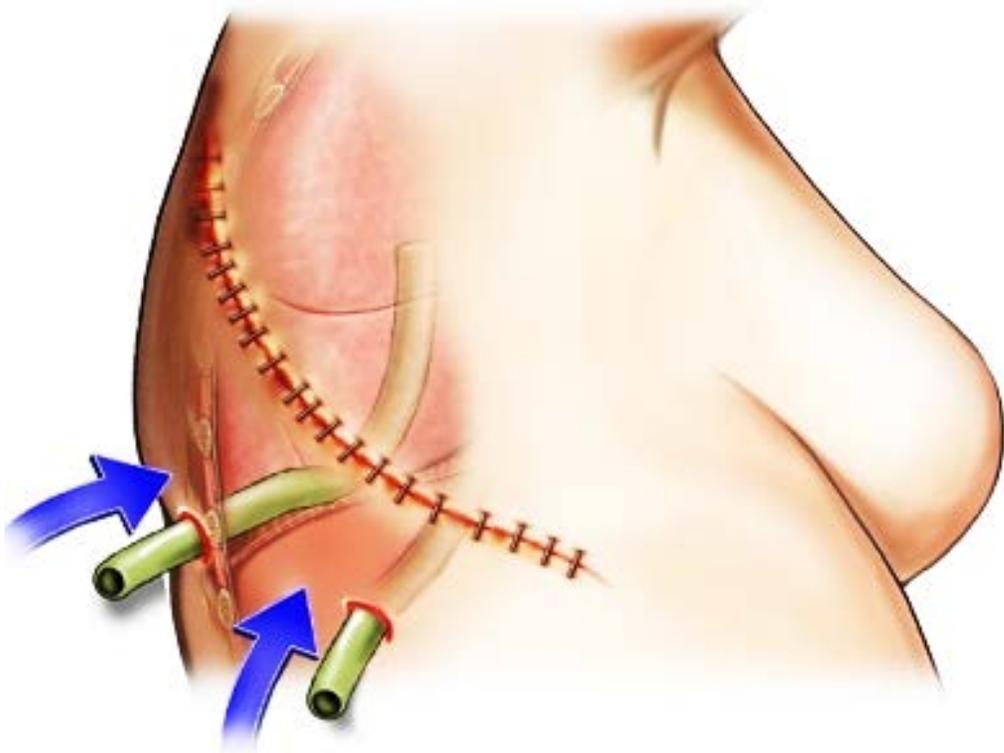
- EXPAREL 266 mg

Study 322: Primary Endpoint Not Met

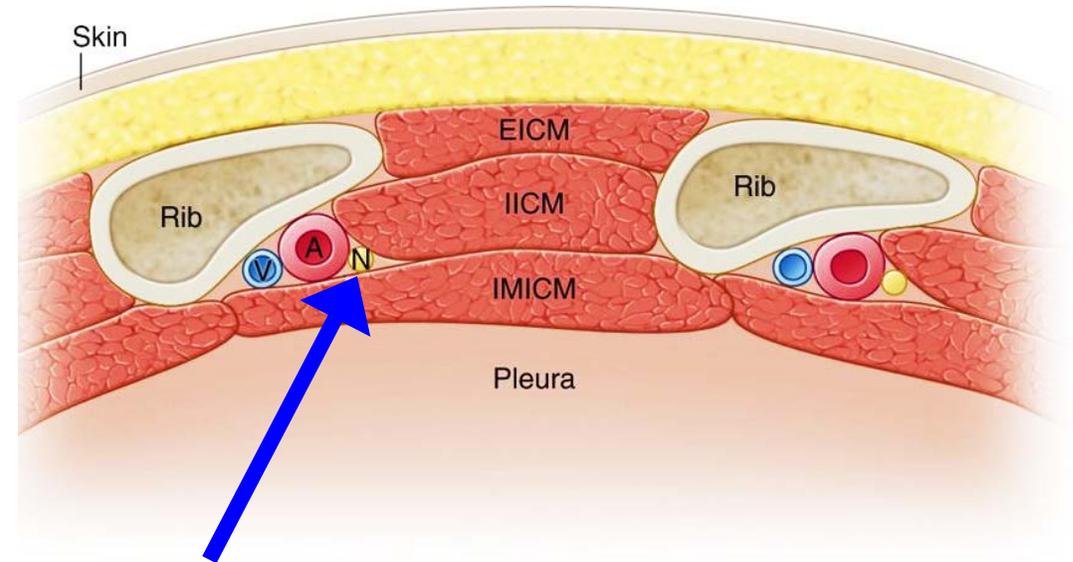


Study 322: Technique Inadequate to Achieve Successful Block for Pain Relief

No nerve block performed for chest tube



Only 3 nerves blocked, while 5-7 necessary



Study 322: Limitations of Study Drug Administration Impacted Efficacy

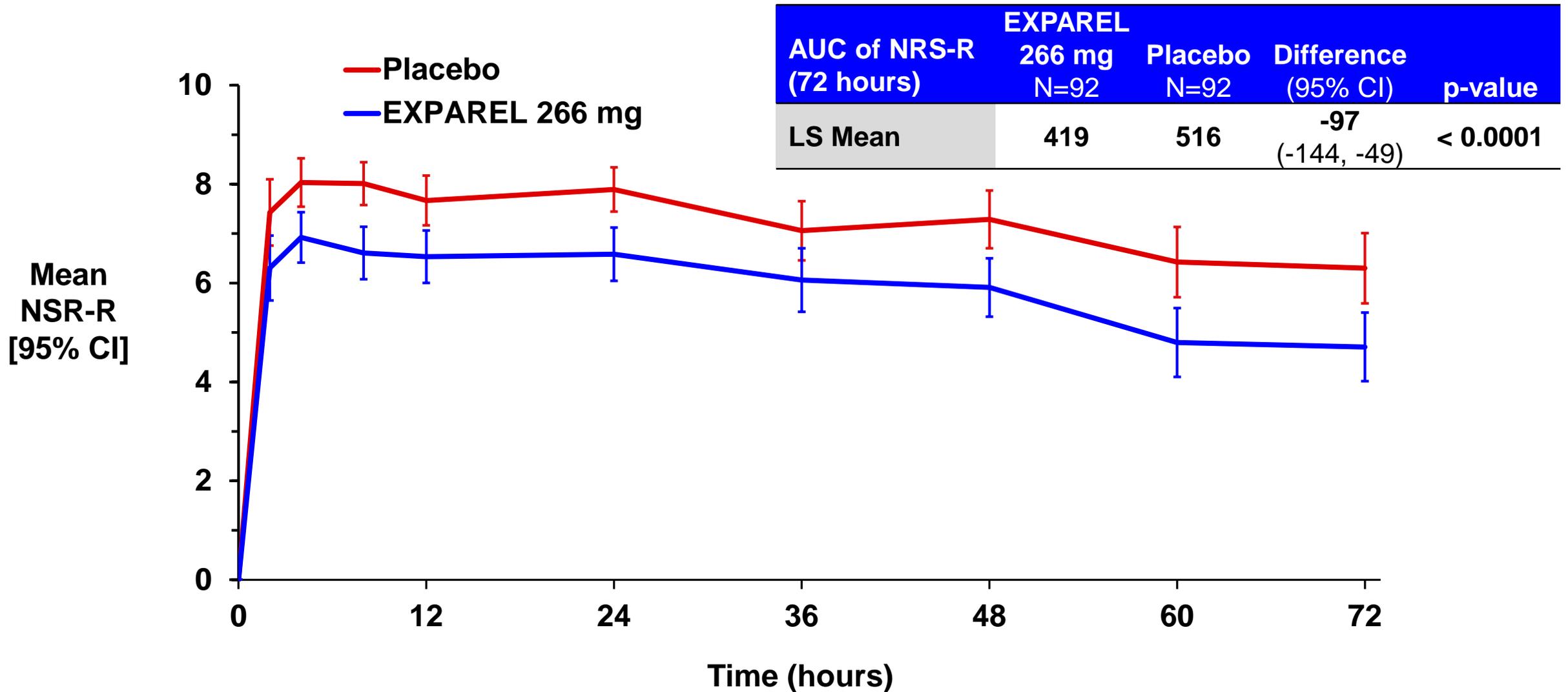
- EXPAREL absorbed and cleared very quickly
 - Consistent with combination of intravascular, intrapleural, and intramuscular injection
- Efficacy cannot be meaningfully evaluated
 - Nerve block not achieved due to administration technique

Study 323 (Part 2)

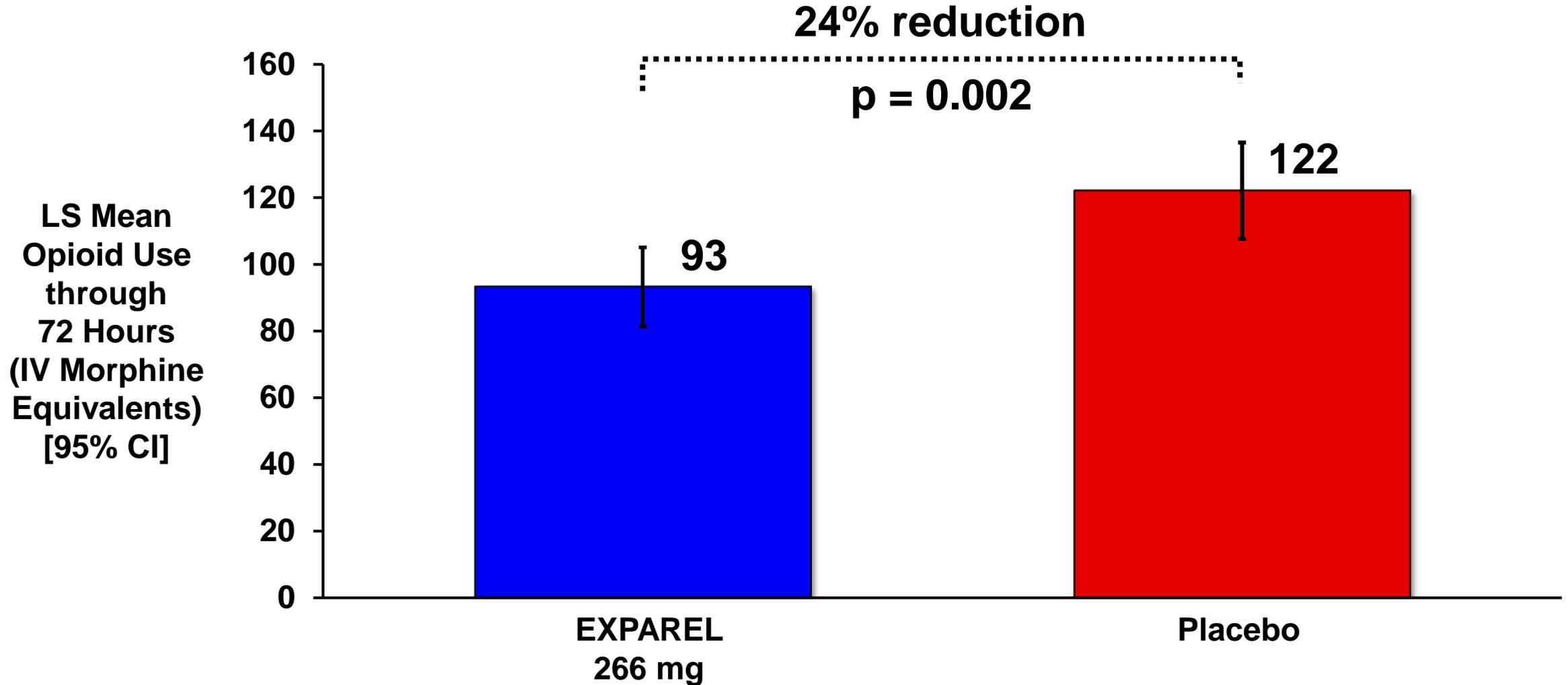
Femoral nerve block in TKA

- EXPAREL 266 mg

Study 323 (Part 2): Primary Endpoint Met



Study 323 (Part 2): Less Opioid Consumption with EXPAREL through 72 Hours



Study 323 (Part 2): Less Opioid Consumption with EXPAREL through 72 Hours

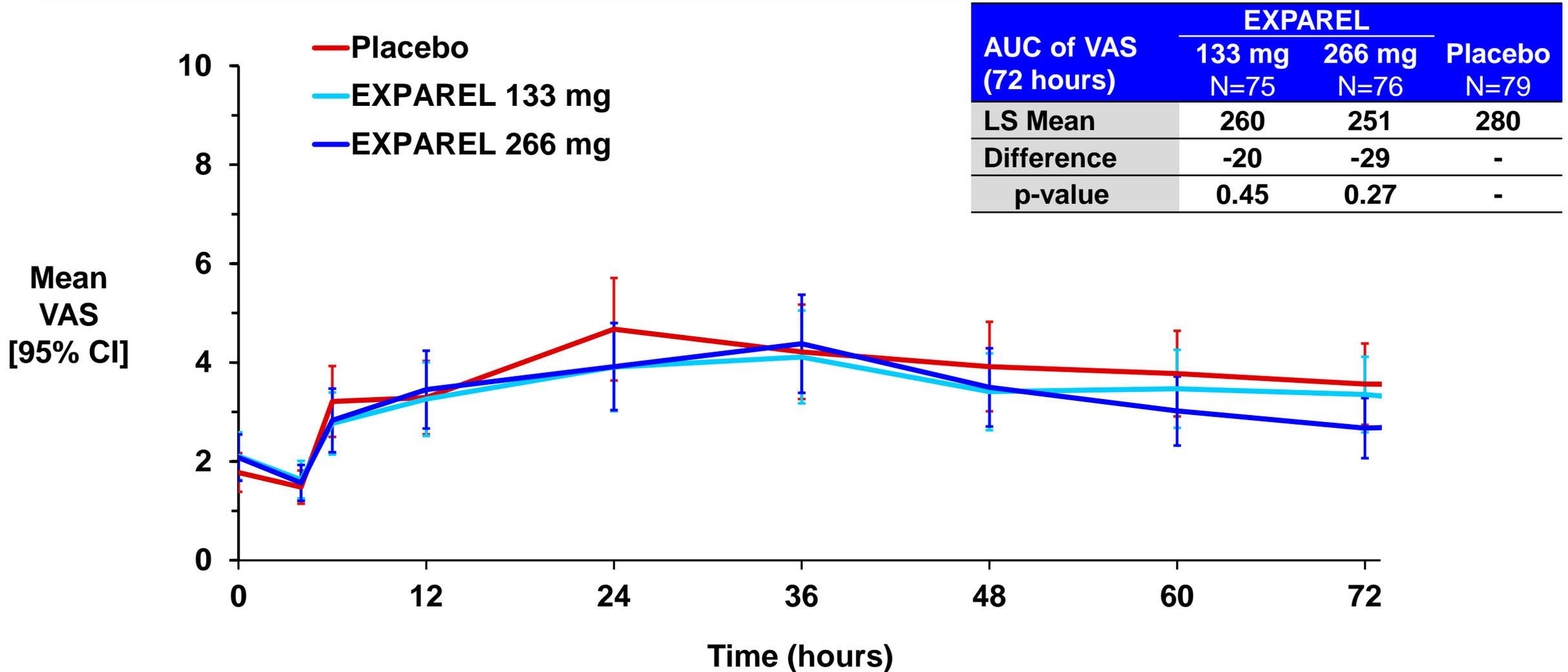
- % opioid-free through 72 hours
 - Not a ranked secondary endpoint
 - All patients used at least 1 opioid rescue medication
- Time to first opioid use
 - Similar in both groups
 - Median ~30 min

Study 326

Femoral nerve block in TKA

- EXPAREL 133 mg and 266 mg
- Surgeons performed periarticular infiltration of posterior capsule with bupivacaine (EXPAREL and placebo)

Study 326: Primary Endpoint Not Met



Aspects of Study Design and Conduct May Have Influenced Efficacy Findings

- Different design of control arm
 - Study 323: placebo nerve block
 - Study 326: placebo nerve block + bupivacaine HCl 40 mg posterior capsule infiltration
- Lower cumulative pain scores in both EXPAREL and placebo arms in Study 326
 - 40–46% lower pain scores in Study 326 vs. Study 323
 - Reduced study power

Bupivacaine-Controlled Investigator-Initiated Trials in sNDA

Study 1601 – Dupuytren’s Contracture Release

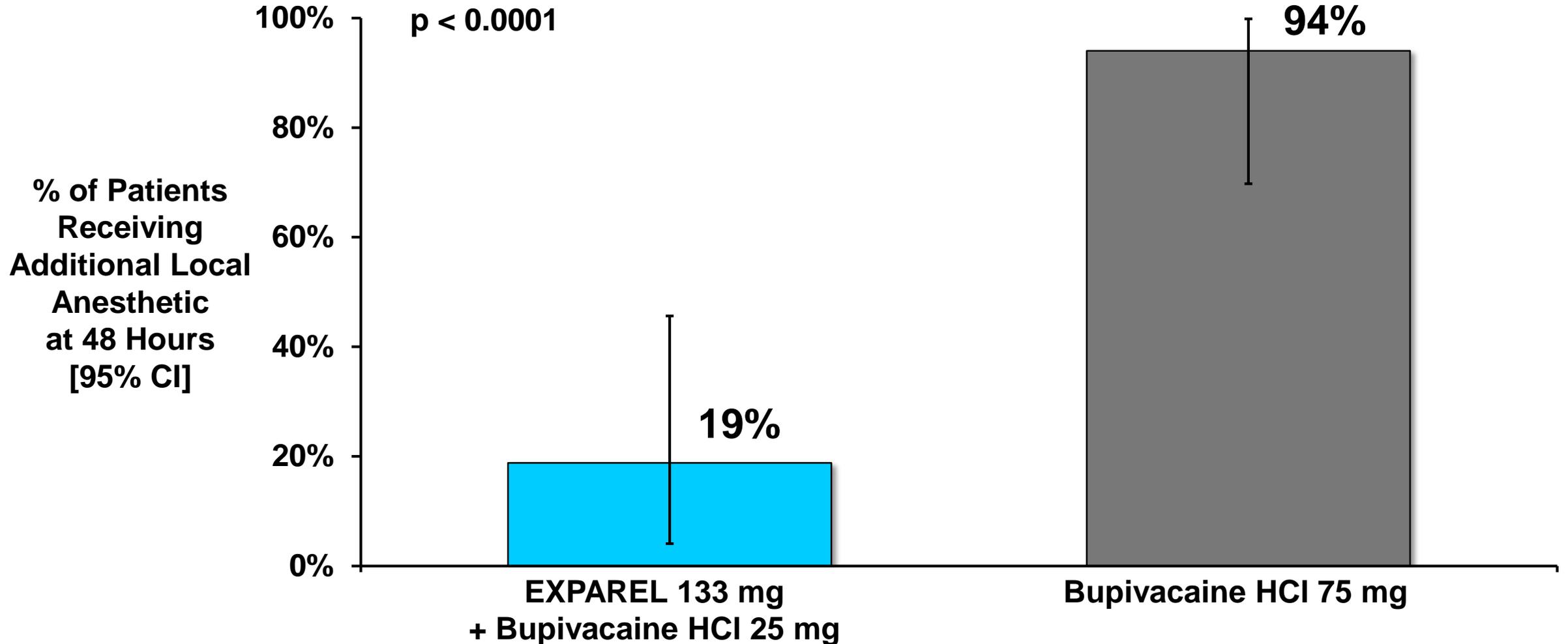
Study 1602 – Scarf Osteotomy

- Additional nerve block clinical settings
- EXPAREL use combined with bupivacaine

Study 1601: Dupuytren's Contracture Release Non-Surgical Acute Pain Model

- 32 patients randomized 1:1
 - EXPAREL 133 mg + bupivacaine HCl 25 mg
 - Bupivacaine HCl 75 mg
- Median and ulnar nerve block under ultrasound guidance
- Standard multimodal post-procedural analgesia
- Efficacy endpoints
 - Need for additional local anesthetic after 48 hours
 - Patient-reported worst pain over first 72 hours
 - Presence of patient-reported numbness

Study 1601: Fewer EXPAREL Patients Needed Additional Local Anesthetic at 48 Hours



Study 1601: EXPAREL Patients Had Lower Cumulative Pain Scores and Reported Numbness

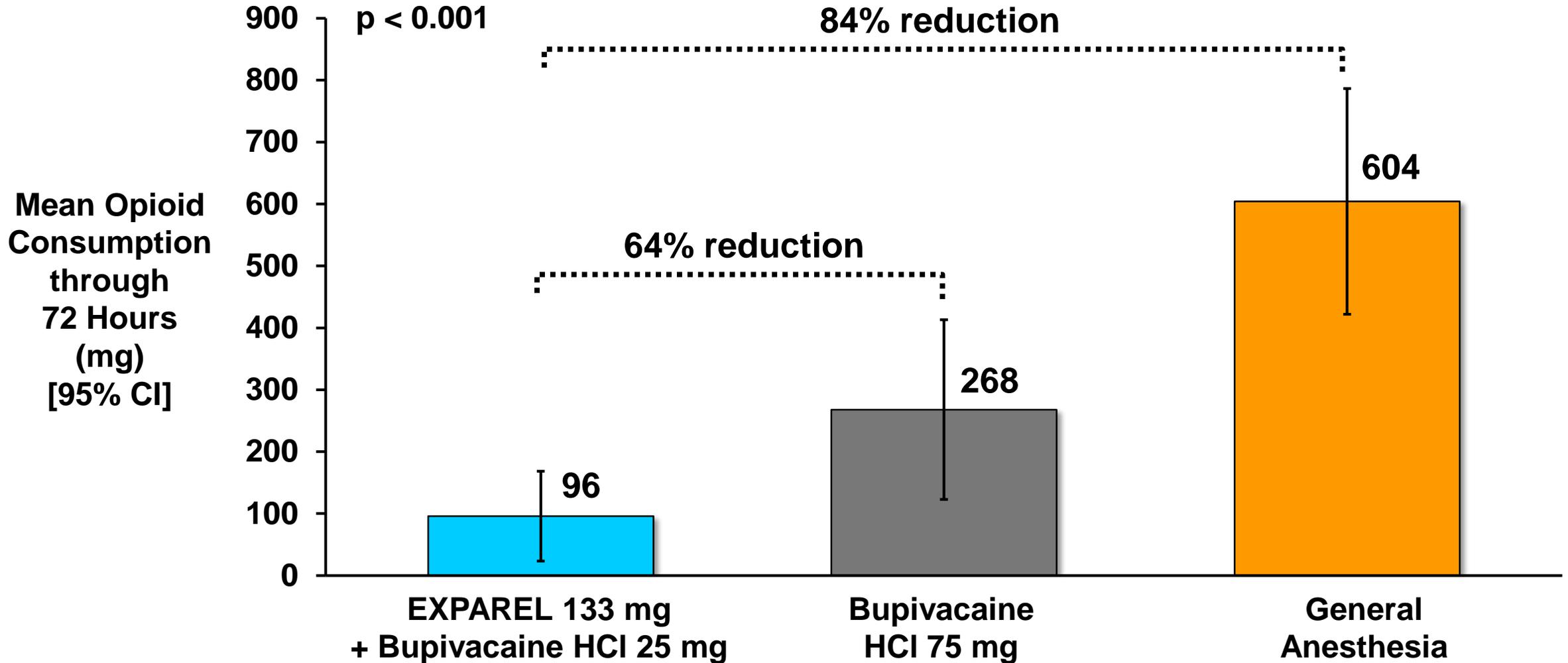
- Cumulative worst pain scores significantly lower with EXPAREL + bupivacaine vs. bupivacaine alone
 - Day 1-3 ($p = 0.01$)

% with Reported Numbness (Day)	EXPAREL 133 mg + Bupivacaine 25 mg N=16	Bupivacaine 75 mg N=16
Day 3	68%	0%
Day 4	44%	0%

Study 1602: Surgical Acute Pain Model in Scarf Osteotomy (Valgus Hallux Deformity)

- 40 patients randomized 1:1:1
 - EXPAREL 133 mg + bupivacaine 25 mg
 - Bupivacaine HCl 75 mg
 - General anesthesia
- Posterior tibial and deep peroneal nerve block under ultrasound guidance
- Standard multimodal post-procedural analgesia
- Efficacy endpoints
 - Opioid consumption in first postoperative week
 - Patient-reported worst pain over first 72 hours
 - Presence of patient-reported numbness

Study 1602: EXPAREL Patients Needed Fewer Opioids through 72 Hours



Study 1602: EXPAREL Patients Had Lower Pain Scores and Reported Numbness

- Repeated-measures analysis
 - EXPAREL + bupivacaine associated with lower pain scores compared to general anesthesia

% with Patient-Reported Numbness	EXPAREL 133 mg + Bupivacaine 25 mg N=12	Bupivacaine 75 mg N=13	General Anesthesia N=12
Day 3	75%	21%	8%
Day 5	33%	0%	0%

Summary of EXPAREL Efficacy for Regional Analgesia

- Nerve block efficacy demonstrated in two well-controlled trials
 - 133 mg and 266 mg doses
 - Upper extremity (nerve plexus)
 - Lower extremity (single major nerve)
 - Significant reductions in total opioid use
- Efficacy in two active-controlled, investigator-initiated trials in distal extremity peripheral nerve blocks
 - Surgical and non-surgical acute pain
- First non-opioid extended-release analgesic to provide long-lasting pain control in single administration

Safety

Richard Scranton, MD, MPH

Chief Scientific Officer

Pacira Pharmaceuticals, Inc.

EXPAREL Pharmacokinetics (PK)

PK of Local Anesthetics Not Related to Local Analgesic Efficacy

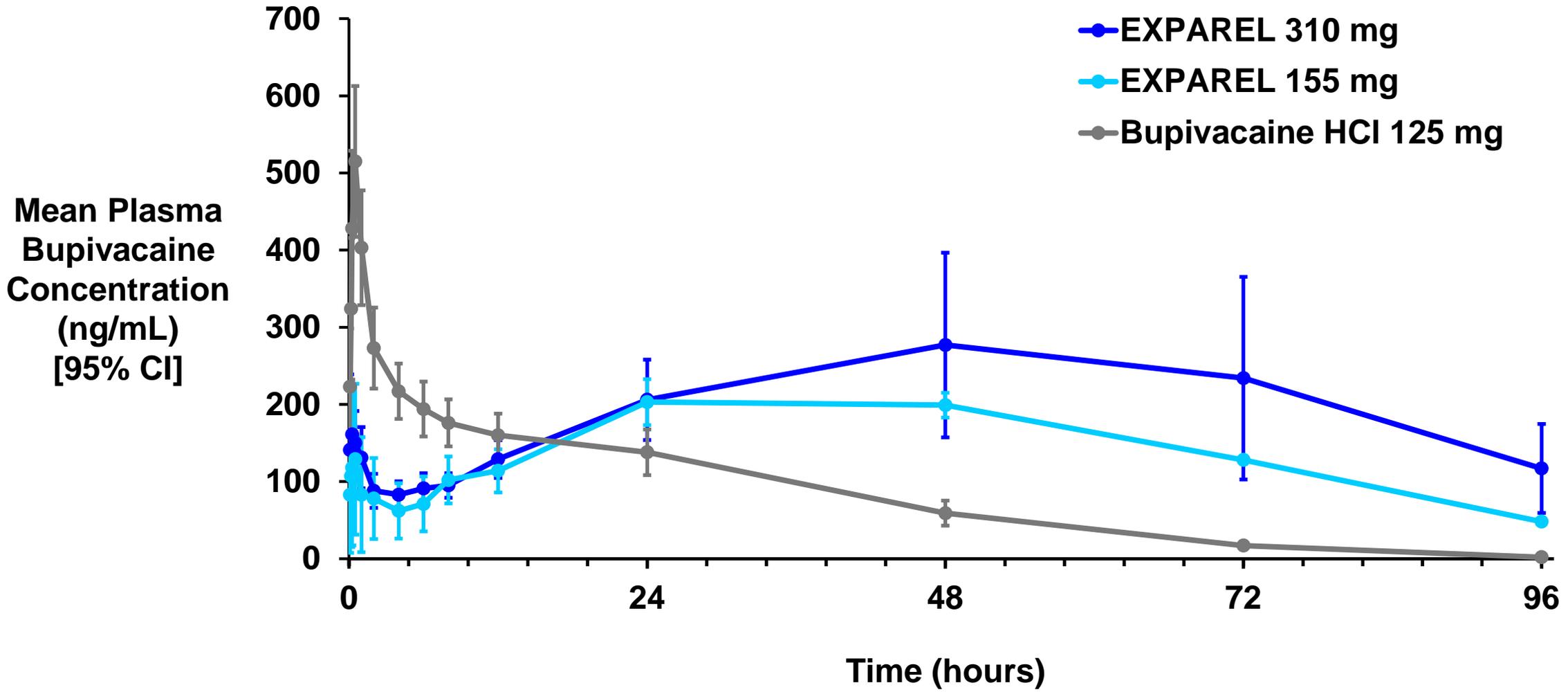
- Analgesia based on local availability at specific anatomical location rather than systemic concentration
 - Unlike systemic agents (e.g., opioids)
- PK data useful for safety, since very high plasma bupivacaine concentrations (> 2,000 ng/mL) associated with¹⁻³
 - Neurotoxicity (e.g., twitching, seizures)
 - Cardiotoxicity (e.g., hypotension, arrhythmia)

1. Jorfelt et al *Acta Anaesth Scandinav* 1968;12:153-69.

2. Knudsen et al. *Br J Anaesth* 1997;78:507-14.

3. Bardsley et al. *Br J Clin Pharmacol* 1998;46:245-9.

EXPAREL Associated with Lower Maximum Concentrations than Bupivacaine HCl



Generalizability of Local Anesthetic PK

- FDA briefing book identified variability in EXPAREL PK profile with different nerve block and administration techniques
 - Cited lack of rationale for extrapolation of EXPAREL PK and safety data to other nerve blocks
- PK of all local anesthetics for different nerve blocks, including EXPAREL, influenced by:
 - Dose
 - Vascularity of administration site
 - Administration technique (e.g., needle vs. catheter)
 - Inter-patient variability

Bupivacaine Label: Factors that Impact Systemic Absorption of All Local Anesthetics

Current label for MARCAINE (bupivacaine HCl):

- *“The rate of systemic absorption of local anesthetics is dependent upon the total dose and concentration of drug administered, the route of administration, the vascularity of the administration site, and the presence of epinephrine in the anesthetic solution.”*

Safety Results

Patient Exposures in Phase 2/3 Nerve Block Studies

Study	EXPAREL			Placebo
	133 mg	266 mg	Any Dose	
Phase 2				
203	-	-	38	0
211	1	-	2	1
323 (Part 1)	24	24	70	24
Phase 3				
322	-	94	94	91
323 (Part 2)	-	92	92	91
326	75	76	151	79
327	69	15	84	71
Pooled Total	169	301	531	357

Overall Summary of Adverse Events (AEs)

Type of AE, %	Pooled Nerve Block Studies			Study 326		
	EXPAREL		Placebo N=357	EXPAREL		Placebo N=79
	133 mg N=169	266 mg N=301		133 mg N=75	266 mg N=76	
AE	91%	86%	84%	97%	97%	96%
Severe AE	3%	6%	8%	4%	4%	3%
AE leading to study discontinuation	0	1%	2%	0	0	1%
SAE	5%	10%	8%	7%	11%	8%
AE leading to death	0	< 1%	1%	0	0	0

SAEs Occurring in ≥ 3 EXPAREL Patients

Preferred Term, %	Pooled Nerve Block Studies			Study 326		
	EXPAREL			EXPAREL		
	133 mg N=175	266 mg N=301	Placebo N=357	133 mg N=75	266 mg N=76	Placebo N=79
SAEs	5%	10%	8%	7%	11%	8%
Pyrexia	0	1%	< 1%	0	0	0
Post-procedural hematoma	2%	< 1%	0	4%	1%	0
Pneumonia	< 1%	< 1%	< 1%	0	0	0
Myocardial infarction	0	1%	< 1%	0	0	0
Urinary tract infection	0	1%	0	0	0	0

All Deaths in Clinical Studies Assessed as Unrelated to Study Drug

#	Treatment	Age / Race / Sex	Fatal AE Preferred Terms	Relationship to Study Drug
1	EXPAREL 266 mg	73 / W / M	Cardiac arrest; Heart injury; Cardiac failure acute	Unrelated
2	EXPAREL 266 mg	72 / W / M	White blood cell count increased; Renal failure; Cardiac arrest	Unrelated
3	Placebo	63 / W / M	Acute kidney injury; Respiratory failure; Coma uremic	Unrelated
4	Placebo	40 / W / M	Myocardial infarction	Unrelated
5	Placebo	71 / W / M	Pneumonia; Sepsis; Renal failure; Cardiac arrest	Unrelated
6	Placebo	75 / W / M	Pneumothorax	Unrelated

Adverse Events of Special Interest (AESIs)

- Local Anesthetic Systemic Toxicity
- Falls
- Sensory and Motor Function

Local Anesthetic Systemic Toxicity

- Rare constellation of CNS and CV signs and symptoms associated with toxic plasma concentrations
 - Generally above 2,000 ng/mL for bupivacaine¹⁻³
- Probable causes
 - Inadvertent intravascular injection
 - Used in excessive doses

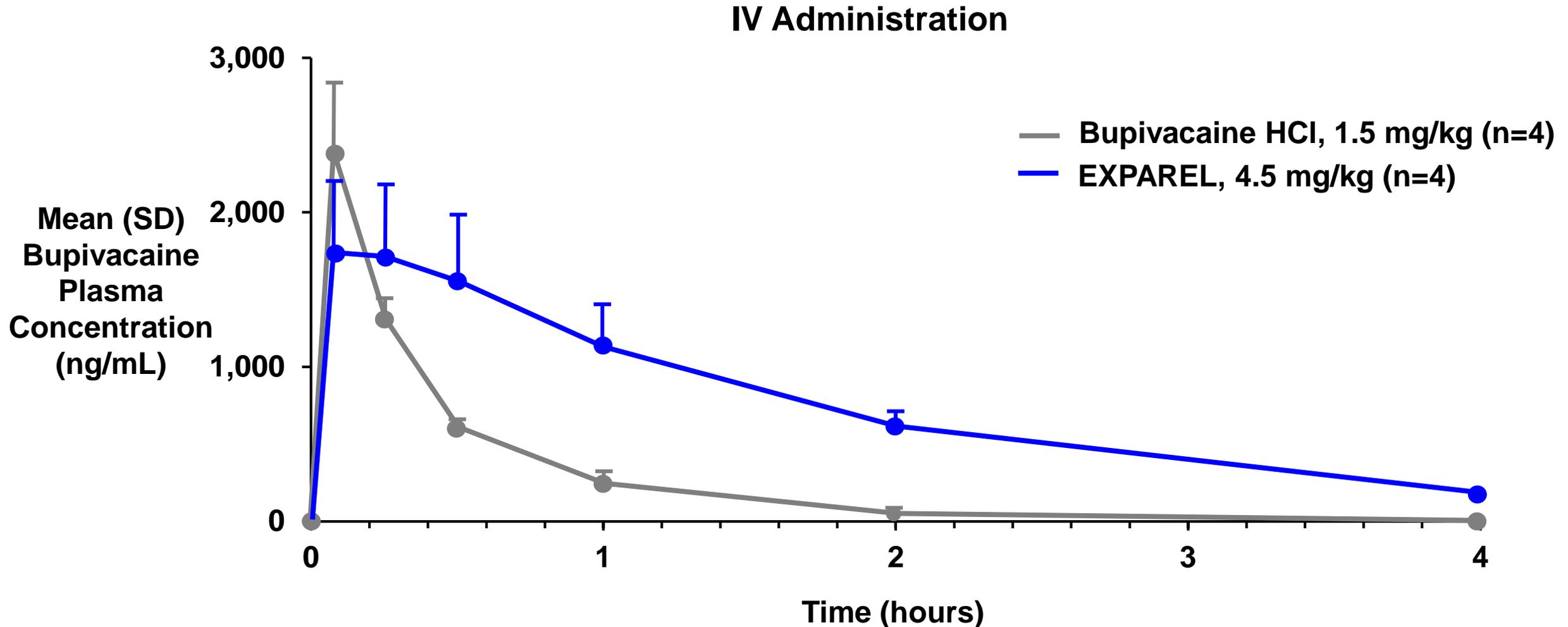
Pharmacovigilance Analyses Do Not Suggest Increased Risk of LAST with EXPAREL

- No cases in clinical studies
- Pacira reviewed potential cases in postmarketing database
 - 3 million postmarketing exposures during time period
 - 63 cases where LAST could not be ruled out
- Assuming all cases definitive
 - Incidence with EXPAREL = 0.2 per 10,000 patients
 - Lower than nerve blocks with immediate-release local anesthetics (2.0–2.8 per 10,000 patients)¹

Pre-clinical Studies Evaluated Relative PK and Safety for Inadvertent Administration

- Animal studies of inadvertent administration of EXPAREL vs. bupivacaine HCl
 - Intravenous
 - Intra-arterial
 - Epidural
 - Intrathecal

Pre-Clinical Data Suggest EXPAREL Provides Safety Margin Against Local Anesthetic Systemic Toxicity



Adverse Events of Special Interest (AESIs)

- Local Anesthetic Systemic Toxicity
- Falls
- Sensory and Motor Function

Incidence of Falls Comparable Between EXPAREL Doses, Higher than Placebo

AESI, n (%)	EXPAREL		Placebo N=357
	133 mg N=169	266 mg N=301	
Fall	4 (2.4%)	8 (2.7%)	1 (< 1%)

- All falls among EXPAREL patients occurred in TKA studies

Proposed Precaution for Femoral Nerve Block

- Precaution in label when used as femoral nerve block if early mobilization and ambulation is part of patient's recovery plan
- May be cases when long-acting femoral block would be clinically appropriate
 - Lower extremity trauma, deformity correction, amputation

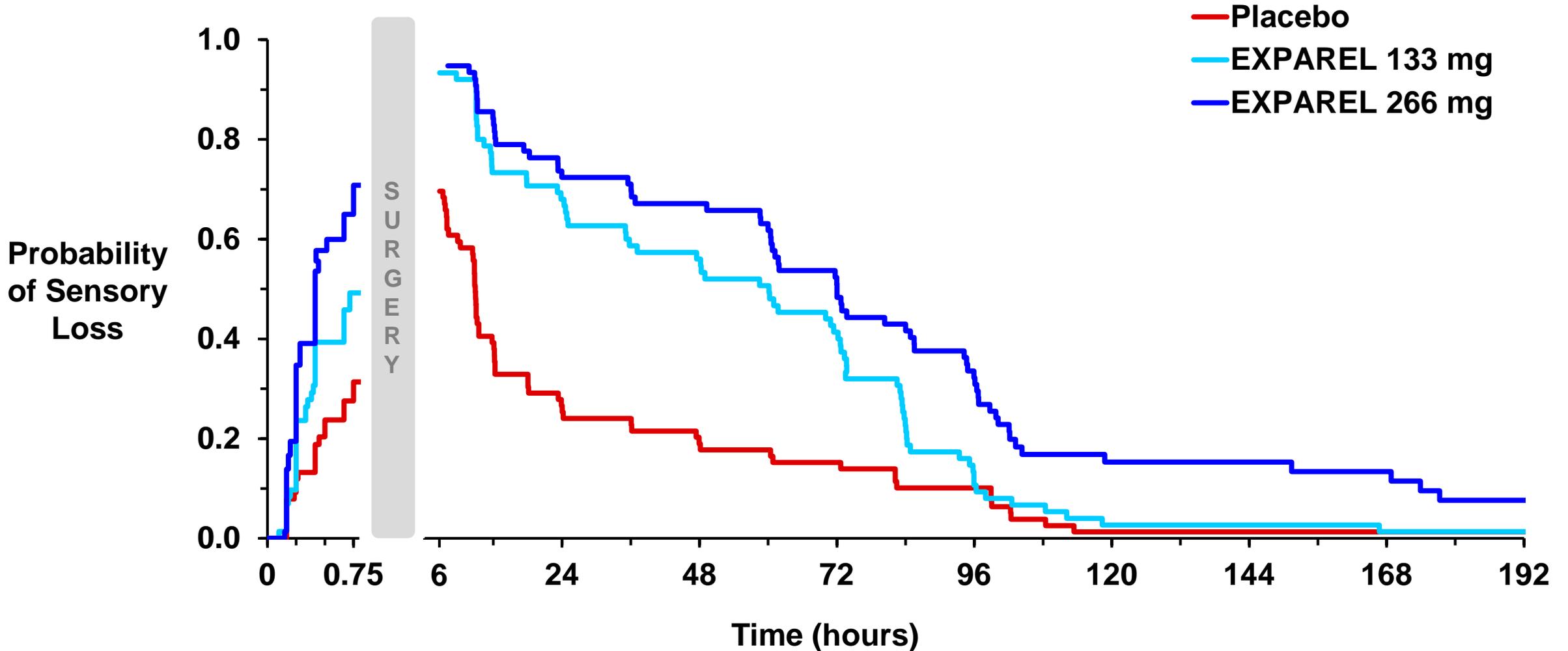
Adverse Events of Special Interest (AESIs)

- Local Anesthetic Systemic Toxicity
- Falls
- Sensory and Motor Function

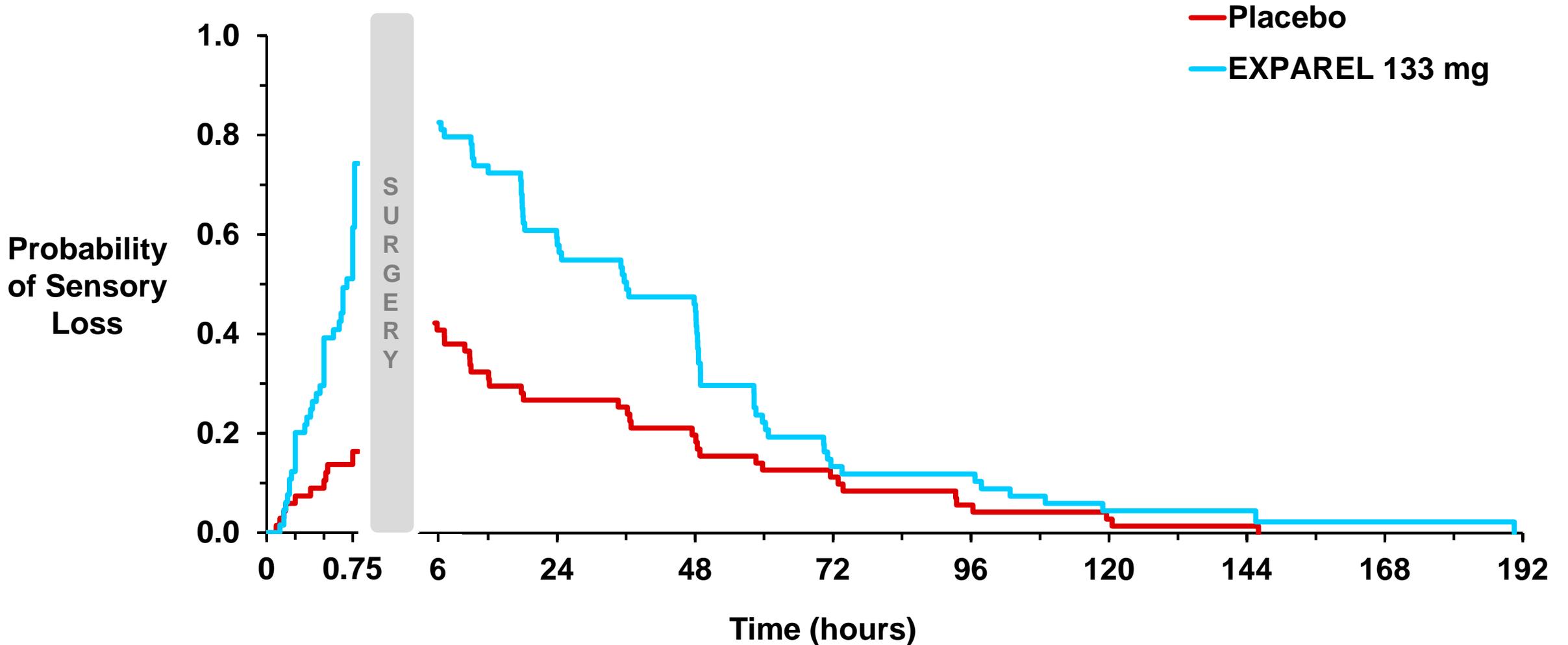
Sensory and Motor Function Evaluations

- Assessed in Studies 326 (TKA) and 327 (TSA/RCR)
- Sensory loss defined as absence of sensation to
 - Cold
 - Pinprick
 - Light touch
- Motor function
 - Study 326: knee flexion, extension
 - Study 327: thumb ab-/adduction, opposition, elbow flexion

Study 326: Evidence of Sensory Loss and Return



Study 327: Evidence of Sensory Loss and Return



Summary of EXPAREL Clinical Safety

- Safe and well tolerated as single-injection nerve block to produce regional analgesia in various surgical procedures
- No meaningful differences in safety profile compared with currently-approved indication
- Safe, long-acting, non-opioid pain management option following surgery or injury
- Favorable safety profile
 - Well-known profile from approved indication
 - 3.5 million patient exposures

Clinical Perspective

Jeffrey Gadsden, MD

Chief of Orthopaedics, Plastics, and Regional Anesthesiology

Associate Professor of Anesthesiology

Duke University School of Medicine

Personal Experience with EXPAREL

- > 1000 patients administered EXPAREL since 2011
 - Both infiltration and nerve block
- Faulty paradigm: opioids have low risk of addiction
- Limitations with traditional local anesthetics
- Need adjuncts for long-lasting pain relief with fewer opioids

Data Show EXPAREL has Positive Benefit-Risk Profile for Nerve Block

- Safe for nerve block
- Effective in wide range of nerve blocks
- Potential to meaningfully reduce healthcare utilization and opioid use

Evidence for EXPAREL Safety

- Bupivacaine used as nerve block for decades
- EXPAREL is extended-release bupivacaine
 - Same molecule encapsulated in slow-release form
 - Molecule interacts with nerve fiber in same way
- Considerable pre-clinical, clinical, and postmarketing data

Extended-Release Profile Offers Safety Advantages Over Immediate-Release Bupivacaine

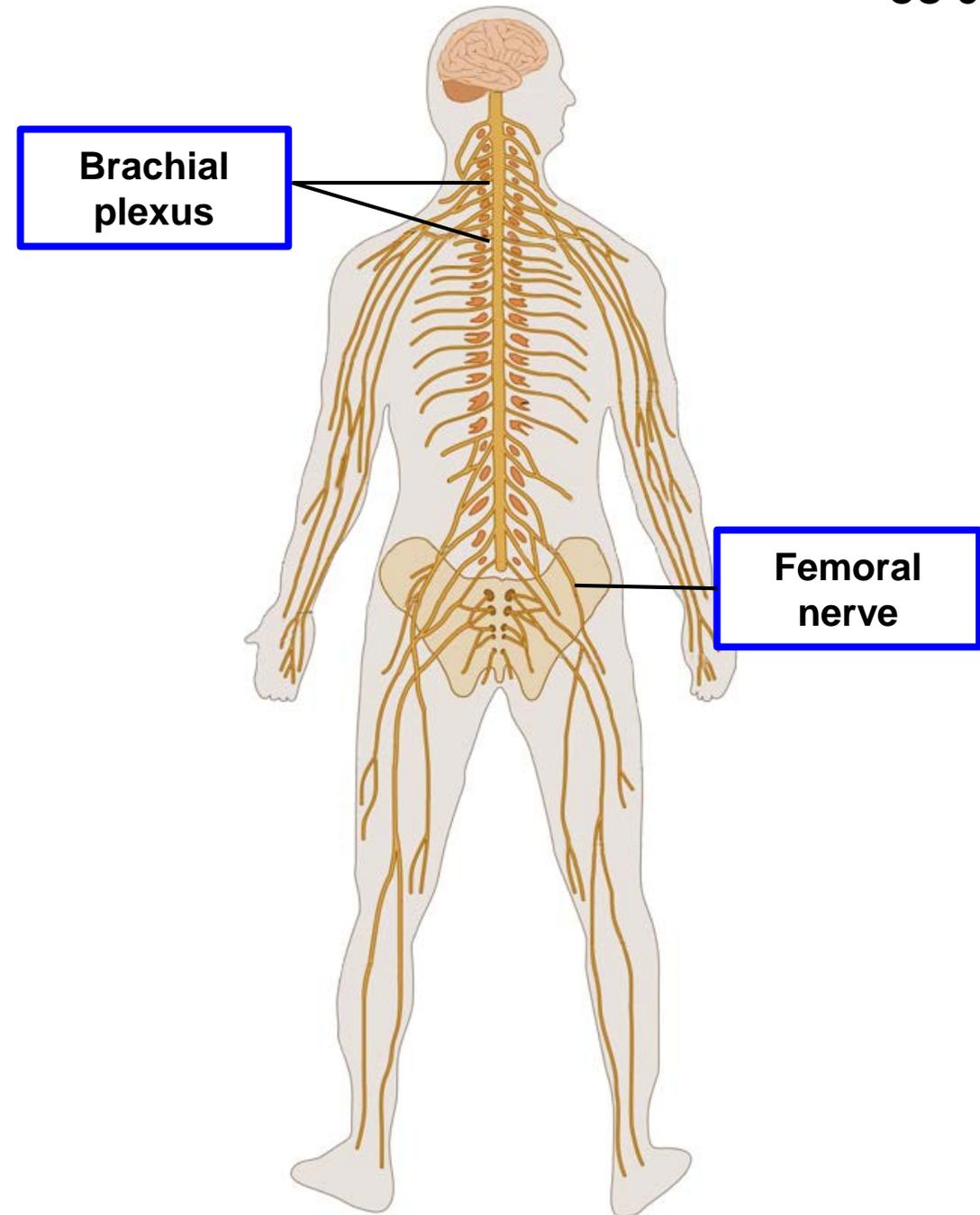
- Lower drug exposure vs. continuous nerve block catheters
- Encapsulated bupivacaine provides safeguard against LAST
- Pre-clinical studies
 - Intravascular administration of EXPAREL did not produce high bupivacaine concentrations associated with toxicity

PK Not Used to Evaluate Efficacy or Guide Dosing of Local Anesthetics

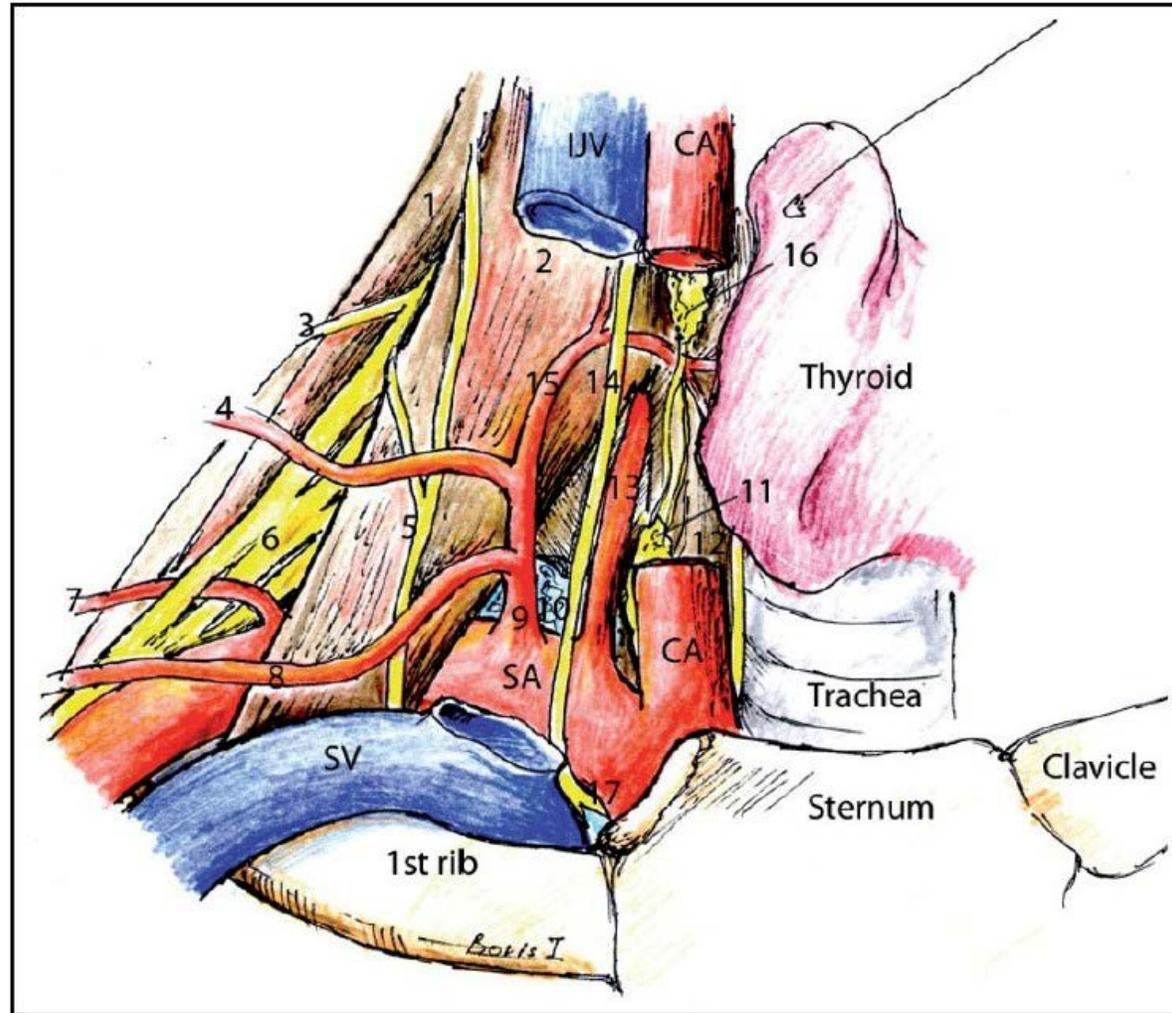
- Factors to consider when dosing
 - Size and region of area being treated
 - Vascularity of the tissue
 - Duration of analgesia required
 - Physical condition of the patient
- Variability in T_{\max}
 - Expected due to variations in tissue vascularity
 - Inconsequential to clinical decision-making
- Primary clinical concern is high C_{\max} , which causes LAST

EXPAREL Nerve Block Program Evaluated Representative Nerves

- Study 327: brachial plexus
 - Upper extremity
 - Collections of smaller nerves
- Study 323: femoral nerve
 - Lower extremity
 - Single large nerve



Applicability of Brachial Plexus to Other Nerves



EXPAREL Offers Potential to Reduce Healthcare Utilization and Improve Postsurgical Care

- Earlier ambulation (no catheters or pumps)
- Earlier achievement of physical therapy milestones
- Reduced nausea and vomiting
- Earlier return of bowel function

Publications Show That Pain Relief with EXPAREL Can Reduce Opioid Use and Length of Stay

Institution	Clinical Setting	Comparator	Opioid Use	Length of Stay
U of Minnesota ¹	TAP: Hysterectomy	Bupivacaine	-52%	-6 hours (outpatient)
Mayo Clinic ²	Gynecologic Oncology	Bupivacaine	-55%	No difference
Memorial Sloan Kettering ³	Breast Reconstruction	Pre-ERAS	-35%	-1 day
University Hospitals ⁴	Open Hernia Repair	Bupivacaine	-32%	-1.6 days
VA Medical Center ⁵	TKA	Cohort prior to EXPAREL	-44%	No difference
U of Illinois ⁶	TKA	Multi-drug cocktail	-60%	-0.5 days

1. Hutchins et al. *Gynecol Oncol* 2015;138:609-13.

2. Kalogera et al. *Obstet Gynecol* 2016;128:1009-17.

3. Afonso et al. *Plast Reconstr Surg* 2017;139:1053-61.

4. Fayeziadeh et al. *Am J Surg* 2016;212:399-405.

5. Sakamoto et al. *JAMA Surg* 2017;152:90-5.

6. Kirkness et al. *Am J Health Syst Pharm* 2016;73:e247-54.

EXPAREL is Safe and Effective as Nerve Block

- Shorter-acting anesthetics wear off after 12–24 hours
 - Only options to prolong analgesia for moderate-to-severe pain are catheters or opioids
- EXPAREL provides sustained pain relief for 2–5 days
 - Reduces need for opioids or additional local anesthetic
- EXPAREL is part of multi-modal strategy to manage pain and reduce opioid use

Conclusion

Richard Scranton, MD, MPH

Chief Scientific Officer

Pacira Pharmaceuticals, Inc.

sNDA Addresses Each CRL Data Request

- ✓ Demonstrated efficacy in 1 additional setting
 - Study 327 (brachial plexus)
- ✓ Provided additional PK data through T_{max} and characterized onset and duration
 - Studies 326 and 327 (femoral and brachial plexus)
- ✓ Cardiac safety analyses showed no evidence of toxicity
 - Studies 323 and 322 (femoral and intercostal)

Data Provided to Address FDA Briefing Book Concerns

FDA Concern	Key Conclusions
PK Variability	<ul style="list-style-type: none">▪ PK predicts safety, not efficacy▪ Lower maximum levels with EXPAREL than immediate-release bupivacaine▪ Variability expected with dose, vascularity, and administration site
Applicability of Data to Other Nerve Blocks	<ul style="list-style-type: none">▪ EXPAREL is a long-acting form of bupivacaine (used in US since 1972)▪ Efficacy and safety in 2 studies▪ Representative nerve block models allow for broad indication
Comparator Group	<ul style="list-style-type: none">▪ Placebo-controlled studies for regulatory approval▪ Bupivacaine-controlled investigator studies in sNDA▪ Published literature supports additional benefit of extended-release
Local Anesthetic Systemic Toxicity	<ul style="list-style-type: none">▪ Rare event with all local anesthetics including EXPAREL▪ Postmarketing and animal data suggest risk of LAST is lower for EXPAREL

Efforts to Use EXPAREL to Reduce Opioid Prescribing after Procedures

Today's Evidence

EXPAREL reduces
opioid use in
acute care setting

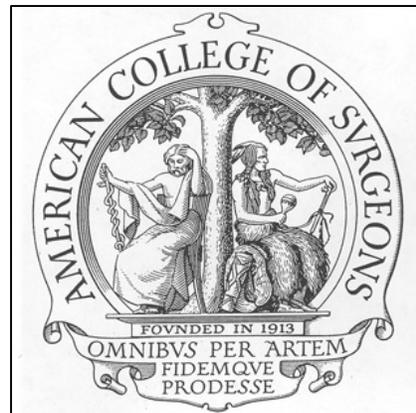


Long-term Goal

Reducing opioid
prescribing after
procedures

- Provider education required to change prescribing behavior

Pacira Partnerships to Manage Pain and Minimize Opioid Use



Clinical Effectiveness Study to Evaluate Reduction in Opioid Prescribing



American Association of Oral
and Maxillofacial Surgeons

aetna[®]

- Study objective: significant reduction in opioids dispensed
- Many young adults first exposed to opioids following wisdom teeth removal
- Train oral surgeons on appropriate EXPAREL use and opioid reduction

Summary of Conclusions

- Data addresses CRL and FDA concerns
- EXPAREL proposed indication
 - Infiltration / field block: harmonized with other local anesthetics
 - Nerve block: supported by safety and efficacy data
- EXPAREL can reduce opioid use in hospital after surgery
- Pacira committed to postmarket studies and partnerships to maximize benefits of opioid reduction with EXPAREL

Supplemental NDA (sNDA) for EXPAREL[®] (bupivacaine liposome injectable suspension) as a Nerve Block for Regional Analgesia



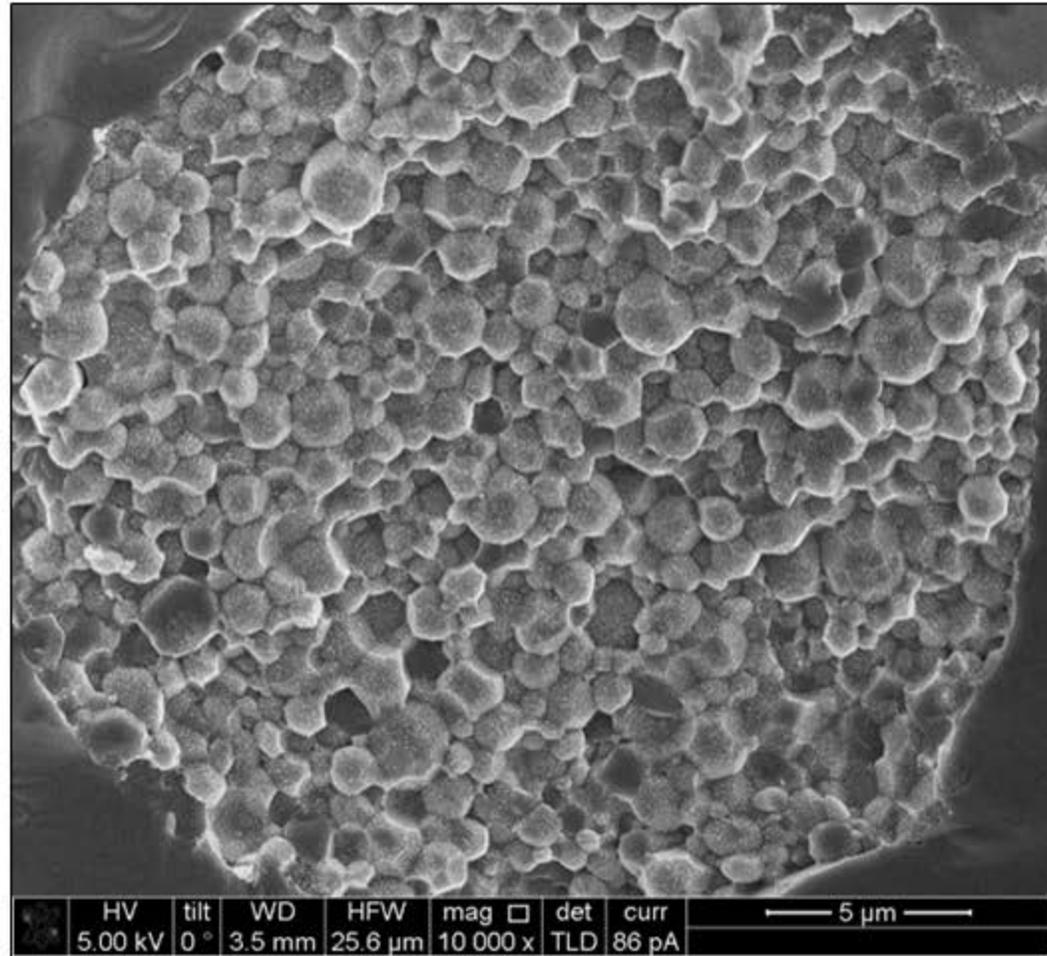
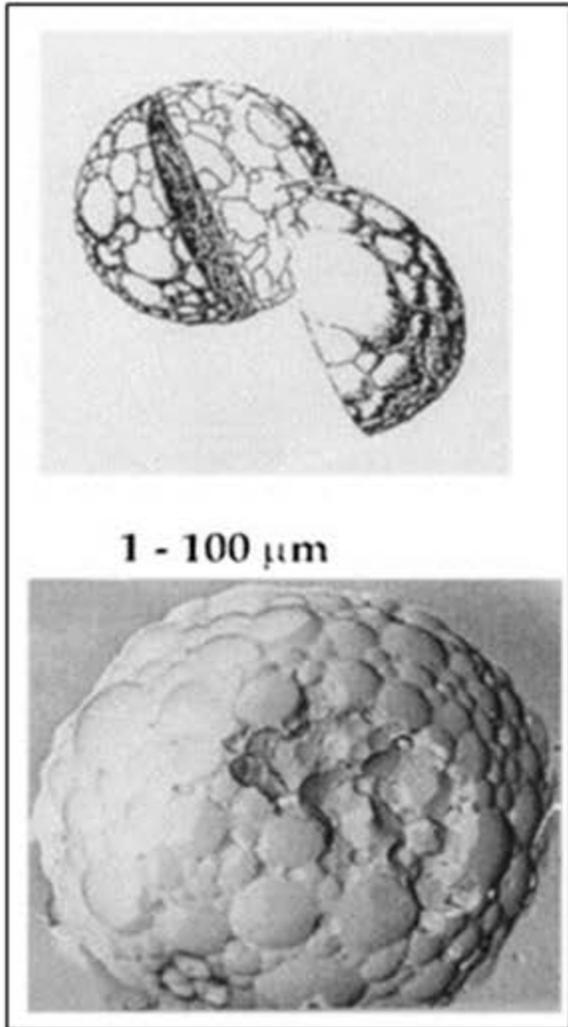
February 14-15, 2018

Pacira Pharmaceuticals, Inc.

Anesthetic and Analgesic Drugs Advisory Committee

Backup Slides Shown

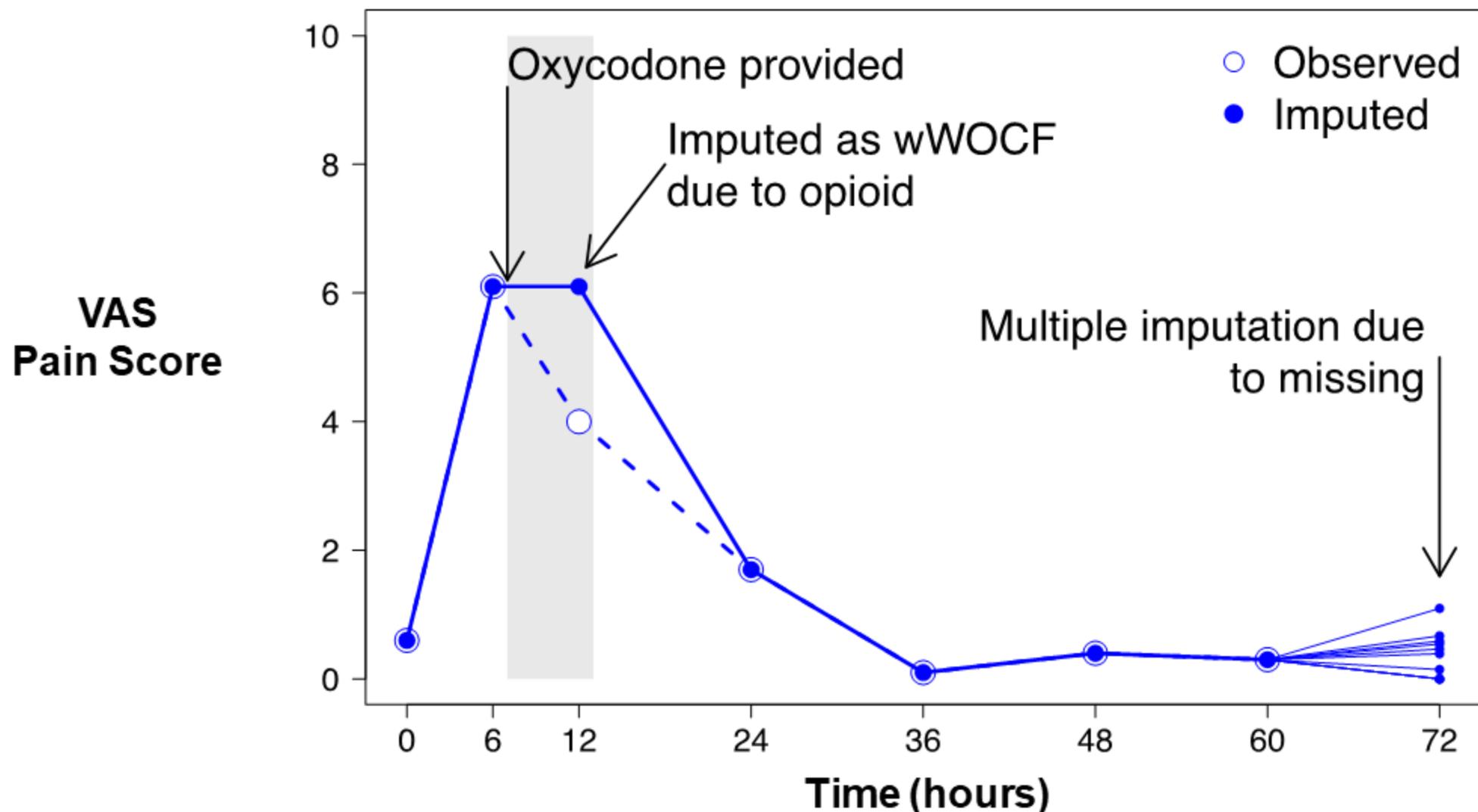
Electron Micrograph of EXPAREL: Median Particle Size (Range) = 25 (10-60) Microns



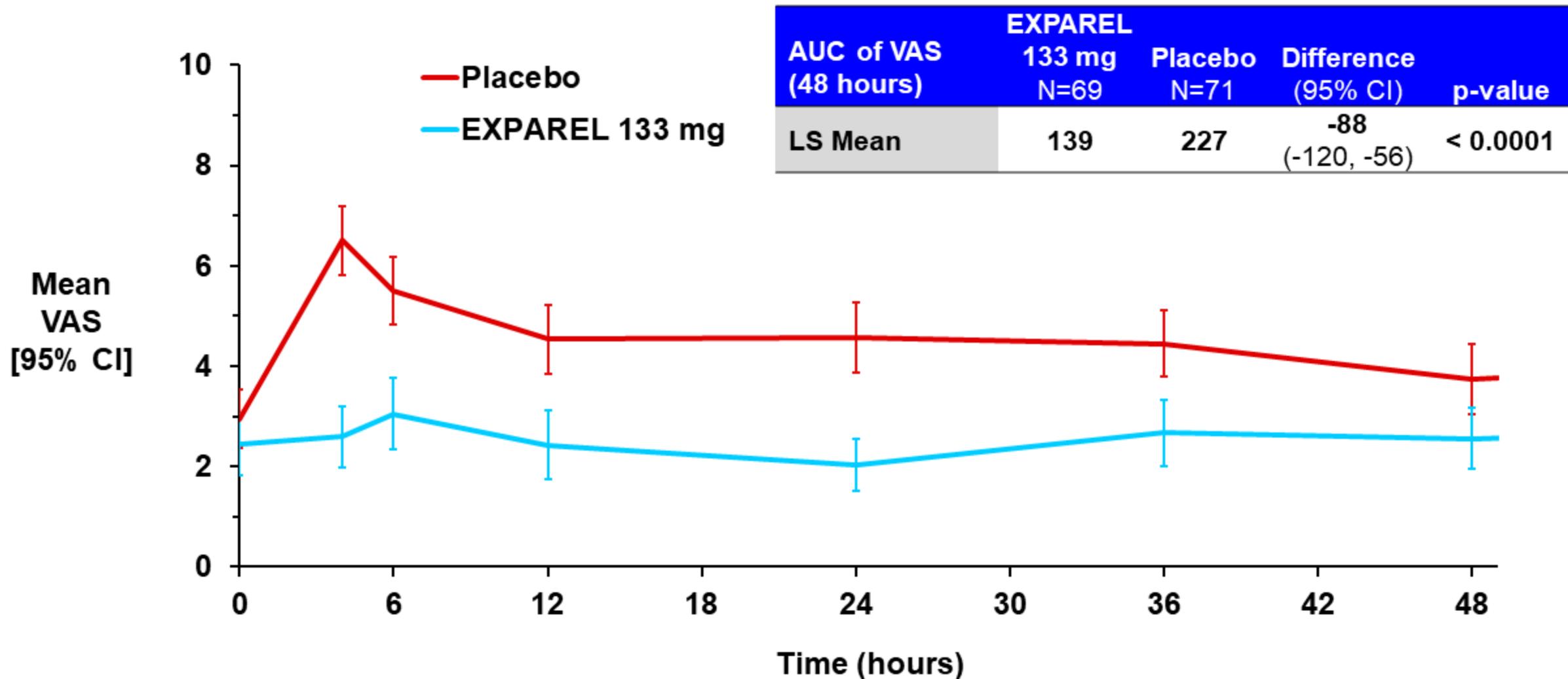
Study 326: Falls in EXPAREL Patients

Age/Sex/Race	Study Day	Case Details	Sequelae
133 mg			
55/F/W	2	--	None
67/F/W	3	Slid down bathroom wall after walking to restroom with walker	None
70/M/W	4	Lost balance in bathroom, used door handle as support but door opened instead	None
59/F/AA	18	Lost balance because she was not ambulating with prescribed walker and fell on operative knee	None
266 mg			
69/F/W	3	Fell from edge of bed while reaching for crutches	None
56/F/W	4	--	None
76/F/W	4	Fell on buttocks while walking; wore socks instead of shoes	None
89/M/W	5	Noncompliant use of walker and refused help from wife; fell very slowly and sustained no injuries	None
48/M/W	2, 5	Fell backwards sitting on commode. Counseled on how to safely sit and get up. Fell again 3 days later in kitchen shortly after discharge from SNF	None

Imputation Methods for Studies 326 & 327



Study 327: Primary Endpoint (without Imputation)



PILLAR Study: Phase 4 Multi-Center RCT in Total Knee Arthroplasty (TKA)

- Patients randomized 1:1 to infiltration with:
 - EXPAREL 266 mg admixed with bupivacaine HCl 100 mg (n=70)
 - Bupivacaine HCl 100 mg alone (n=69)
- Oral opioids for rescue, no PCA allowed

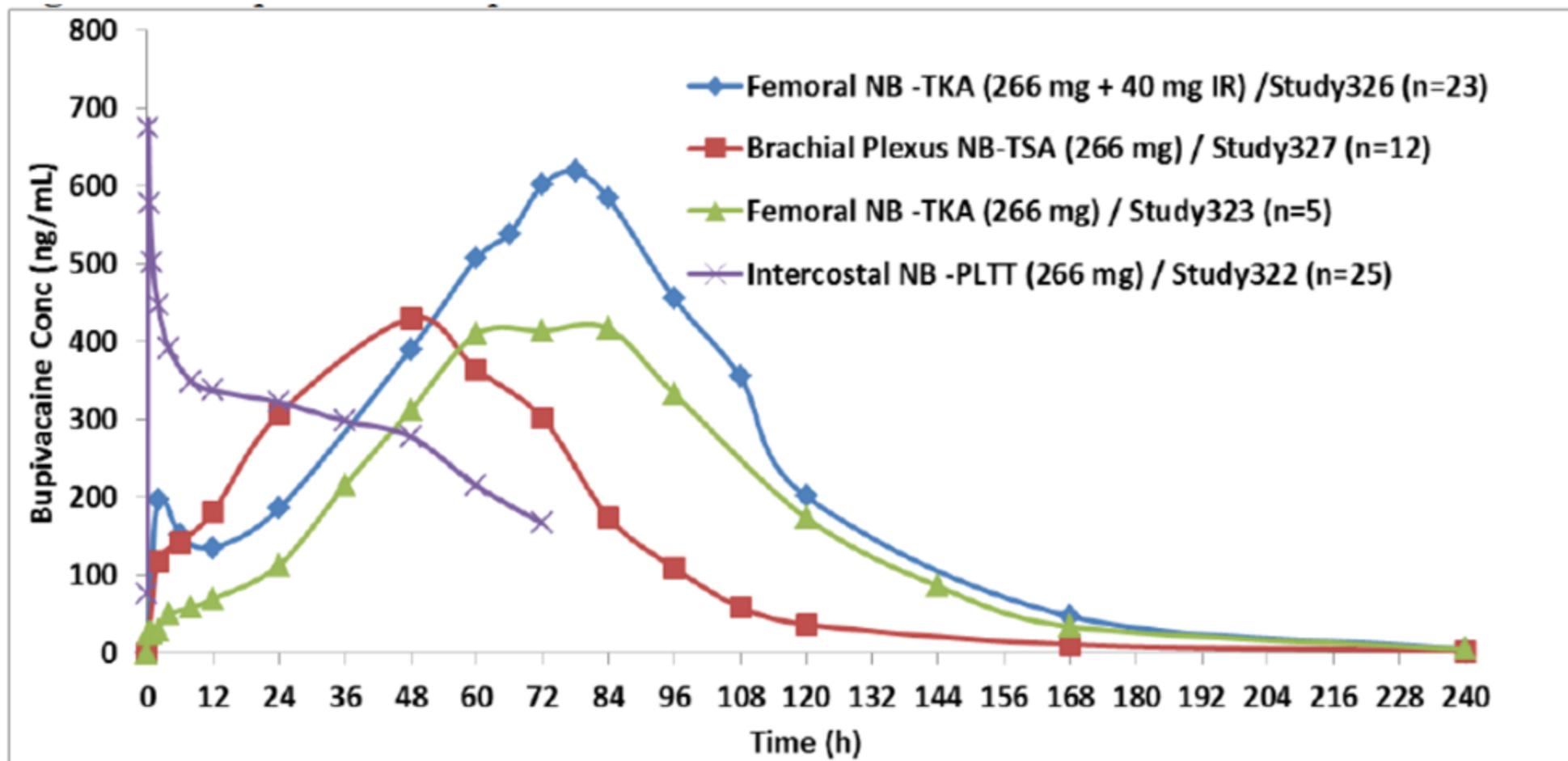
Results:

- **78% decrease in opioid use through 48 hours** (19 vs 85 mg; $P=0.005$)
- **Significantly better pain control** (mean VAS 181 vs 209; $P=0.038$)
- **10% EXPAREL patients opioid-free through 72 hours** (vs 0%; $P<0.01$)
- **Prolonged time-to-first opioid rescue** (4.1 vs 2.9 hrs; $P=0.023$)

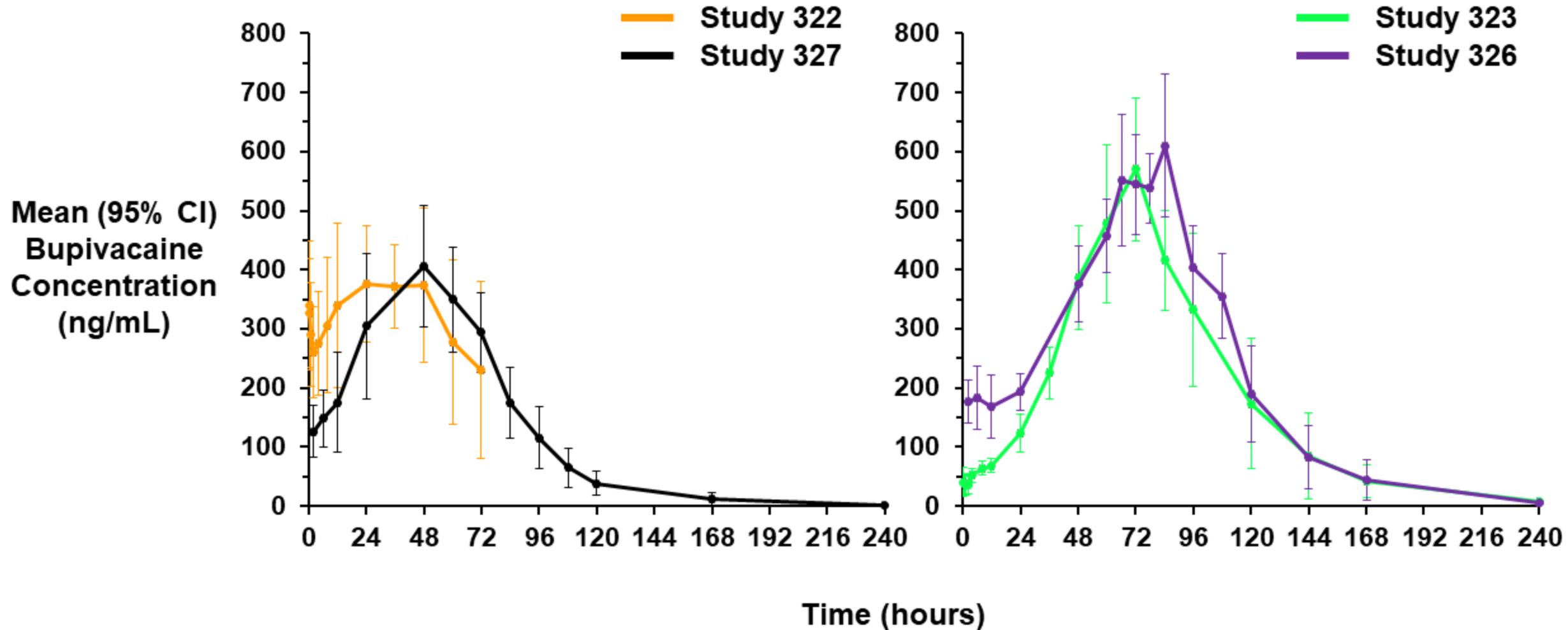
Study 327: Procedure Type

	EXPAREL N=69	Placebo N=71
Rotator Cuff Repair, n (%)	50 (72.5)	55 (77.5)
Total Shoulder Arthroplasty, n (%)	19 (27.5)	16 (22.5)

FDA Figure 6: Comparison of PK profile across the four nerve block studies



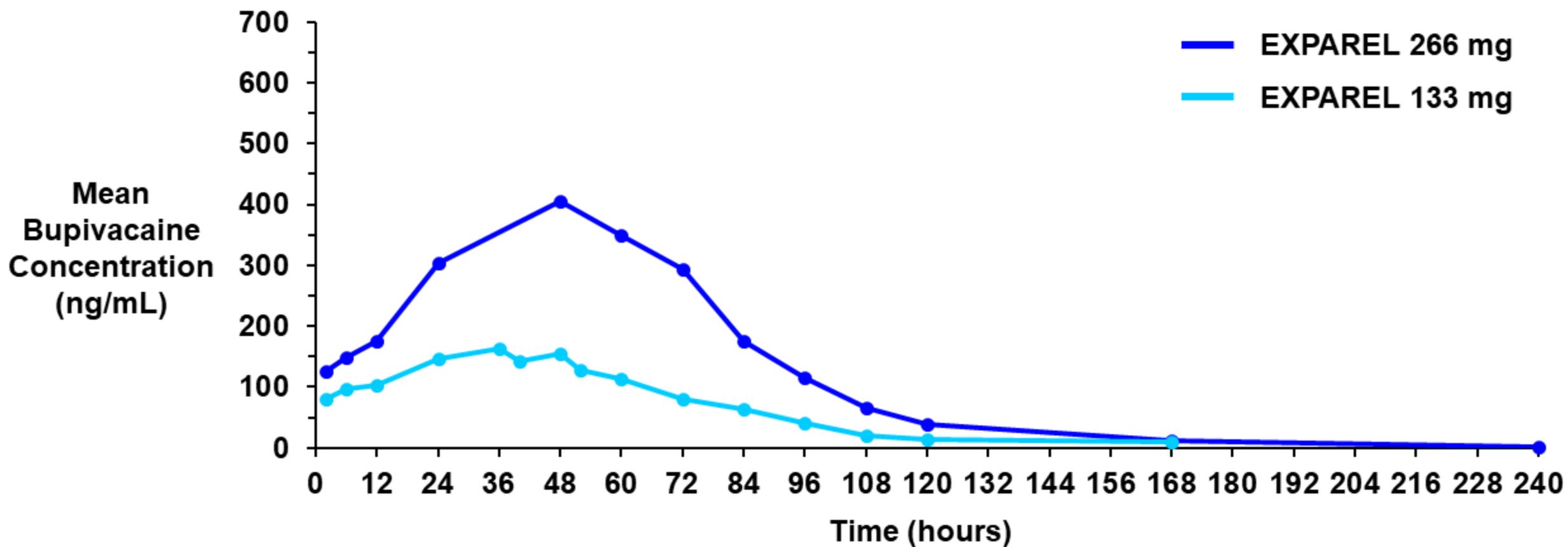
PK of 266 mg Dose by Vascularity



EXPAREL Intercostal Block and Wound Infiltration Versus Continuous Epidural for Open and Minimally Invasive (MI) Thoracotomy

Study	Results
Rice et al 2015¹ N=108	<ul style="list-style-type: none"> ▪ 41% reduction in pain through POD2 for open thoracotomy (p = 0.01) ▪ 42% reduction in opioids through POD2 for open thoracotomy (p < 0.02) ▪ Comparable pain and opioid outcomes for MI surgery ▪ 1 day reduction in length of stay (3.5 vs 4.5 days; p = 0.004) ▪ 31% of epidural patients required modification of infusion
Mehran et al 2018² N=1737	<ul style="list-style-type: none"> ▪ Comparable complication, mortality, readmission to ICU, and reoperation rates ▪ 1 day reduction in length of stay (3 vs 4 days; p < 0.0001)

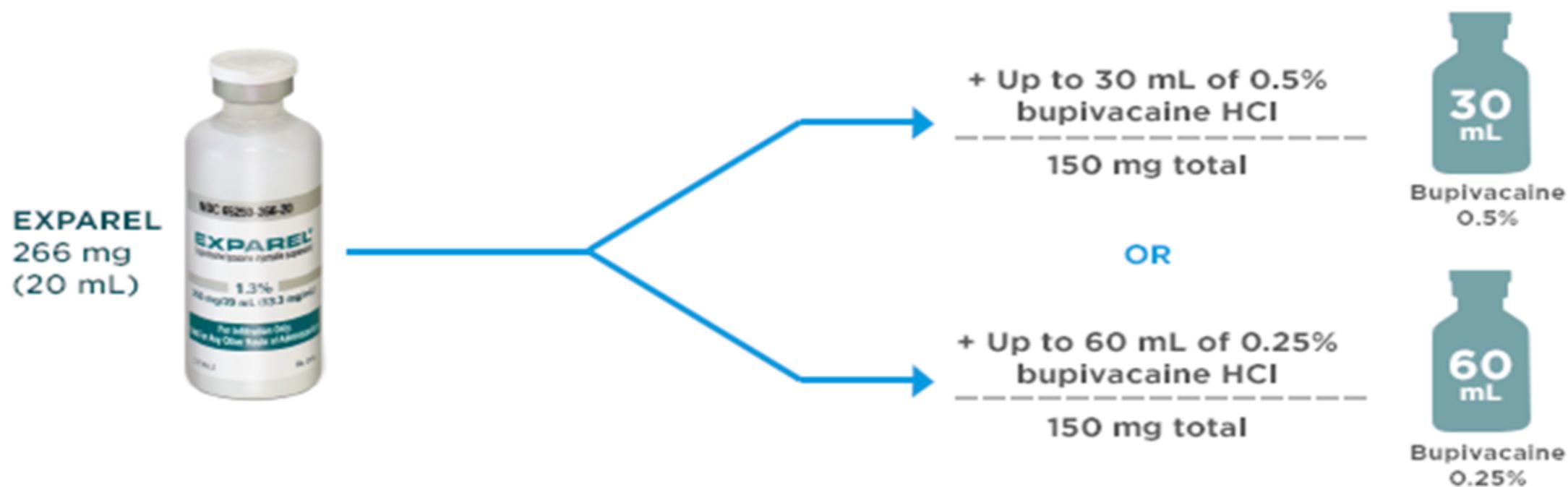
Study 327: PK Profile of EXPAREL



	0	6	12	24	36	48	60	72	84	96	108	120	168	240
266 mg (n)	15	13	13			15	13	15	15	14	13	14	8	3
133 mg (n)	62	39	65	22	38	34	39	13	12	11	7		2	

Admixing with Bupivacaine HCl

- EXPAREL can be admixed with Bupivacaine HCl; maximum 1:2 ratio

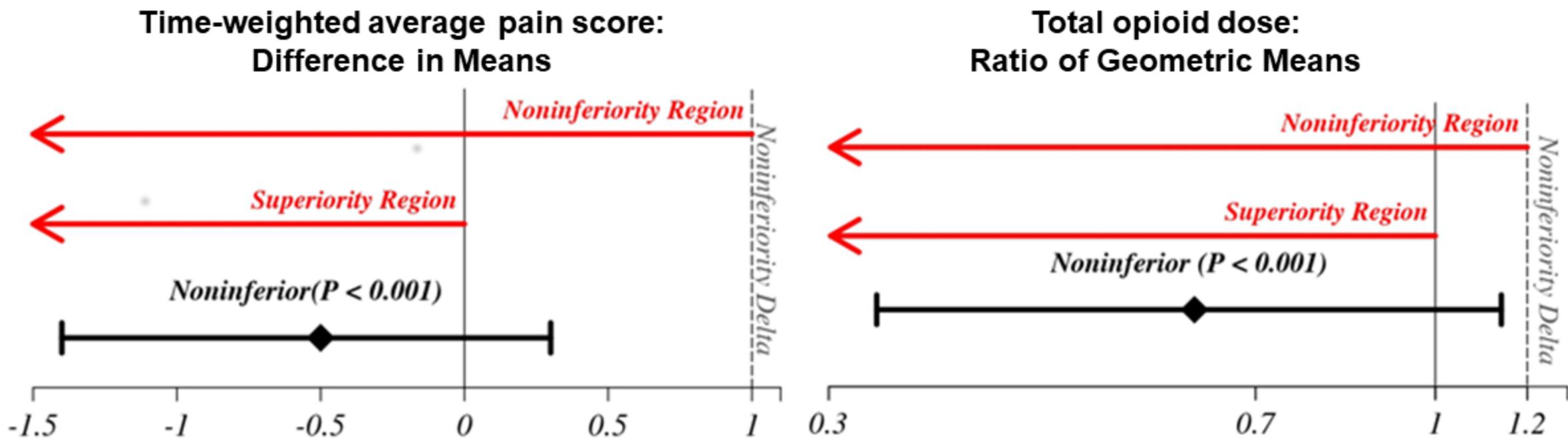


Published Single-Center Comparative Studies (Non-Sponsored)

Specialty	Total N	No. Studies	RCT Obs	% Favorable
Orthopedic	15,862	64	23 41	66%
OB/GYN	967	10	5 5	70%
Plastic	875	9	1 8	89%
General	1,848	9	0 9	100%
Cardiothoracic	2,164	6	0 6	83%
Colorectal	887	5	1 4	80%
Urologic	345	3	2 1	100%
Other*	784	6	2 4	67%

*Other: dental, ophthalmologic, pediatric ENT and multiple procedures

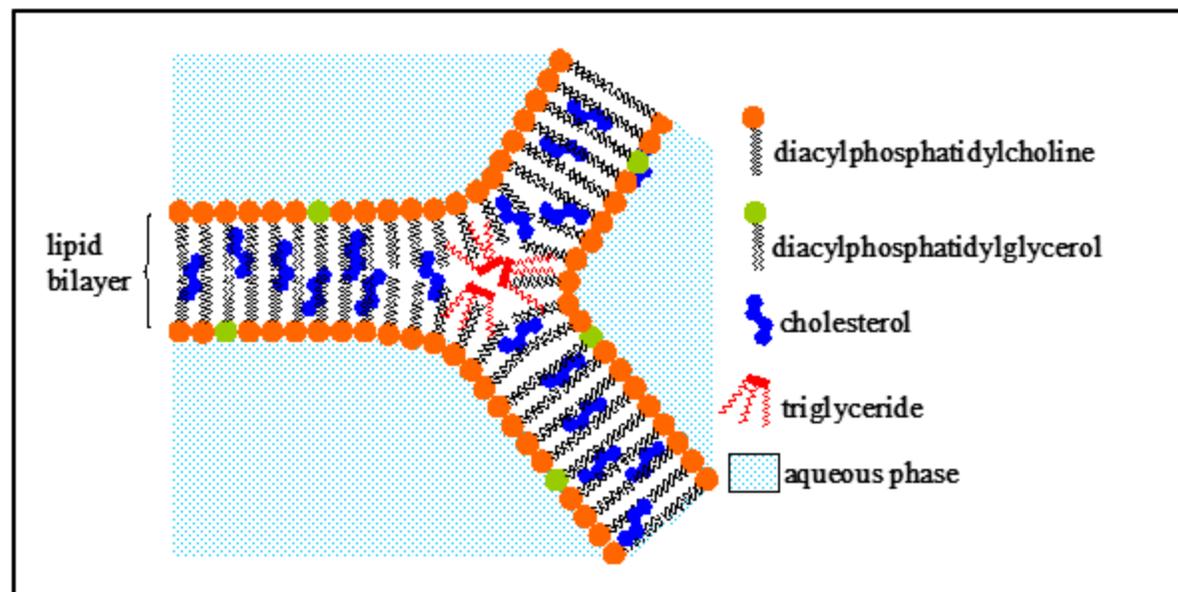
Transversus Abdominis Plane (TAP) Block with EXPAREL Non-Interior to Continuous Epidural Analgesia for Major Lower Abdominal Surgery



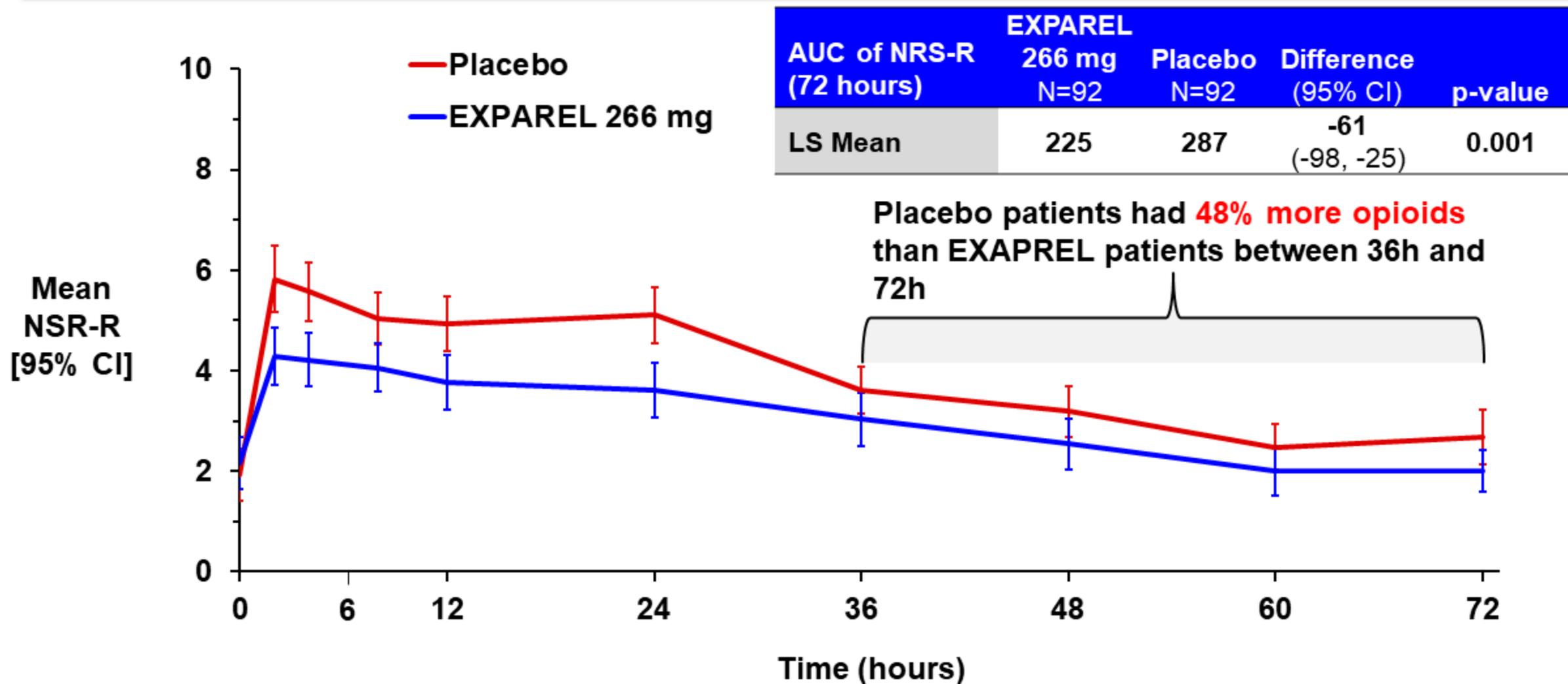
EXPAREL TAP (n=108) noninferior to continuous epidural (n=108) on both outcomes (both $P < 0.001$)

Source of Liposomes

- DepoFoam includes cholesterol and other lipids
- Cholesterol derived from sheep wool grease
- Other lipids synthetic
 - Chemically pure
 - Metabolized by the normal pathways
 - Mimic naturally occurring lipids



Study 323: Primary Endpoint (without Imputation)



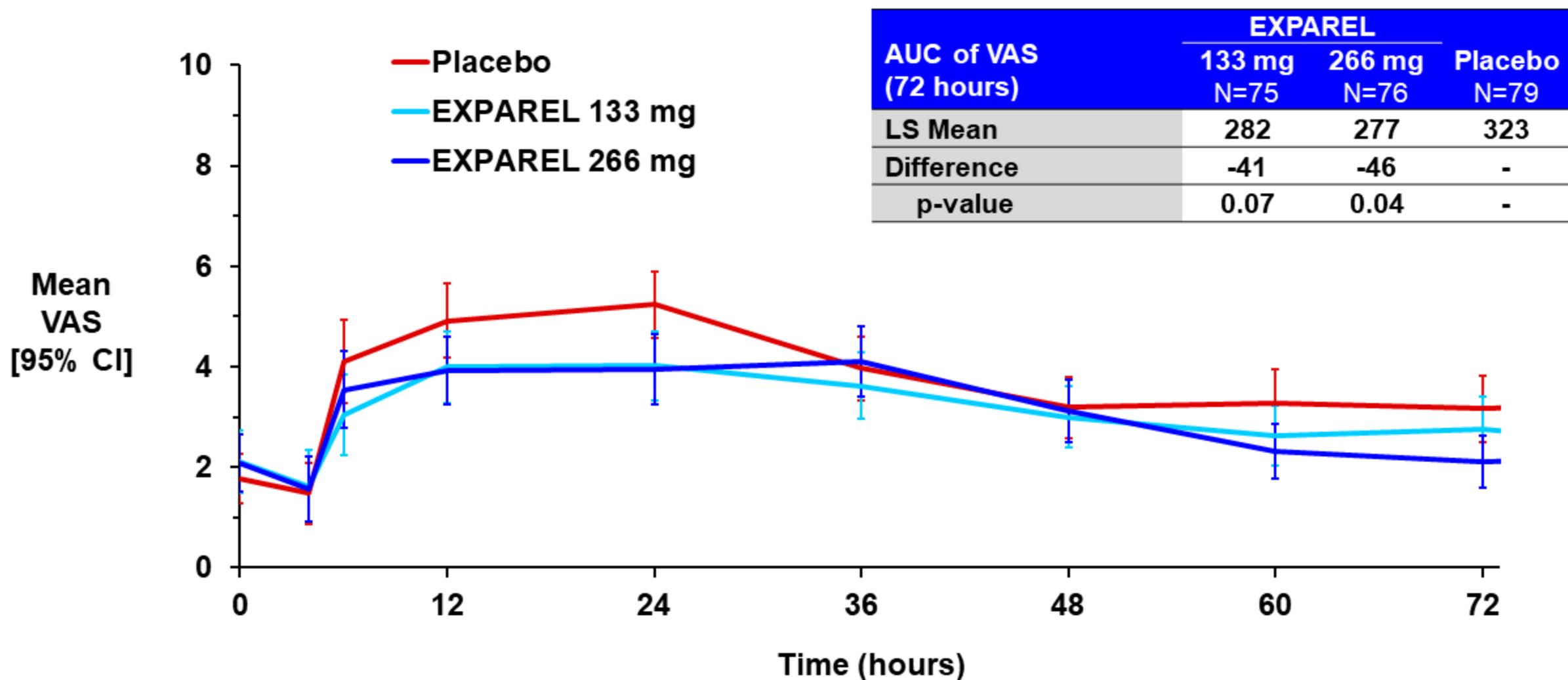
Study 323: Significantly Lower Pain Scores with EXPAREL at Each Postoperative Time Point

Time point	LS Mean NRS-R		P-value for Treatment Difference
	EXPAREL	Placebo	
2 hours	6.3	7.2	0.020
4 hours	6.9	7.8	0.022
8 hours	6.6	7.7	0.002
12 hours	6.5	7.4	0.018
24 hours	6.5	7.6	0.005
36 hours	6.0	6.8	0.045
48 hours	5.9	7.0	0.003
60 hours	4.8	6.2	<0.001
72 hours	4.7	6.0	<0.001

Study 327: Significantly Lower Pain Scores with EXPAREL at Each Postoperative Time Point

Time point	LS Mean VAS		P-value for Treatment Difference
	EXPAREL	Placebo	
PACU	2.6	6.3	<0.001
6 hours	3.0	6.7	<0.001
12 hours	3.1	5.9	<0.001
24 hours	2.7	5.8	<0.001
36 hours	2.9	4.9	<0.001
48 hours	3.4	4.4	0.029
60 hours	3.1	4.3	0.011
72 hours	2.8	4.2	0.004

Study 326: Primary Endpoint (without Imputation)



Pre Clinical IV/IA Study Design (CRL 504333)

Test Material	Route of administration	Dose level (mg/kg)	Dose concentration (mg/mL)	Number of animals			
				Main Study Day 2 Necropsy		Recovery Study Day 15 Necropsy TK animals	
				Males	Females	Males	Females
Saline Control	IV	0	0	3	3	2	2
Bupivacaine	IV	1.5/0.75 ^a	7.5	3	3	2	2
EXPAREL	IV	1.5	13.3	3	3	2	2
EXPAREL	IV	4.5	13.3	3	3	2	2
Saline Control	IA	0	0	3	3	2	2
Bupivacaine	IA	0.1	7.5	3	3	2	2
EXPAREL	IA	1.5	13.3	3	3	2	2
EXPAREL	IA	4.5/3.0 ^b	13.3	3	3	2	2

a. Recovery/TK animals received 1.5 mg/kg but the dose was reduced to 0.75 mg/kg for the main study animals based on observed clinical signs

b. Recovery/TK animals received 4.5 mg/kg but the dose was reduced to 3.0 mg/kg for main study animals based on observed clinical signs

IV: intravenous, IA: Intra-arterial

Summary of Pre Clinical IV/IA Study Toxicology Findings Relative to Embolism (CRL 504333)

- EXPAREL was injected into the saphenous/cephalic veins (1.5, 4.5 mg/kg) and carotid artery (1.5, 3.0 mg/kg for tox and 1.5, 4.5 mg/kg for TK)
- Tissues were collected for histopathology on Day 2 for 6 dogs per group and Day 15 for 4 dogs per group
- We evaluated comprehensive tissues and organs
- **No test article related microscopic findings were noted for any tissue or organ in any dog from any group either on Day 2 or Day 15**
- **Any observations noted were considered incidental and unrelated to the administration of EXPAREL or Bupivacaine**

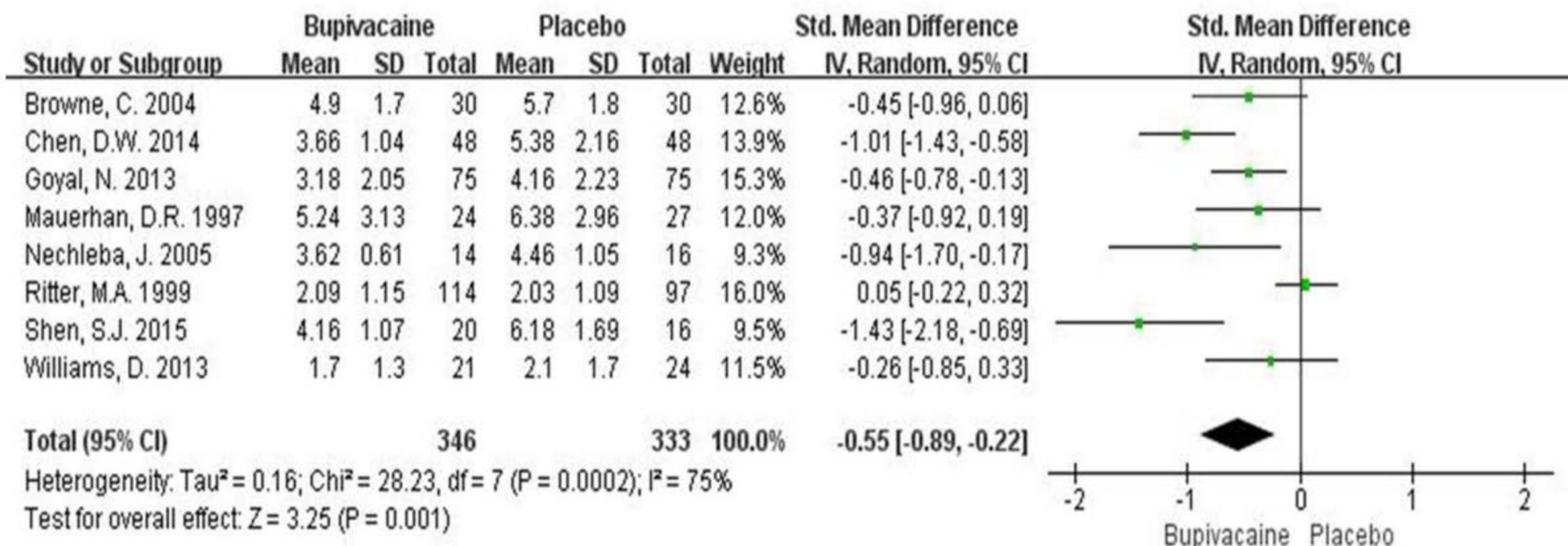
Comprehensive List of Tissues and Organs Evaluated

Gland, prostate	Tissue	Nerve, sciatic
Glad, salivary	Artery	Ovary
Gland, thyroid	Bone marrow, femur	Pancreas
Gross lesions/masses	Bone marrow, sternum	Skin
Gut-associated lymphoid tissue	Bone, femur	Small intestine, duodenum
Heart	Bone, sternum	Small intestine, ileum
Injection site (groups 1 to 4) Intra arterial	Brain	Small intestine, jejunum
Injection site (Carotid – Groups 5 to 8)		
Kidney	Cervix	Spinal cord
Large intestine, cecum	Epididymis	Spleen
Large intestine, colon	Esophagus	Stomach
Large intestine, rectum	Eye	Testis
Larynx	Gallbladder	Thymus
Liver	Gland, adrenal	Tongue
Lung	Gland, lacrimal	Trachea
Lymph node, mandibular	Gland, mammary	Ureter
Lymph node, mesenteric	Gland, parathyroid	Urinary bladder
Muscle, skeletal	Gland, pituitary	Uterus
Nerve, optic		Vagina

FAERS: 4 Deaths Among 39 Possible Cases of Local Anesthetic Systemic Toxicity

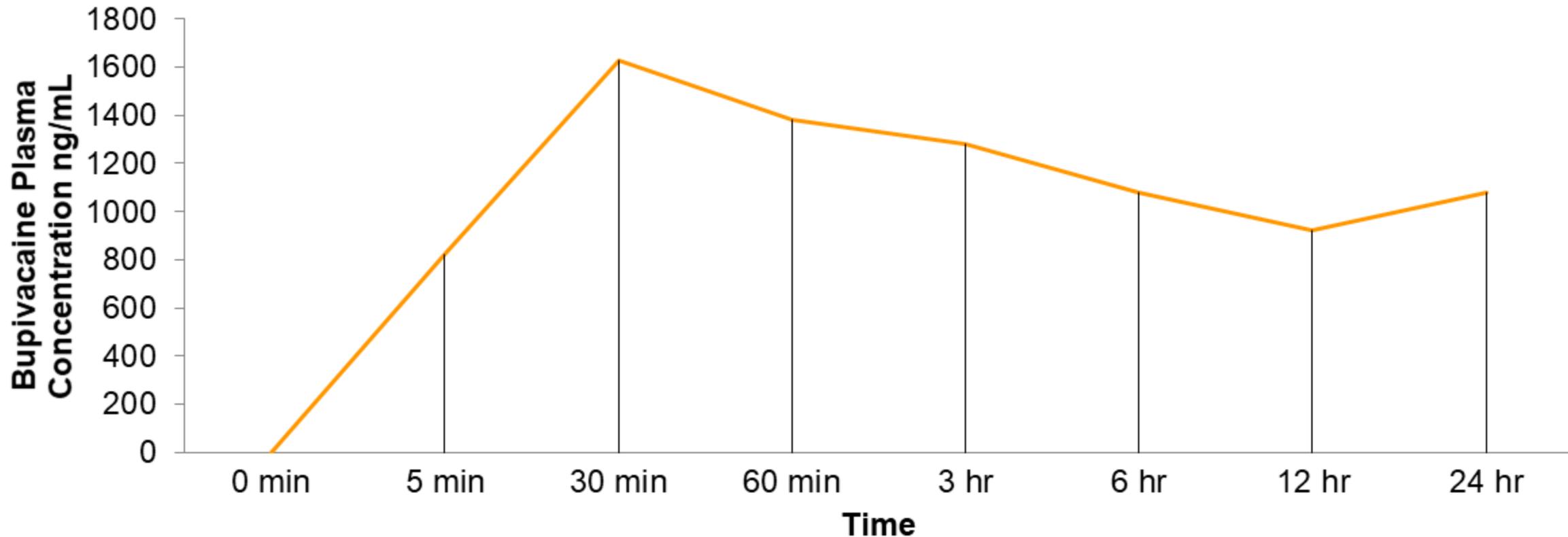
Sex	Age	Day of Death	Other LAs	Confounders	HCP reported as LAST
F	50	0	No	Abnormal baseline EKG	No
F	n/a	2	Yes (bupivacaine)	Patient received bupivacaine infiltration, then EXPAREL infiltration, then more bupivacaine infiltration	Yes
F	87	3	Yes (bupivacaine and ropivacaine)	Described as a very sick patient with extensive cardiac history	No
M	56	N/A	No	--	Unknown

50% Failure Rate for Placebo-Controlled Bupivacaine Trials in Joint Arthroplasty



PK Profile of Immediate-Release Bupivacaine During Continuous Brachial Plexus Block

Bupivacaine 0.25% dosed at .25 mg/kg/hr, mean patient weight 77 kg, mean bupivacaine dose 19.25 mg/hr, total dose 462 mg

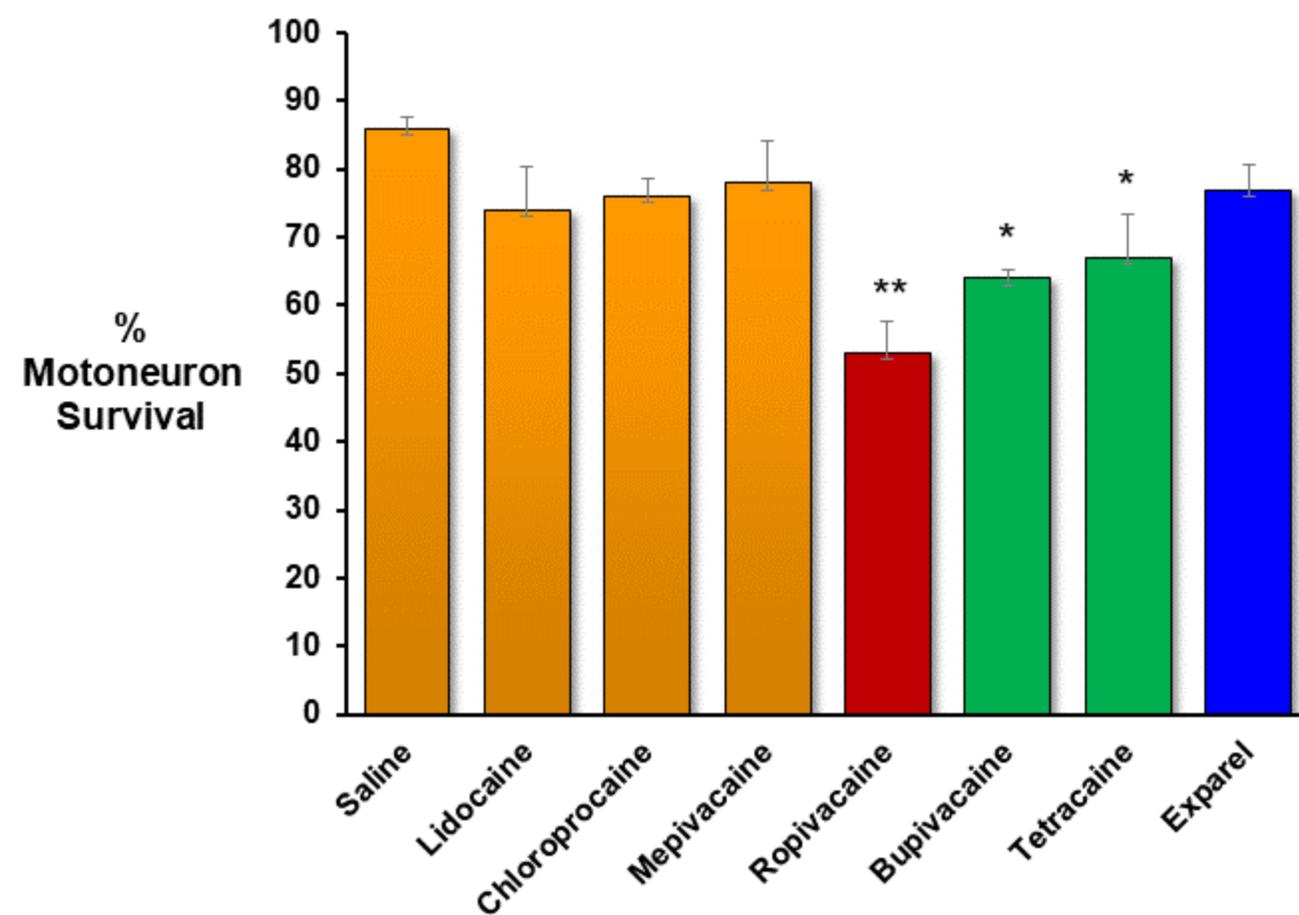


EXPAREL Use in Nerve Blocks: Published Single-Center Studies (Non-Sponsored)

Study	Comparator	Pain	Opioids	Length Of Stay	Function	AEs
Wang et al 2016 TKA; N=222	Continuous Ropivacaine	GREEN	YELLOW	GRAY	GRAY	GRAY
Vandepitte et al 2017 Shoulder Arthroplasty; N=52	Bupivacaine	GREEN	YELLOW	GRAY	GRAY	YELLOW
Rice et al 2015 Thoracotomy; N=108	Epidural	GREEN	GREEN	GREEN	GRAY	GREEN
Mehran et al 2018 Thoracotomy; N=1737	Epidural	GRAY	GRAY	GREEN	GRAY	YELLOW
Khalil et al 2015 Thoracotomy; N=35	Epidural	GREEN	YELLOW	GREEN	GRAY	GREEN
Parascandola et al 2017 Thoracotomy; N=113	Bupivacaine	GRAY	GREEN	YELLOW	GRAY	YELLOW
Day et al 2018 Pharyngoplasty; N=60	Lidocaine	GREEN	GREEN	GREEN	GREEN	YELLOW

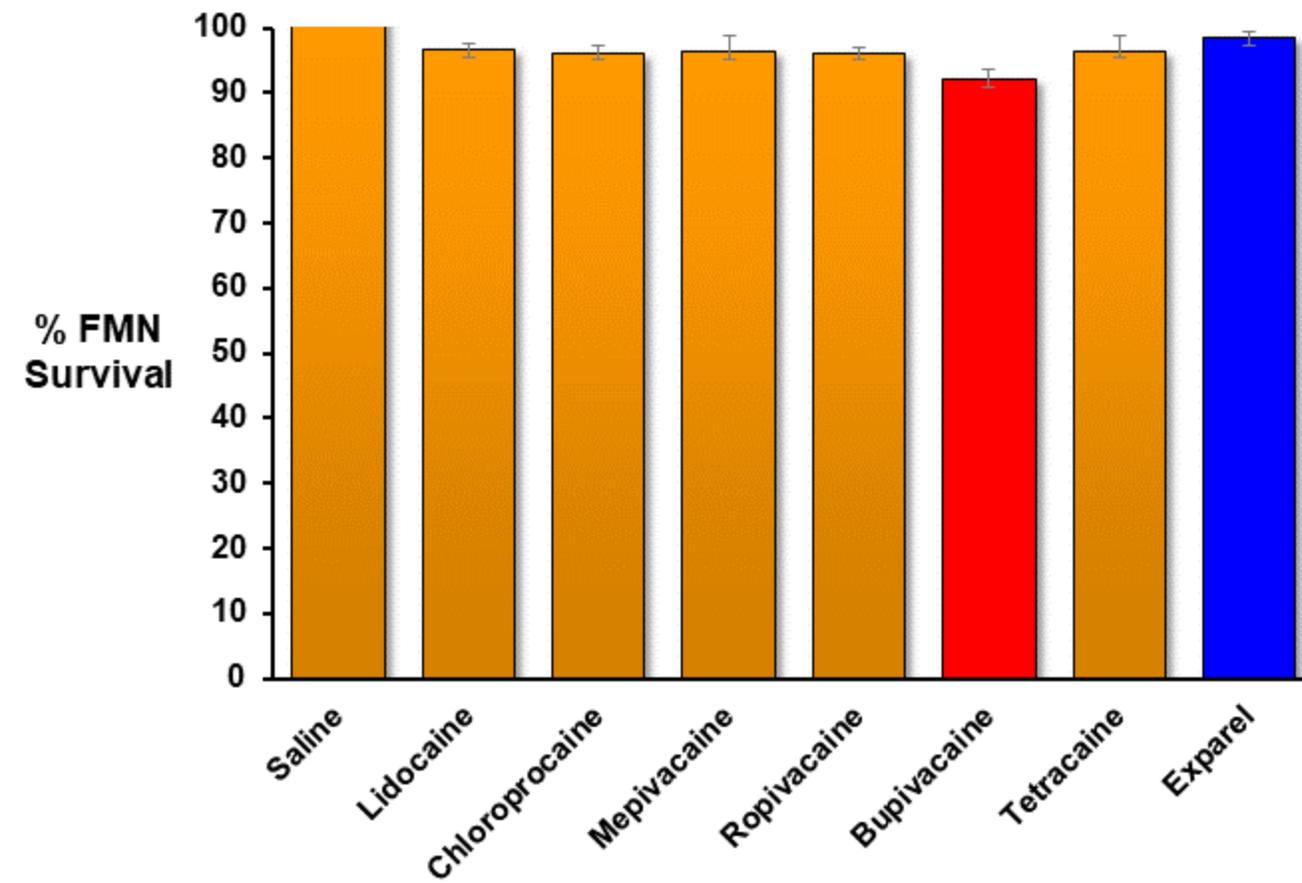
GREEN = Statistically favorable for EXPAREL | **YELLOW** = No difference between groups | **GRAY** = Not assessed

EXPAREL Does Not Exacerbate Neuron Death after Nerve Transection



- Mouse facial nerve transection
- Application of Local Anesthetic
- Determine % neuron survival at 4 weeks
- Importantly, EXPAREL did not exacerbate neuron death

EXPAREL Does Not Exacerbate Neuron Death after Nerve Crush



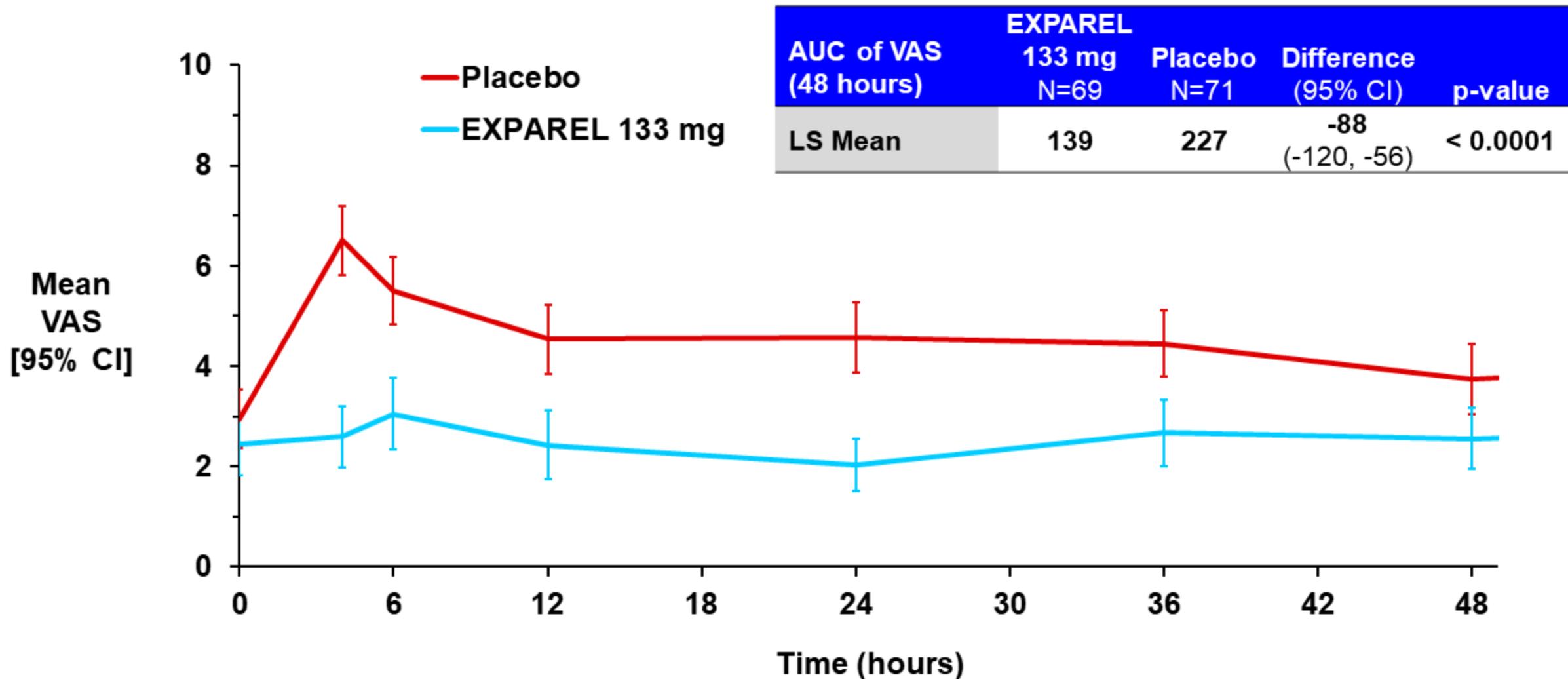
- Mouse facial nerve crush
- Application of local anesthetic
- Determine % neuron survival at 4 weeks
- Importantly, EXPAREL did not exacerbate neuron death

4 Published Reports: EXPAREL Well-tolerated with No Neurotoxicity

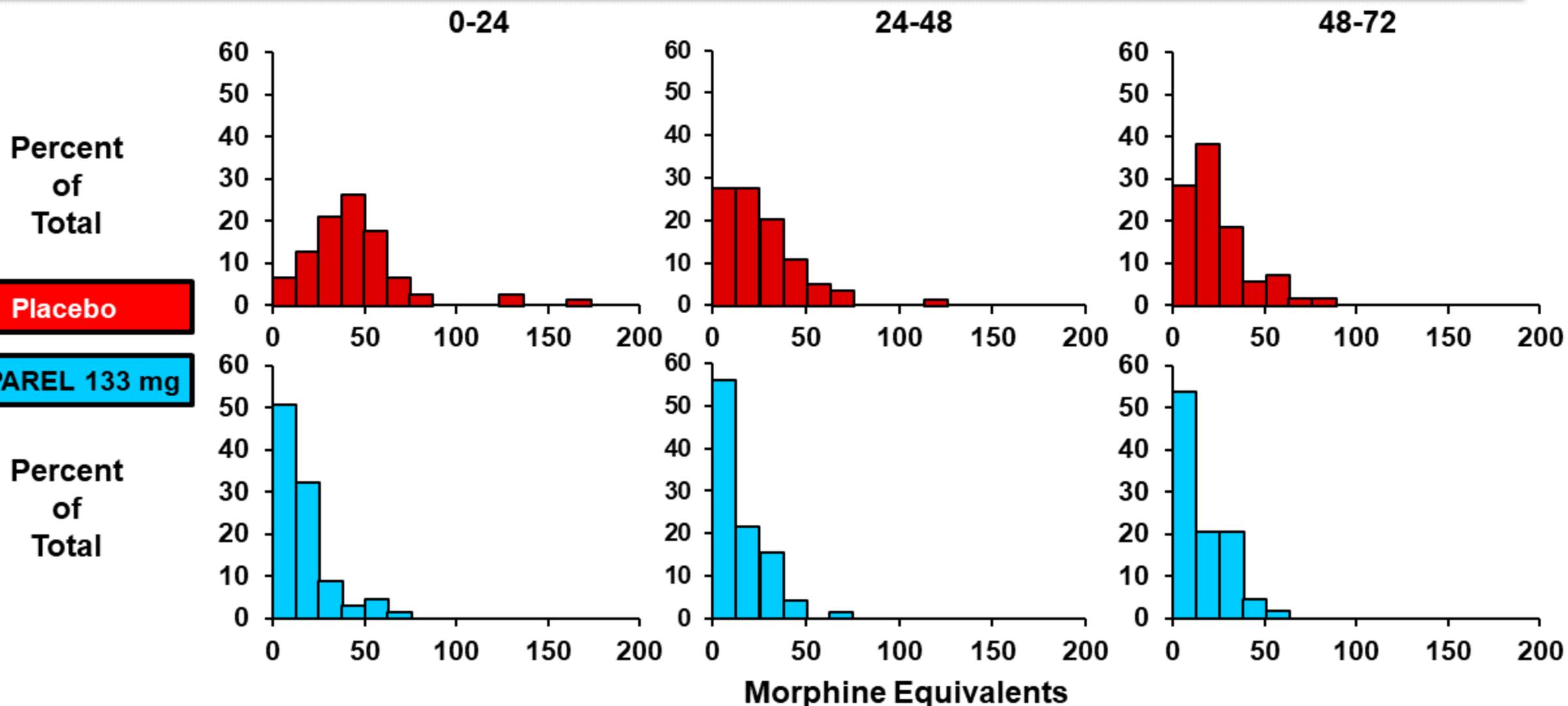
Author/Date	Design	Findings
Richard et al (2012) ¹	<ul style="list-style-type: none"> Rabbit and Dog - Brachial Plexus EXPAREL (9, 18, 30* mg/kg) vs Bupivacaine (9 mg/kg) vs Saline Histopathology day 3 and 15 	<ul style="list-style-type: none"> No persistent sensory or motor deficits Minimal to mild granulomatous inflammation of adipose tissue No evidence of nerve toxicity even at 3 times concentration of free bupivacaine
McAlvin et al (2014) ²	<ul style="list-style-type: none"> Rat - Sciatic nerve EXPAREL vs bupivacaine (0.5% and 1.13%) Local tissue inflammation, myotoxicity and neurotoxicity day 4 and 14 	<ul style="list-style-type: none"> Slight increase in inflammation compared to 0.5% bupivacaine Equivalent myotoxicity No evidence of nerve toxicity
Damjanovska et al (2015) ³	<ul style="list-style-type: none"> Pig – Sciatic nerve EXPAREL perineural vs intraneural Sensory and motor 14 days Histomorphogenic and immunohistochemical 	<ul style="list-style-type: none"> No persistent sensory or motor deficits No changes in nerve fiber density or myelin width Minimal inflammation (few lymphocytes) PCR for immune markers equivalent
Hutchins and Taylor (2017) ⁴	<ul style="list-style-type: none"> Rat – Sciatic nerve EXPAREL vs new formulation bupivacaine 	<ul style="list-style-type: none"> Liposomal bupivacaine did NOT show any measurable neurotoxicity

1. Richard et al. *J Drug Deliv* 2012;2012962101.2. McAlvin et al. *Biomaterials* 2014;35:4557-64.3. Damjanovska et al. *Anaesthesia* 2015;70:1418-26.4. Hutchins & Taylor. *J Pain Res* 2017;10:2807-13.

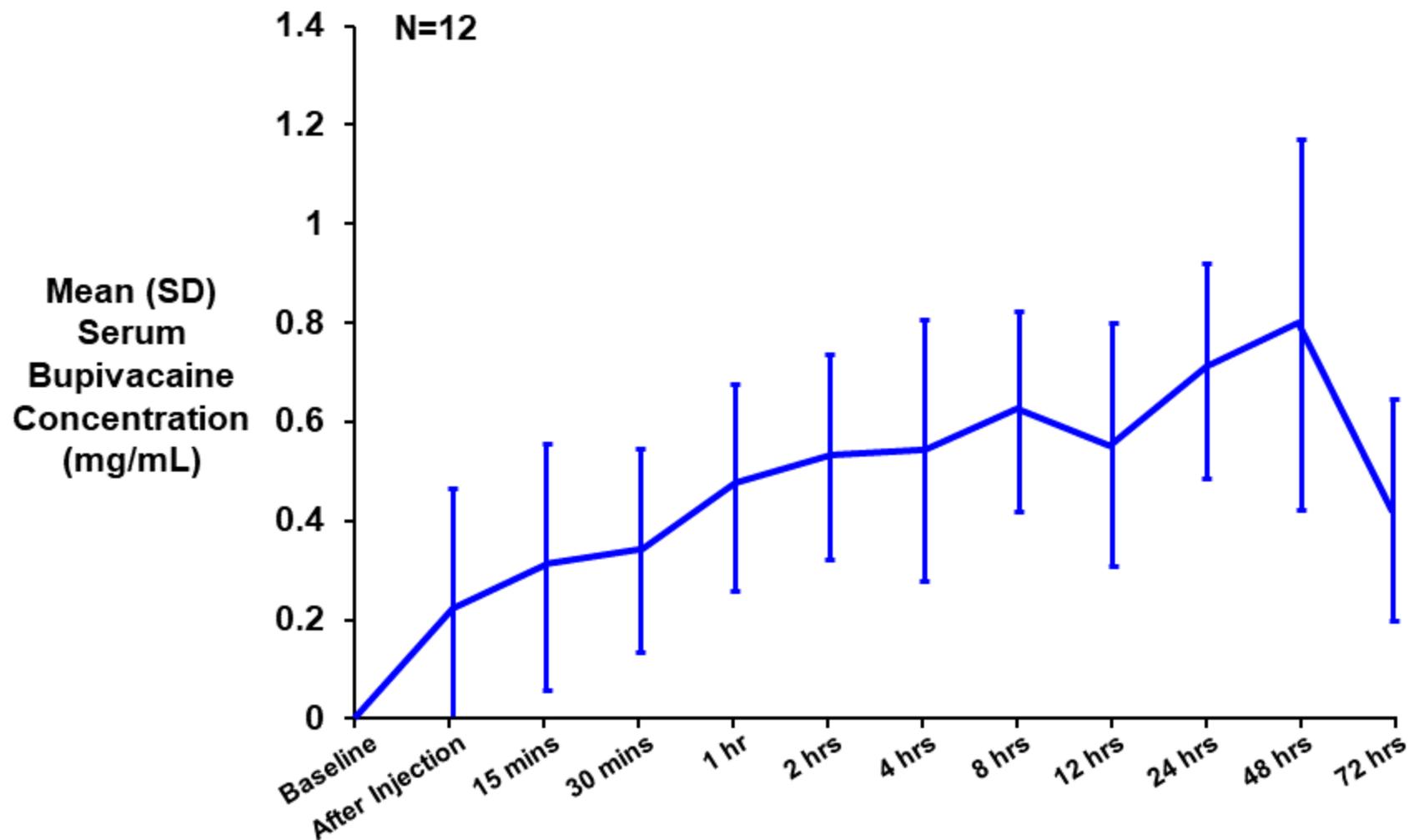
Study 327: Primary Endpoint (without Imputation)



Study 327: Opioid Use by Day

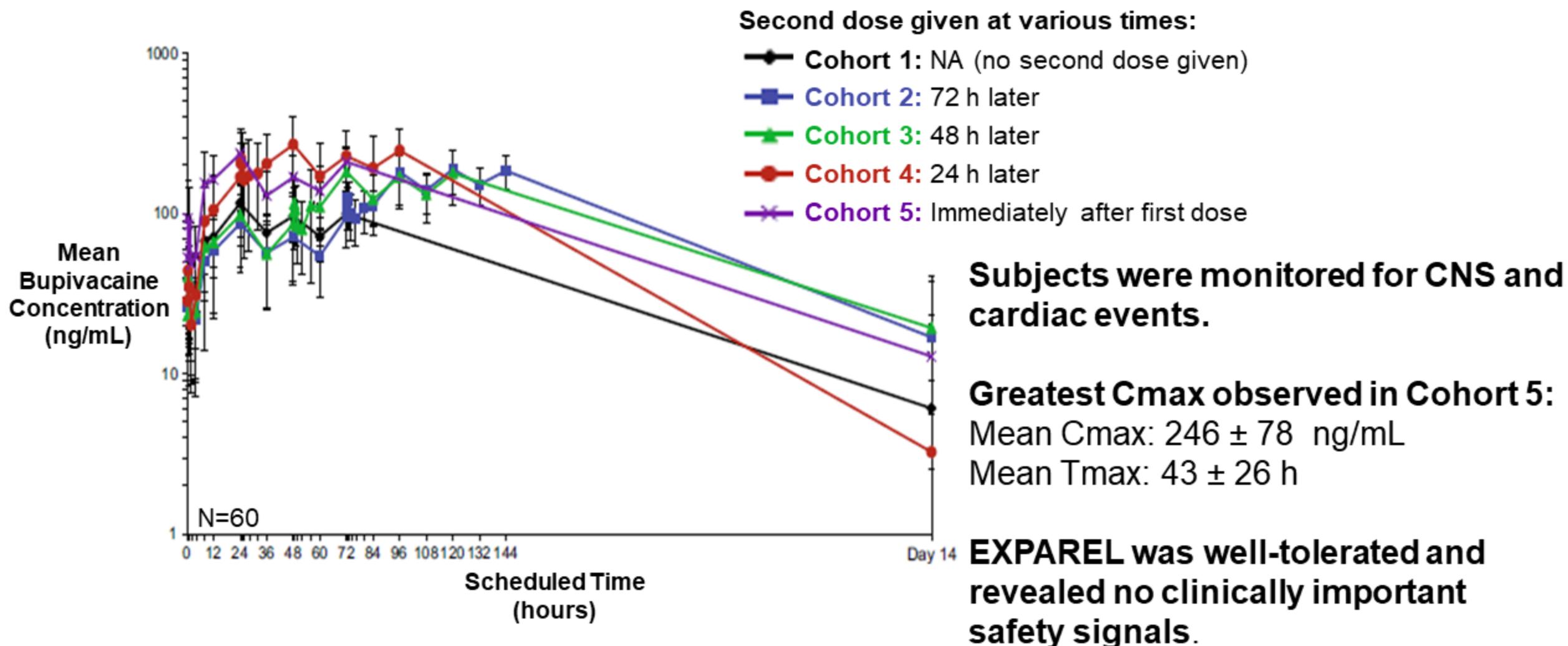


Pharmacokinetics of EXPAREL Admixed with Bupivacaine in Simultaneous Bilateral TKA

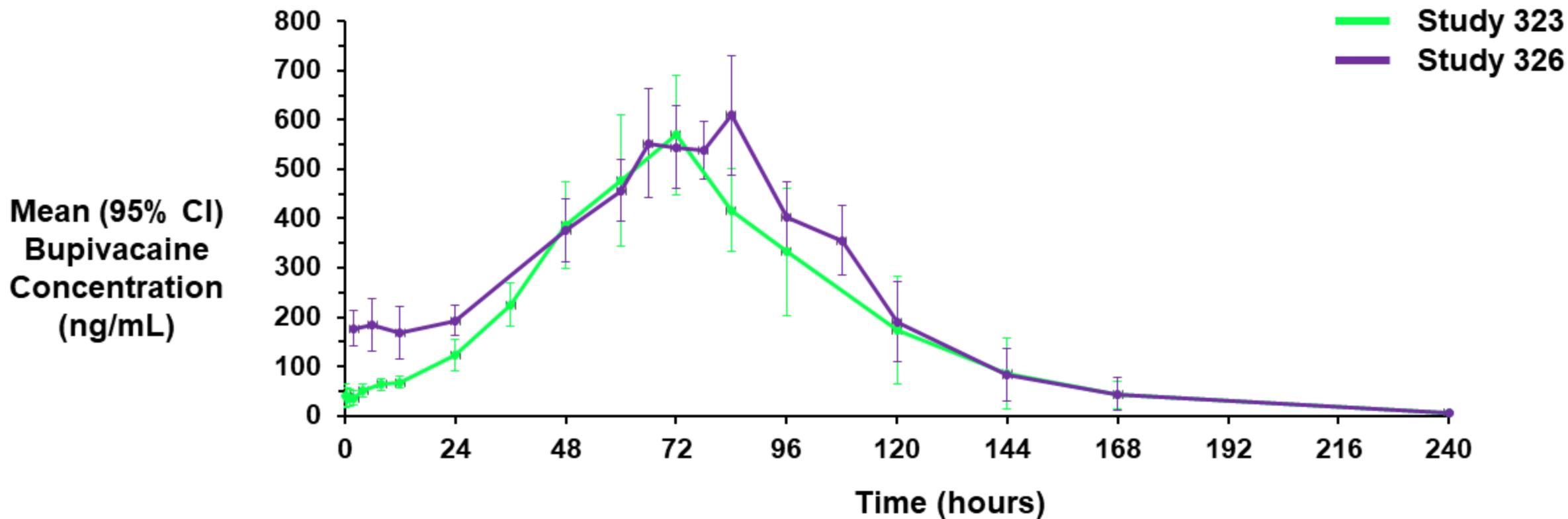


- Total dose:
 - EXPAREL 532 mg + bupivacaine HCl 150 mg divided between knees
- Mean Cmax:
 - 800 ng/mL
- Range:
 - 400-1200 ng/mL
- No identified neurologic or cardiac complications

Repeat Dosing of 266 mg in Healthy Volunteers



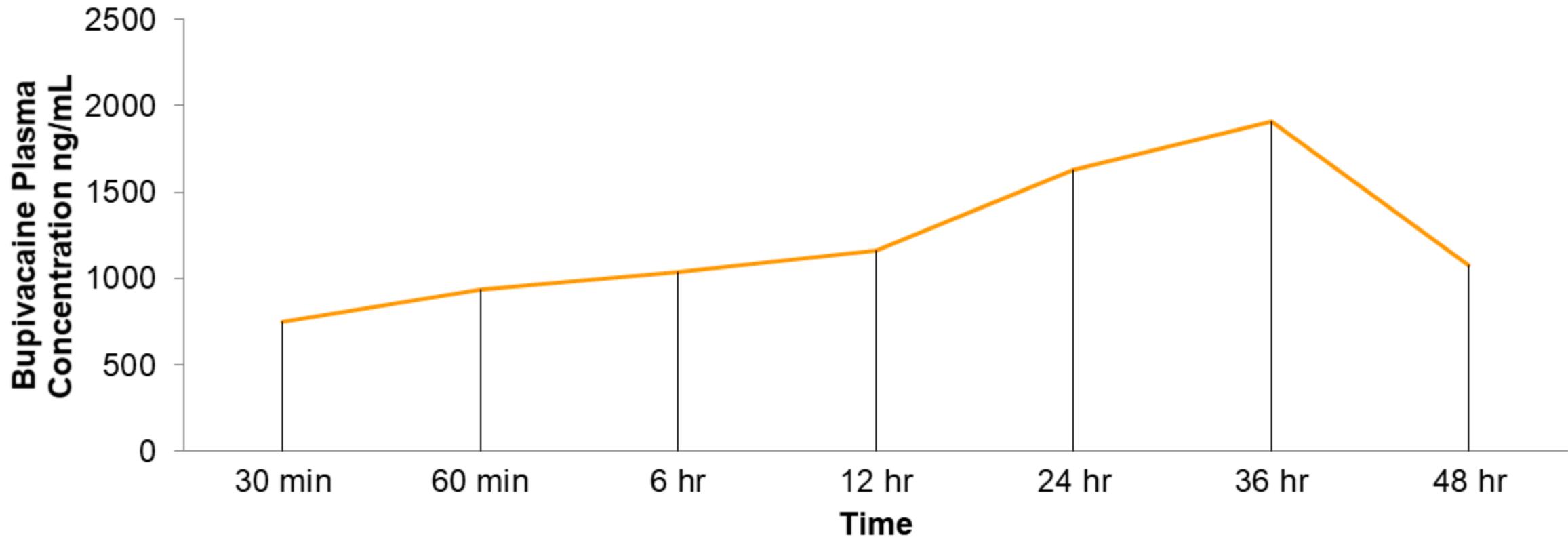
EXPAREL PK Profiles Similar in Femoral Nerve Block in Studies 323 and 326



Study 323, n	22	20	22	20	21	18	20	3	5	-	5	5	4	3
Study 326, n	75	27	51		49	70	50	24	46	43	17	15	19	6

PK Profile of Immediate-Release Bupivacaine During Continuous Femoral Nerve Block

Bupivacaine 0.5% bolus 2.5 mg/kg followed by bupivacaine 0.125% 0.25 mg/kg/hr for 48 hours. Mean patient weight 69 kg, mean bolus 173 mg, mean bupivacaine dose 17.25 mg/hr, total bupivacaine dose 1001 mg



EXPAREL Concomitant Use with Other Local Anesthetics

- EXPAREL should not be admixed with local anesthetics other than bupivacaine. Non-bupivacaine-based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more.
- The toxic effects of these drugs are additive and their administration should be used with caution including monitoring for neurologic and cardiovascular effects related to toxicity.
- The maximum dosage of EXPAREL should not exceed 266 mg (20 mL). Pacira makes no recommendation regarding the dosing of other local anesthetics used in conjunction with EXPAREL.
- Pacira has not evaluated the safety of EXPAREL with other local anesthetics infiltrated at the same site.
- Pacira has not evaluated the administration of EXPAREL followed by another local anesthetic given by any route (intravenous, topical, etc.) at a different site.

Variability in PK for EXPAREL Comparable to Observed Bupivacaine PK

- From Berrisford 1993; continuous extrapleural **intercostal nerve block** in 12 adults:

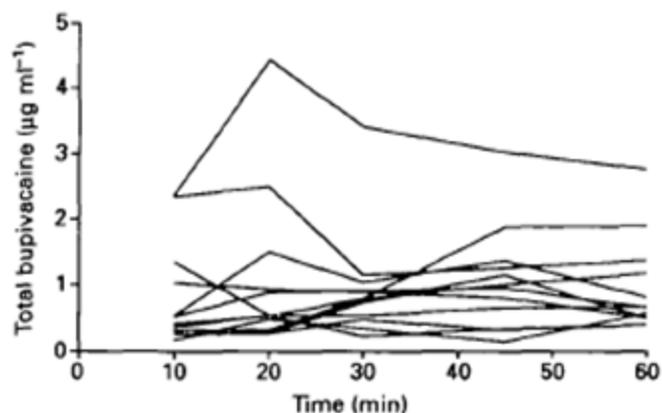


FIG. 1. Plasma bupivacaine concentrations from 12 individual patients after bolus paravertebral injection of 0.5% bupivacaine.

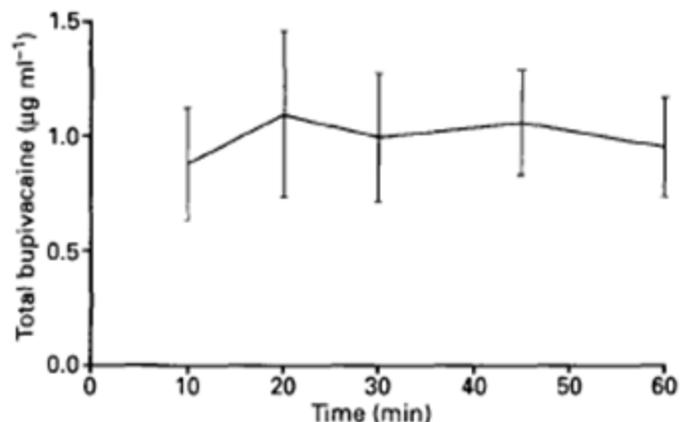


FIG. 2. Mean (SEM) plasma bupivacaine concentrations after bolus paravertebral injection of 0.5% bupivacaine.

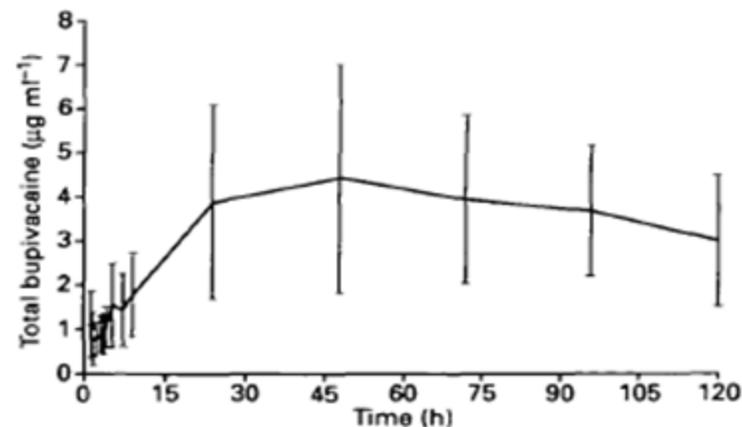


FIG. 3. Mean (SEM) plasma bupivacaine concentrations (racemic) after continuous paravertebral infusion. Time zero represents 60 min after bolus injection.

From Rothstein 1986; bupivacaine 2mg/kg, 3mg/kg, and 4mg/kg **intercostal nerve block** 28 occasions in 27 children 3 mo – 16yr:

Figure 1. Arterial whole blood concentration of bupivacaine ($\mu\text{g/ml}$) as a function of time at the three doses employed. Mean values and standard deviations are indicated. For clarity, points at 2 and 4 min have been omitted in the 4 mg/kg group.

