FDA ADVISORY COMMITTEE MEETING BRIEFING DOCUMENT

EXPAREL®

(bupivacaine liposome injectable suspension)

MEETING OF THE ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE

MEETING DATE: 14-15 February 2018

AVAILABLE FOR PUBLIC RELEASE

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

List of Acronyms/Abbreviations

Abbreviation	Definition
AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
API	Active pharmaceutical ingredient
ASA	American Society of Anesthesiologists
AUC	Area under the curve
AV	Atrioventricular
BMI	Body mass index
CCH	Collagenase clostridium histolyticum
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
C_{max}	Maximum concentration
CNS	Central nervous system
CRL	Complete Response Letter
ECG	Electrocardiogram
ERT	eResearch Technologies, Inc
FDA	Food and Drug Administration
HCl	Hydrochloride
HHS	Department of Health and Human Services
IA	Intra-arterial
IM	Intramuscular
IV	Intravenous
LAST	Local anesthetic systemic toxicity
LOCF	Last observation carried forward
LS	Least squares
NRS-A	Numeric rating scale with activity
NRS-R	Numeric rating scale at rest
NSAID	Nonsteroidal anti-inflammatory drug
OUD	Opioid use disorder
PACU	Post-anesthesia care unit
PADER	Periodic Adverse Drug Experience Report
PCA	Patient controlled analgesia
PK	Pharmacokinetic(s)
PRN	As needed
PT	Preferred Term
q6h	Every 6 hours

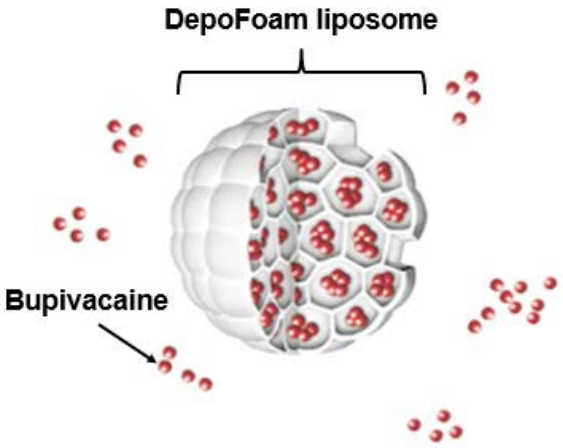
Abbreviation	Definition
RCR	Rotator cuff repair
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
sNDA	Supplemental New Drug Application
$t_{1/2}$	Half life
TKA	Total knee arthroplasty
T_{max}	Time to achieve maximum concentration
TSA	Total shoulder arthroplasty
US	United States
USPI	United States Prescribing Information
VAS	Visual analog scale
wWOCF	Windowed worst observation carried forward

1 EXECUTIVE SUMMARY

EXPAREL® (bupivacaine liposome injectable suspension) is a long-acting, non-opioid analgesic. Bupivacaine, the active pharmaceutical ingredient (API) in EXPAREL, is a local anesthetic that has been used for infiltration/field block and peripheral nerve block for decades in the United States (US) and around the world. EXPAREL has been approved by the Food and Drug Administration (FDA) since October 2011 with an indication for administration into the surgical site to produce postsurgical analgesia. To date, EXPAREL is the only FDA-approved long-acting, non-opioid analgesic. Since its approval, EXPAREL has been used extensively, with an estimated 3.5 million patient exposures in the US. With support from two positive, adequate and well-controlled clinical trials, Pacira Pharmaceuticals, Inc. (Pacira) has filed a supplemental New Drug Application (sNDA) for EXPAREL with a proposed expanded indication for use in nerve block to produce regional analgesia.

EXPAREL consists of microscopic spherical, multivesicular liposomes (DepoFoam® drug delivery system), organized in a honeycomb-like structure comprised of numerous nonconcentric internal aqueous chambers containing bupivacaine (13.3 mg/mL) (Figure 1). Each chamber is separated from adjacent chambers by lipid membranes comprised of naturally occurring or close analogs of endogenous lipids (phospholipids, cholesterol, and triglycerides). Bupivacaine is slowly released from the DepoFoam particles by a complex mechanism involving reorganization of the barrier lipid membranes and subsequent diffusion of the drug.

Figure 1: Structure of EXPAREL Multivesicular Liposome



Because of its pharmacokinetic (PK) properties and the previously demonstrated safe and efficacious prolonged analgesic profile in the clinical setting of infiltration/field block as a local analgesic (Hutchins et al 2015; Chahar 2012), it was reasoned that EXPAREL would also have utility as a regional analgesic when administered as a single-injection nerve block to provide a longer duration of pain management for acute postsurgical pain of considerable intensity and duration. Additionally, EXPAREL would also provide a safe and effective non-opioid pain management treatment option in settings when a long-acting analgesic nerve block is clinically appropriate.

EXPAREL is intended for single-dose administration via infiltration to produce local analgesia and as a nerve block to produce regional analgesia. EXPAREL is available in dosage forms of either 10 mL single-use vial (133 mg bupivacaine free base) or 20 mL single-use vial (266 mg bupivacaine free base), 1.3% (13.3 mg/mL). The recommended dose of EXPAREL for a field block or as a regional nerve block is based on the desired effect for an individual patient taking into account the following factors:

- Duration of analgesia desired
- Dose and volume required for nerve block
- Maximum dose of 266 mg (20 mL)

The current EXPAREL United States Prescribing Information (USPI) specifies that "bupivacaine HCl and EXPAREL may be administered simultaneously in the same syringe, and bupivacaine HCl may be injected immediately before EXPAREL as long as the ratio of the milligram dose of bupivacaine HCl solution to EXPAREL does not exceed 1:2" (Pacira 2016, USPI).

1.1 Rationale for the Use of EXPAREL as a Nerve Block

Acute pain control is a critical element in patient recovery following injury or surgery, as the majority of patients may experience significant pain, particularly in the acute phase. Improved postsurgical or acute pain management contributes to better healing, faster patient mobilization, shortened hospital stays, and reduced healthcare costs (American Society of Anesthesiologists Task Force on Pain Management 2012).

With over 70 million surgeries performed annually in the US, postoperative pain is a ubiquitous condition. While acute pain is a predictable component of the postoperative process, such pain is often poorly managed, resulting in clinical and physiological changes that increase morbidity and mortality (eg, inability to ambulate early), diminish quality of life, and extend length of stay, thereby increasing hospital expenditures (Oderda et al 2007) and reducing patient satisfaction. Effective relief of acute pain with minimal opioid complications, on the other hand, improves clinical outcomes, avoids complications (eg, delay in regaining bowel function, inability to tolerate liquid and solid oral intake), and conserves healthcare resources. As such, the Joint Commission on Accreditation of Healthcare Organizations requires that all accredited healthcare facilities practice safe and quality pain management, promote safe opioid prescribing/use, and minimize the risks associated with treatment (The Joint Commission 2017).

The current consensus clinical practice guidelines of the American Pain Society, the American Society of Regional Analgesia and Pain Medicine, and the American Society of Anesthesiologists recommend utilizing multimodal analgesic regimens to manage acute postsurgical pain (Chou et al 2016). Multimodal analgesia combines two or more agents or techniques that act by different analgesic mechanisms to provide enhanced pain relief with reduced utilization of opioid analgesics. The current modalities of postsurgical analgesic treatment include local anesthetic agents such as lidocaine or bupivacaine for infiltration/field block or nerve block, and systemic agents such as acetaminophen, nonsteroidal

anti-inflammatory drugs (NSAIDs), gabapentinoids, and opioids. Local anesthetics can be used in various ways depending on anatomical location and desired effect:

- Infiltration/field block – typically, a surgeon performs multiple injections of a local anesthetic around the wound, surgical site, or tissue plain to produce local analgesia
- Nerve block – typically, an anesthesiologist targets nerves in a specific area with an injection using ultrasound, nerve stimulation, or anatomical guidance

In clinical practice, certain procedures are more amenable to infiltration/field block while others are more amenable to nerve block. While the administration of the local anesthetic is different with these two approaches, the clinical objective is the same – to block nerves to provide patients relief from acute pain.

The use of single-injection, peripheral nerve blocks in orthopedic procedures has been shown to improve postsurgical analgesia and to reduce postsurgical opioid requirements (Allen et al 1998; Szczukowski et al 2004; Duarte et al 2006; Seet et al 2006; Good et al 2007; Paul et al 2010). However, the duration of analgesia provided by single-injection peripheral nerve blocks is short (typically 12-24 hours) compared with the duration of moderate-to-severe postsurgical pain (often several days or more), which limits their clinical utility as a pain management strategy (Joshi et al 2016; Paul et al 2010). The two current treatment options to prolong the analgesic effect beyond what a single-injection nerve block provides for moderate-to-severe pain are either continuous peripheral nerve blocks or opioid analgesics.

The limitations of continuous peripheral nerve blocks with a catheter and pump are well documented. A continuous peripheral nerve block requires placement of a perineural catheter, a local anesthetic reservoir/pump, infusion management, and catheter site care, which has risks of bacterial colonization, infection, mechanical failure of the pump, catheter migration or dislodgement, wet bandages, and issues with patient compliance/dissatisfaction (Jeng et al 2010; Joshi et al 2016; FDA 2010). Additionally, the placement of an indwelling catheter may be technically challenging and require considerable time.

Opioid analgesics have a long history of use for the management of moderate-to-severe acute and postsurgical pain. However, opioids are associated with many adverse events (AEs) such as respiratory depression, nausea, vomiting, constipation, ileus, confusion, somnolence, pruritus, urinary retention, dysphoria, and delirium requiring intervention (Chernin 2001; Viscusi 2011).

Respiratory depression and death are the most serious risks with postsurgical opioid use. Studies have shown that approximately 1 in 200 patients (0.5%) experience respiratory depression requiring opioid antagonist rescue with naloxone in the postsurgical setting (Rosenfeld et al 2015; The Joint Commission 2012). The requirement for naloxone rescue in the postsurgical setting is higher among patients receiving patient-controlled analgesia (PCA) (approximately 1 in 83 patients) or epidural opioid infusion (approximately 1 in 76) (Rosenfeld et al 2015). Other patient risk factors for respiratory depression with opioids include older age, obesity, sleep apnea, and preexisting pulmonary or cardiac disease (The Joint Commission 2012).

Postsurgical opioid use has also been linked to subsequent persistent opioid use. A recent large study of claims data found that approximately 6% of opioid-naïve patients who underwent surgery and received opioids continued to use opioids 90 days after surgery (Brummett et al 2017). Extrapolated to the US population, this translates to approximately 3 million patients each year. In addition, the incidence of persistent opioid use did not differ among patients undergoing minor (5.9%) or major (6.5%) surgeries, suggesting that many patients are likely continuing opioid therapy for reasons other than the intensity of their pain (Brummett et al 2017).

Expansion of the current indication for EXPAREL – an FDA-approved, long-acting, opioid-free analgesic – to include nerve block would provide physicians and patients with several benefits beyond currently-available pain management options. First, EXPAREL could provide physicians with a long-acting analgesic for procedures that are more amenable to nerve block than field block/infiltration, an indication for which EXPAREL has an extensive history of safe and effective use in over 3.5 million patients in the US. Second, the analgesic effects of a local anesthetic for nerve block could be prolonged via a single-shot technique without the risks and difficulty of placing one or more continuous nerve block catheters. Finally, this approach also has the potential to reduce the exposure of surgical patients to opioids and their associated AEs, as well as reduce the number of opioids available for abuse and diversion in the community.

1.2 Regulatory History

The FDA approved EXPAREL in October 2011 for administration into the surgical site via wound infiltration/field block to produce postsurgical analgesia. This approval was based on two Phase 3, multicenter, randomized, double-blind, placebo-controlled studies that demonstrated efficacy in visceral (hemorrhoidectomy) and nonvisceral (bunionectomy) pain. Overall, the clinical development program included 21 clinical studies and 1 observational study. The initial development program also included Phase 1 and Phase 2 studies evaluating EXPAREL as a nerve block for the upper/thoracic and lower extremities.

Following the initial approval, Pacira conducted three additional studies to support an indication for EXPAREL as a nerve block:

- Study 111, a Phase 1 femoral nerve block study in healthy volunteers
- Study 322, a Phase 3 intercostal nerve block study in patients undergoing thoracotomy
- Study 323, a Phase 2/3 femoral nerve block study in patients undergoing total knee arthroplasty (TKA)

Pacira submitted sNDA 022,496/S-009 for an expanded indication as a nerve block in May 2014. The FDA issued a complete response letter (CRL) in February 2015 and requested additional data. The key requests from FDA included:

- Evidence of efficacy from an adequate and well-controlled trial in at least one additional setting, since Study 322 did not meet its primary efficacy endpoint
- Data characterizing PK through the time to maximum plasma concentration (T_{max})
- Additional analyses of existing cardiac safety data

- Additional data on sensory and motor function to characterize the onset and duration of nerve block.

In consultation with the FDA, Pacira designed two additional Phase 3 multicenter, randomized, double-blind, placebo-controlled trials in order to meet the Agency's request for additional data:

- Study 326, a Phase 3 femoral nerve block study in patients undergoing TKA
- Study 327, a Phase 3 brachial plexus nerve block study in patients undergoing total shoulder arthroplasty (TSA) or rotator cuff repair (RCR).

Following the conduct of these two trials, Pacira resubmitted sNDA 022,496/S-009 in October 2017. Currently, EXPAREL is not approved for marketing in any country outside of the US.

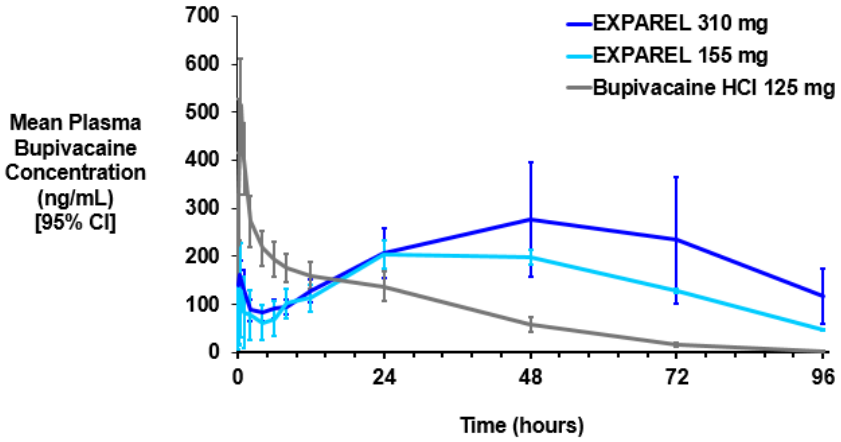
1.3 Clinical Pharmacology

The PK of EXPAREL as a nerve block has been evaluated in six clinical studies at doses ranging from 67 mg to 310 mg of bupivacaine. These included two comparative PK studies of various doses of EXPAREL to bupivacaine HCl (Phase 1 study not discussed) as well as the four Phase 3 clinical trials. In evaluating the PK of EXPAREL, it is important to note that the PK of local anesthetics are less closely associated with analgesic efficacy than the PK of systemic analgesic agents (eg, opioids) given that their analgesic effect is based on their local availability at a specific anatomical location rather than their systemic concentration. However, local anesthetic PK may provide useful information with regard to safety and are less useful in determining the onset and duration of analgesia.

Study 203 was a Phase 2 study of ankle block among patients who underwent bunionectomy and compared the PK profile of EXPAREL (155, 200, and 310 mg) to bupivacaine HCl (125 mg). The key findings of this comparative PK study are representative of the results from both comparative PK studies and include the following:

- The bioavailability of bupivacaine is comparable from similar doses of EXPAREL and bupivacaine HCl.
- All doses of EXPAREL had lower initial maximum concentration (C_{max}) values relative to bupivacaine HCl within the first hour after injection.
- Plasma bupivacaine concentrations following nerve block with bupivacaine HCl decreased rapidly after T_{max} (30 minutes) and were lower than all doses of EXPAREL after 24 hours. For EXPAREL, plasma concentrations persisted following administration and gradually tapered through the 96-hour study period. Consistent with the design of the liposomal formulation, the elimination half-life ($t_{1/2}$) of EXPAREL was approximately 3 to 4-fold longer than bupivacaine HCl (Figure 2).

Figure 2: Mean Plasma Bupivacaine Concentration with EXPAREL and Bupivacaine HCl by Nerve Block in Patients Undergoing Bunionectomy (Study 203)



EXPAREL doses are expressed in terms of bupivacaine free base. Based on the conversion (0.886 mg bupivacaine free base = 1.0 mg bupivacaine HCl), the dose equivalent of bupivacaine HCl 125 mg is 111 mg EXPAREL.

The multiple-dose studies showed a linear relationship between EXPAREL dose and bupivacaine C_{max}, T_{max}, and total exposure (area under the curve [$AUC_{0\text{-}inf}$]) parameters. In addition to the expected PK variability as a result of between-patients and study-to-study factors, the PK profile of EXPAREL varied across the clinical program as a function of dose and the type of nerve block. In order to address FDA's request to characterize PK through T_{max}, Studies 326 and 327 evaluated PK through 120 hours, which captured PK data through T_{max} (ie, 66-74 hours for femoral block and 48-49 hours for brachial nerve plexus block, respectively).

A population PK model was used to evaluate the effects of various patient characteristics on PK. Bupivacaine concentrations following nerve block with EXPAREL were described by a linear two-compartment model with fast and slow absorption routes. The early peak was lower and occurred at a median T_{max} of 0.5-0.75 hours; the later peak was higher and occurred at a median T_{max} of 32-75 hours. The population PK model provided further validation for the linear dose-dependent relationship in PK parameters with EXPAREL. The population PK model also found no effect of mild or moderate renal impairment, mild hepatic impairment, race, or ethnicity on PK. Minor effects on C_{max} were observed for age and sex. Specifically, older age and female sex were associated with modestly higher C_{max} values; however, these effects on C_{max} were not considered clinically meaningful with respect to safety given that the C_{max} values in all subpopulations were lower than those associated with bupivacaine HCl (see Section 4.2.3 for more details).

1.4 Efficacy Findings

Four Phase 3 randomized, placebo-controlled, double-blind multicenter trials evaluated the efficacy of EXPAREL as a nerve block for regional analgesia. The studies were designed to be representative of a broad range of nerve blocks currently being performed in the US, including studies of upper and lower extremities as well as small and larger nerves.

Study Designs

A summary of the Phase 3 study designs is provided in Table 1. (Note: Part 1 of Study 323 was a Phase 2 dose-ranging study of EXPAREL 67 mg, 133 mg, and 266 mg compared to placebo as a femoral nerve block in patient undergoing TKA.)

Table 1: Summary of Phase 3 Study Designs

Study Characteristic	Study 327	Study 322	Study 323 (Part 2)	Study 326
Nerve Block	Brachial plexus (interscalene or supraclavicular)	Intercostal (index nerve, nerve above, and nerve below)	Femoral	Femoral
Surgery Type	TSA/RCR	Thoracotomy	TKA	TKA
Treatment Groups	EXPAREL 133 mg Placebo	EXPAREL 266 mg Placebo	EXPAREL 266 mg Placebo	EXPAREL 133 mg EXPAREL 266 mg Placebo
Number of Patients	140	185	183	230
Primary Endpoint	48-hour AUC of VAS	72-hour AUC of NRS-R	72-hour AUC of NRS-R	72-hour AUC of VAS for pain

TSA = total shoulder arthroplasty. RCR = rotator cuff repair. TKA = total knee arthroplasty. AUC = area under the curve. VAS = visual analog scale. NRS-R = numeric rating scale – at rest.

The studies enrolled adults aged 18 years or older who were scheduled to undergo the procedure corresponding to each trial. All patients could not have planned concurrent surgical procedures, could not be receiving long-action opioid medications, NSAIDS, or dexmedetomidine within 3 days of surgery, and could not use opioid medications of any kind within 24 hours of surgery.

Perioperative medication regimens were consistent with standard of care for the procedures. In general, low dose aspirin for cardioprotection and acetaminophen/paracetamol (up to daily maximum of 3000 mg) were permitted prior to study drug administration. Short-acting opioids were permitted during surgery in all studies. Antiemetics were permitted postoperatively at the investigator's discretion.

Each study protocol provided specific guidance on the use of rescue medication:

- **Studies 327 and 326:** All patients received cyclobenzaprine at the investigator's discretion and acetaminophen or paracetamol, unless contraindicated. Following surgery, immediate-release oxycodone was permitted as a rescue medication for pain control (initiated at 5-10 mg every 4 hours or as needed [PRN]). Intravenous (IV) morphine or hydromorphone was permitted if oral medications could not be tolerated.
- **Study 322:** First-line rescue was IV fentanyl 100 mcg. Second-line rescue was either PCA with morphine or hydromorphone, or an intramuscular morphine injection.
- **Study 323:** First-line rescue was a hydromorphone 0.5 mg IV bolus. Second-line rescue was on-demand PCA with morphine or hydromorphone. Third-line rescue was a femoral nerve block with bupivacaine HCl 1.25 mg/mL.

The primary efficacy endpoint of all studies was the cumulative pain intensity (AUC) over a period of 48 or 72 hours. Studies 322 and 323 measured pain intensity using the numeric rating scale-at rest (NRS-R) and Studies 326 and 327 used a 10-cm visual analog scale (VAS). The NRS-R and VAS scales used comparable anchors (0 = no pain; 10 = worst possible pain). The NRS-R can only take on integer values (eg, 0, 1, 2) while the VAS can take on any numeric value to the nearest tenths place (eg, 5.2, 6.8, 7.0).

Secondary efficacy endpoints included the total amount of opioid rescue medications used, the percentage of patients who did not require opioid rescue medication, and the time to first opioid use. Secondary endpoints were ranked in accordance with clinical importance and analyzed hierarchically in order to maintain each study's respective overall Type-I error rate.

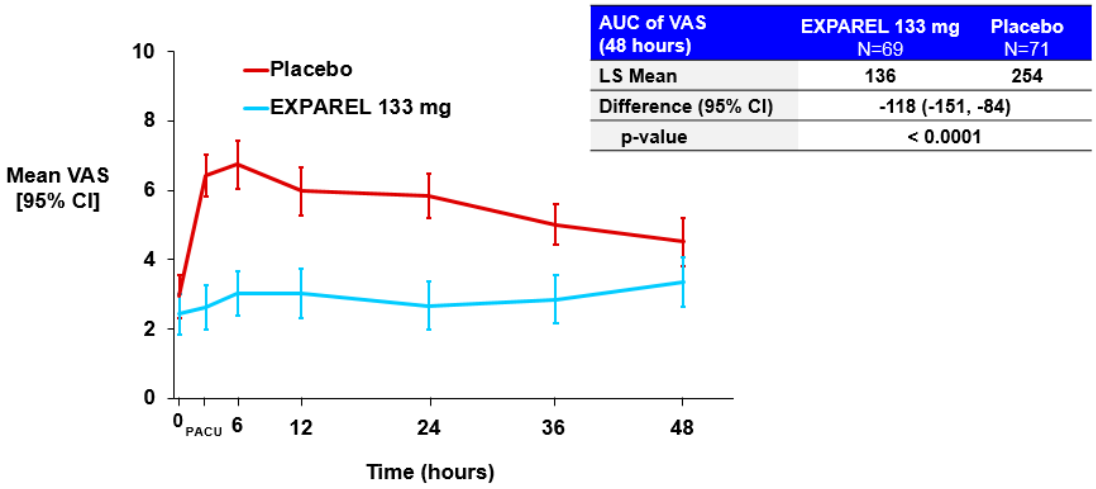
The primary and secondary efficacy endpoints were analyzed using all randomized patients who received study drug and underwent the planned surgery. In Studies 326 and 327, the primary efficacy endpoint was analyzed using analysis of variance (ANOVA) adjusting for age, weight, and height. In Studies 322 and 323, the primary endpoint was evaluated using analysis of covariance (ANCOVA) adjusting for baseline NRS-R pain intensity score. Statistical analyses for the primary endpoints used a conservative imputation approach for rescue medication with the windowed worst observation carried forward (wWOCF) method where all pain scores in a time window following rescue medication (depending on the expected duration of effect of the rescue medication) were imputed using the worst observation prior to taking the rescue medication. The pre-specified methods for handling missing data were last observation carried forward (LOCF) for Studies 322 and 323 and multiple imputation for Studies 326 and 327.

Below, the key results of each study are summarized, beginning with the upper extremity/thoracic studies and then the lower extremity studies.

Study 327 Results (Brachial Plexus Nerve Block in TSA/RCR)

In Study 327, the primary efficacy endpoint was met. The EXPAREL 133 mg group had significantly lower cumulative pain intensity scores (AUC of VAS) through 48 hours than the placebo group ($p < 0.0001$). The mean VAS pain intensity scores remained at approximately 2 to 3 on the 10-cm VAS scale in the EXPAREL group throughout the study compared to mean VAS scores of approximately 5 to 7 cm in the placebo group (Figure 3).

Figure 3: Primary Efficacy Endpoint Results (Study 327)

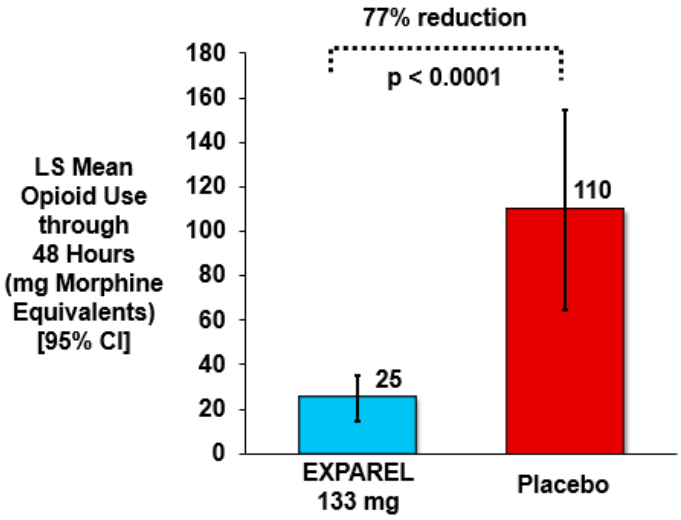


AUC of VAS (48 hours)	EXPAREL 133 mg N=69	Placebo N=71
LS Mean	136	254
Difference (95% CI)	-118 (-151, -84)	
p-value	< 0.0001	

PACU = post-anesthesia care unit

Study 327 also met all pre-specified secondary efficacy endpoints demonstrating reductions in opioid consumption. The mean total amount of opioid rescue medication used was 77% lower in the EXPAREL group than the placebo group (Figure 4; $p < 0.0001$). Significantly more patients who received EXPAREL did not use any opioid rescue medications (13%) compared to placebo patients (1%) ($p = 0.008$). The time to first opioid medication use was also significantly longer with EXPAREL (median, 4 hours) than placebo (median, 35 minutes) ($p < 0.0001$).

Figure 4: LS Mean Total Opioid Use Through 48 Hours (Study 327)



Overall, Study 327 demonstrated that EXPAREL was efficacious for regional nerve block in an upper extremity and reduced the use of opioid medications.

Study 322 Results (Intercostal Nerve Block in Thoracotomy)

In Study 322, the primary efficacy endpoint was not met. The mean cumulative pain intensity (AUC of NRS-R) was not statistically different in the EXPAREL 266 mg and the placebo groups (472 vs 459; p = 0.56).

Following a comprehensive review, Pacira concluded that the variability in and suboptimal administration of the study drug substantially impacted the study results. In Study 322, study drug was administered by the surgeon via instillation prior to wound closure rather than by the anesthesiologist via injection under ultrasound guidance (as was done in the other Phase 3 studies). This led to considerable variability in the placement and retention of EXPAREL within the intercostal musculature. Pharmacokinetics analyses showed that EXPAREL was absorbed and cleared rapidly (median T_{max} of 1 hour in Study 322 compared to 49-74 hours in other studies using the 266 mg dose), consistent with injection in a highly vascular field. Additional details can be found in Section 5.5.

Taking these limitations into account, Pacira concluded that the efficacy of EXPAREL as a regional nerve block cannot be meaningfully evaluated in Study 322 because nerve block was not achieved due to the manner in which study drug was administered.

Study 323 – Part 1 Results (Femoral Nerve Block in TKA)

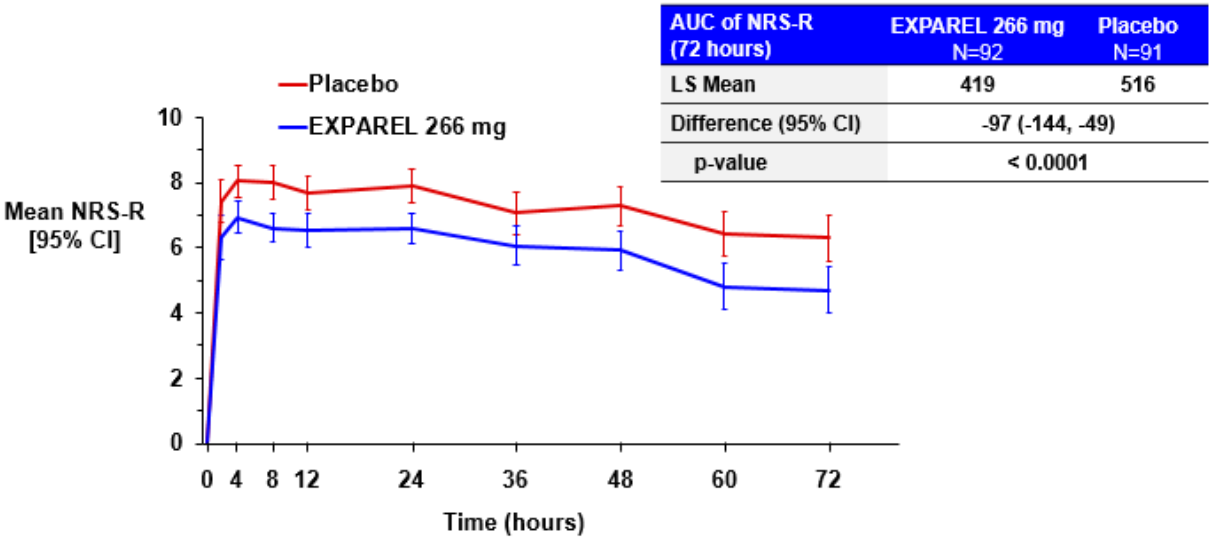
In Study 323 – Part 1 (ie, the Phase 2 portion of the study), both the 133 mg and 266 mg dose of EXPAREL resulted in statistically significant pain reduction relative to placebo, with a least squares (LS) mean difference in 72-hour AUC of -103 and -94 (p = 0.024 and p = 0.039), respectively. The difference between the EXPAREL 67 mg group and the placebo group was not statistically significant (p = 0.95). The 266 mg dose also showed favorable results for time to first opioid rescue (median 1.3 hours) compared to placebo (median 0.4 hours) (p = 0.0004).

Based on these results, as well as the demonstration of similar safety across dose groups, an independent Unblinded Dose Selection Committee concluded that the 266 mg dose should be moved forward for further testing in Part 2 of Study 323.

Study 323 – Part 2 Results (Femoral Nerve Block in TKA)

In Study 323 – Part 2 (ie, the Phase 3 portion of the study), the primary efficacy endpoint was met. The mean cumulative pain intensity (AUC of NRS-R) through 72 hours was significantly lower in the EXPAREL 266 mg group than the placebo group (p < 0.0001). The mean pain intensity was approximately 2 points lower on the NRS-R after surgery, and the benefit over placebo was maintained through 72 hours (Figure 5).

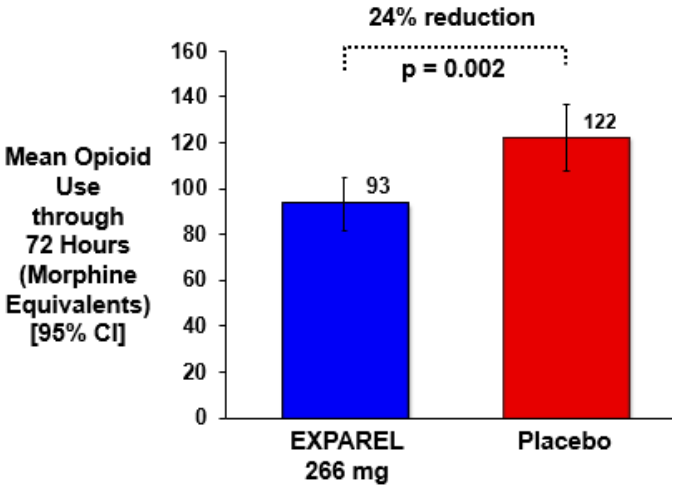
Figure 5: Primary Efficacy Endpoint Results (Study 323 Part 2)



AUC of NRS-R (72 hours)	EXPAREL 266 mg N=92	Placebo N=91
LS Mean	419	516
Difference (95% CI)	-97 (-144, -49)	
p-value	< 0.0001	

Patients in the EXPAREL group experienced less pain while simultaneously requiring fewer opioids for postsurgical pain control than the placebo group. Figure 6 illustrates that the mean amount of opioid rescue medication was 24% lower among EXPAREL patients (p = 0.002). The percentage of patients free from opioid rescue medication was not a ranked secondary endpoint in Study 323; while all patients in both groups received at least 1 rescue medication, fewer patients in the EXPAREL group required all three lines of rescue medications (8% vs 19%). The time to first opioid use was approximately 30 minutes in both treatment groups and was not significantly different.

Figure 6: Mean Total Opioid Use Through 72 Hours (Study 323 – Part 2)



Overall, Study 323 demonstrated that EXPAREL 266 mg provided efficacious regional analgesia in a lower extremity while also reducing the total amount of required postsurgical opioid medication use.

Study 326 (Femoral Nerve Block in TKA)

The design of Study 326 was based on the results of the prior positive Phase 3 study in TKA (Study 323 – Part 2). In Study 326, the primary efficacy endpoint was not met. The mean cumulative pain intensity score (AUC of VAS) through 72 hours was not significantly different in the EXPAREL 133 mg or 266 mg groups compared to placebo (Table 2).

Table 2: Primary Endpoint Results (Study 326)

AUC of VAS through 72 hours	EXPAREL 133 mg N=75	EXPAREL 266 mg N=76	Placebo N=79
LS Mean (SE)	260 (19)	251 (19)	280 (18)
Treatment Difference (95% CI)	-20 (-72, 32)	-29 (-80, 23)	-
p-value vs. placebo	0.45	0.27	-

Given the prior finding of efficacy with femoral nerve block in TKA in Study 323, Pacira conducted an in-depth assessment of the factors that may have contributed to the incongruence in efficacy findings in the two TKA studies, Studies 323 and 326. Key insights include:

- Study 326 included administration of a posterior capsule infiltration of bupivacaine HCl to all (EXPAREL and placebo) patients. Thus, the placebo group in Study 326 received active treatment in addition to placebo nerve block (unlike Study 323).
  The cumulative pain scores in the EXPAREL and placebo groups were approximately 40-50% lower in Study 326 than Study 323, which may have been due to the additional active treatment (ie, posterior capsule infiltration) administered to both groups.
- Approximately 47% of patients were enrolled at a single site, which provided more rescue medication and had lower reported pain scores, on average, than the other sites in the study. Among the other study sites, the relative treatment difference versus placebo for the 266 mg dose in Study 326 was similar to Study 323, which is consistent with the finding that EXPAREL is efficacious as a nerve block for lower extremities.
- Taken together, the confluence of factors related to the study design and conduct led to lower pain scores than anticipated, which reduced the study's power to detect a treatment difference.

Efficacy in Supportive Studies (Study 1601 and Study 1602)

Study 1601 and 1602 were single-site investigator-initiated trials that evaluated the efficacy of EXPAREL admixed with bupivacaine HCl for regional analgesia in comparison to nerve block with bupivacaine HCl alone or general anesthesia. In clinical practice, EXPAREL may be administered with bupivacaine HCl (as described in Section 3.2) to achieve a higher degree of immediate regional analgesia than produced by EXPAREL alone. Combined administration with bupivacaine HCl is described in the EXPAREL USPI for infiltration/field block and is expected to be relevant for a regional analgesia indication.

In Study 1601, 32 patients undergoing Dupuytren's contracture release were randomized 1:1 to receive median and ulnar nerve blocks with either EXPAREL (133 mg, 5 mL) admixed with bupivacaine HCl (0.5%, 2.5 mL), or bupivacaine HCl alone (0.5%, 7.5 mL), per nerve. In Study 1602 (N=40), patients undergoing scarf osteotomy to correct severe hallux valgus deformity were randomized 1:1:1 to receive distal tibial and deep peroneal nerve blocks at the ankle level with EXPAREL (133 mg, 5 mL) admixed with bupivacaine HCl (0.5%, 2.5 mL) per nerve, bupivacaine HCl alone (0.5%, 7.5 mL) per nerve, or general anesthesia.

Results from both studies demonstrated that EXPAREL plus bupivacaine HCl provided improved analgesia compared to bupivacaine alone:

- In Study 1601, fewer patients who received EXPAREL admixed with bupivacaine HCl (20%) required additional local anesthetic for finger manipulation 48 hours after injection compared with patients who received bupivacaine HCl alone (94%; $p < 0.001$).
- In Study 1602, EXPAREL plus bupivacaine HCl reduced postsurgical opioid consumption by 64% compared to bupivacaine HCl alone ($p < 0.001$).
- In both studies, the worst pain scores reported over the first 72 hours following nerve blocks were significantly lower in the EXPAREL plus bupivacaine HCl groups compared to the active comparator groups ($p = 0.010$ [Study 1601], $p = 0.003$ [Study 1602]).

Summary of Efficacy

The efficacy of a single-dose administration of EXPAREL 133 mg or 266 mg as a nerve block to provide regional analgesia for up to 72 hours was demonstrated in two adequate and well-controlled studies in upper and lower extremities and in small and large nerves. In these studies, patients were able to achieve analgesic efficacy while also significantly reducing their use of opioid rescue medications by approximately 25% to 75% across the studies. In Study 327, an appreciable proportion of EXPAREL patients did not require opioid rescue medication at all. The factors contributing to each negative Phase 3 study have been thoroughly investigated with likely causes identified.

Overall, the data demonstrate that EXPAREL as a nerve block is an efficacious non-opioid analgesic that provides long-lasting pain control in a single administration.

1.5 Safety Findings

The safety profile of EXPAREL is consistent with the well-established safety profile of its current approved indication for infiltration/field block, which has more than 3.5 million patient exposures to date. The safety database for EXPAREL includes 2,047 individuals exposed to EXPAREL in 29 clinical studies, 531 of whom received EXPAREL as a single-dose nerve block across 6 Phase 2 or Phase 3 studies.

The type and frequency of safety events were consistent with the use of a local anesthetic as a nerve block for the various surgical procedures performed. The most common AEs were nausea, pyrexia, and constipation, and were similar in incidence to those previously reported by patients

receiving EXPAREL in the clinical program for infiltration/field block. The incidence of AEs, serious AEs (SAEs), severe AEs, and AEs leading to discontinuation were similar for the EXPAREL and placebo groups pooled across the clinical nerve block studies.

Six deaths were reported in the pooled nerve block studies (2 patients receiving EXPAREL 266 mg and 4 patients receiving placebo). All deaths occurred in Study 322 (thoracotomy), which was the most invasive of the procedures evaluated and included patients with the most serious indication for surgery (ie, lung cancer). None of the deaths was assessed by the investigator as related to the study drug.

The only new safety concern identified in the regional analgesia clinical program that was not previously identified for the current indication was an AE of falls. All falls in the EXPAREL groups occurred in the TKA studies (4/169 [2%] with EXPAREL 133 mg and 8/301 [3%] for EXPAREL 266 mg) and one fall occurred in the placebo group of the TSA/RCR study (1/357 [<1%]). The incidence of falls with EXPAREL after TKA is similar to the rate reported in the peer-reviewed literature for TKA regardless of the type of anesthesia used (Memtsoudis et al 2014). Pacira is proposing that the product label incorporate a precaution that "EXPAREL is not recommended for use as a femoral nerve block if early mobilization and ambulation is part of the patient's recovery plan" to minimize the risk of falls. However, it should be noted that there may be cases when early ambulation is not part of a patient's recovery plan (eg, lower extremity trauma, tumor removal, deformity correction, amputation) and, in such cases, a long-lasting femoral nerve block would be clinically appropriate.

Local anesthetic systemic toxicity (LAST) is a rare, potentially life-threatening adverse reaction resulting from significant local anesthetic plasma concentrations that generally occur following accidental intravascular (ie, IV or intra-arterial [IA]) injection. Local anesthetic systemic toxicity manifests as a rapid-onset constellation of cardiac (eg, tachycardia, rhythm disturbances, cardiac arrest) and central nervous system (CNS) effects (eg, tonic-clonic seizures, respiratory arrest).

In order to assess the risk of local anesthetic systemic toxicity with EXPAREL and the potential for a delayed onset due to the slow-release properties of EXPAREL, Pacira has conducted the following investigations:

- A search of AEs related to local anesthetic effects
- A comprehensive review of the global safety database including Pacira's clinical study database, postmarketing data, and the scientific literature to identify possible cases of local anesthetic systemic toxicity
- Several pre-clinical studies to evaluate the comparative safety and PK profile of EXPAREL compared to bupivacaine HCl following IV, IA, epidural, and intrathecal administration to assess the relative risks of accidental administration

The local anesthetic systemic toxicity AE search and postmarketing evaluation did not suggest any additional risk of local anesthetic systemic toxicity with EXPAREL. No cases in the clinical studies were consistent with local anesthetic systemic toxicity. A comprehensive review of the postmarketing database identified 63 spontaneous reports in approximately 3 million patient

exposures (ie, exposures at the time of the review) in which local anesthetic systemic toxicity could not be ruled out. This reported rate of 0.2 per 10,000 patients is lower than the rate of 2.0-2.8 per 10,000 patients associated with peripheral nerve blocks with conventional local anesthetics (El Boghdadly et al 2016). The findings from the global safety database align with a series of pre-clinical studies, which found that the maximum plasma bupivacaine concentrations following IV or epidural administration of EXPAREL were similar to a threefold *lower* dose of bupivacaine HCl, suggesting that EXPAREL poses no greater risk for local anesthetic systemic toxicity (Joshi et al 2015).

In response to an FDA request, Pacira and outside experts conducted a comprehensive review and analysis of Holter recordings collected in Studies 322 and 323. The electrocardiogram (ECG) results and incidence of cardiac disorders showed no clinically significant concerns after administration of EXPAREL.

Finally, to characterize the onset and duration of nerve block, Studies 326 and 327 included thorough evaluations of sensory and motor function loss and return. In both studies, sensory and motor function were present at baseline and, as expected, patients receiving a nerve block experienced a loss of such function as the nerve block took effect and regained function as the effect of the block wore off.

1.6 Conclusions

The totality of the data from the clinical program to support this sNDA demonstrates that EXPAREL is safe and effective as a nerve block to produce regional analgesia. The efficacy of EXPAREL has been demonstrated in two adequate and well-controlled Phase 3 trials in both upper and lower extremities and in both small and large nerves, which are representative of the majority of nerve blocks currently being performed in the US. These studies meet the FDA's requirements for a new analgesic indication based on the 2014 Draft Guidance (FDA 2014).

The favorable safety profile of EXPAREL has been well-established in the clinical development program and in the post-approval setting. EXPAREL has been studied in 2,047 individuals across 29 clinical studies. Of these, 531 individuals received EXPAREL as a nerve block in 6 Phase 2 or Phase 3 studies. The safety profile of EXPAREL as a regional nerve block was consistent with the safety profile for the approved indication for local infiltration/field block. The safety data from the clinical program is supported by 6 years of post-approval experience with more than 3.5 million patient exposures in the US.

2 RATIONALE FOR THE USE OF EXPAREL AS NERVE BLOCK

Summary

- Local anesthetics can be used as infiltration/field blocks for local analgesia around a wound or surgical site, or as nerve blocks for regional analgesia. Differences in the dosing and volume of local anesthetic utilized depend on the nerves being blocked, the anatomical location, and clinical situation being addressed.
- Acute pain that is poorly managed is associated with worse clinical outcomes and the progression to chronic pain and further disability.
- Conventional local anesthetics for peripheral nerve block provide approximately 12-24 hours of analgesia, which often is insufficient to manage longer-lasting postoperative pain. The two treatment options currently utilized to provide longer-term postoperative relief of moderate-to-severe pain are continuous peripheral nerve blocks or, more commonly, opioid analgesics.
  - Continuous peripheral nerve blocks via catheter and pump can be technically challenging to place and are associated with clinical challenges (eg, infection, catheter migration, pump failure).
  - Opioid analgesics are associated with common opioid-related adverse events (eg, nausea, vomiting, constipation), respiratory depression, and persistent use among patients. Opioids are also associated with diversion, misuse, and abuse in the community.
- EXPAREL has been a safe and effective analgesic when used for local infiltration/field block. An expansion of the current indication to nerve block would provide a long-acting, non-opioid treatment option for multimodal pain management.

2.1 Current Treatment Landscape for Postsurgical Pain Management

Acute pain control is a critical element in patient recovery following injury or surgery, as the majority of patients may experience significant pain, particularly in the acute phase. Improved postsurgical and/or acute pain management contributes to better healing, faster patient mobilization, shortened hospital stays, and reduced healthcare costs (American Society of Anesthesiologists Task Force on Pain Management 2012).

While acute pain is a predictable component of the postoperative process, such pain is often poorly managed, resulting in clinical and physiological changes that increase morbidity and mortality (eg, inability to ambulate early), diminish quality of life, and extend length of stay, thereby increasing hospital expenditures (Oderda et al 2007) and reducing patient satisfaction. In additional, the Department of Health and Human Services (HHS) has recognized the link between inadequate acute pain management and the development of chronic pain. The HHS 2016 National Pain Strategy advocates for clinicians to “take active measures to prevent the progression of acute to chronic pain and its associated disabilities” (HHS 2016). Effective relief of acute pain with minimal opioid complications, on the other hand, may improve clinical

outcomes, avoid complications (eg, delay in regaining bowel function, inability to tolerate liquid and solid oral intake), and conserve healthcare resources. As such, the Joint Commission on Accreditation of Healthcare Organizations requires that all healthcare facilities practice safe and quality pain management, promote safe opioid prescribing/use, and minimize the risks associated with treatment (The Joint Commission 2017).

The current consensus clinical practice guidelines of the American Pain Society, the American Society of Regional Analgesia and Pain Medicine, and the American Society of Anesthesiologists recommend utilizing multimodal analgesic regimens to manage acute postsurgical pain (Chou et al, 2016). Multimodal analgesia combines two or more agents or techniques that act by different analgesic mechanisms to provide enhanced pain relief with reduced utilization of opioid analgesics. The current modalities of postsurgical analgesic treatment include treatment with local anesthetic agents such as lidocaine or bupivacaine for infiltration/field block and nerve block and systemic agents such as opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and acetaminophen as well as other agents such as gabapentinoids.

Local anesthetics are used in one of two ways depending on pain severity and anatomical location:

- Infiltration/field block – typically, a surgeon performs multiple injections of a local anesthetic around the wound, surgical site, or tissue plane to produce local analgesia
- Nerve block – typically, an anesthesiologist targets nerves in a specific area with an injection using ultrasound, nerve stimulation, or anatomical guidance. All nerve blocks are accomplished by injection of a local anesthetic into a tissue space that contains nerve(s). In this regard, there is no difference between a nerve block of an individual nerve or a block of a nerve plexus. The only difference is in the dose and volume of local anesthetic required, which depend on the number of nerves to be blocked and the anatomical location.

In clinical practice, certain procedures are more amenable to infiltration/field block while others are more amenable to nerve block. While the procedure for administration of the local anesthetic is different between these two uses, the ultimate goal is the same – to block nerves to provide relief from acute pain.

2.2 Limitations of Current Postsurgical Analgesic Treatment Options

The use of single-injection, peripheral nerve blocks in orthopedic procedures has been shown to improve postsurgical analgesia and to reduce postsurgical opioid requirements (Allen et al 1998; Szczukowski et al 2004; Duarte et al 2006; Seet et al 2006; Good et al 2007; Paul et al 2010). However, the duration of analgesia provided by single-injection peripheral nerve blocks is short (typically 12-24 hours) compared with the duration of moderate to severe postsurgical pain (several days), which limits their clinical utility as a pain management strategy (Paul et al 2010). The two current treatment options to prolong the analgesic effect past what a single-injection nerve block provides for moderate or severe pain are either continuous peripheral nerve blocks or opioid analgesics.

2.2.1 *Continuous Peripheral Nerve Blocks*

The limitations of continuous peripheral nerve blocks with a catheter and pump are well documented. A continuous peripheral nerve block requires placement of a perineural catheter, a local anesthetic reservoir/pump, infusion management, and catheter site care which has risks of bacterial colonization, infection, mechanical failure of the pump, catheter migration or dislodgement, wet bandages and issues with patient compliance/dissatisfaction (Jeng et al 2010; Joshi et al 2016; FDA 2010). Additionally, the placement of an indwelling catheter can be technically challenging and may take additional time.

2.2.2 *Opioid Analgesics*

Opioid analgesics have a long history of use for the management of moderate to severe acute and postsurgical pain. However, opioids are associated with adverse events (AEs) such as respiratory depression, nausea, vomiting, constipation, ileus, confusion, somnolence, pruritus, urinary retention, dysphoria, and delirium. Management of these opioid-related AEs often requires medical treatment, including but not limited to antiemetics, anticonstipation and antipruritus agents (Chernin 2001; Viscusi 2011). Opioids were one of three classes of drugs identified by The National Action Plan for Adverse Drug Event Prevention as a high-priority area of focus for the reduction of harm to patients (Office of Disease Prevention and Health Promotion 2014).

Respiratory depression and death are the most serious risks with postsurgical opioid use. Studies have shown that approximately 1 in 200 patients (0.5%) experience respiratory depression requiring rescue with naloxone in the postsurgical setting (Rosenfeld et al 2015; The Joint Commission 2012). The requirement for naloxone rescue in the postsurgical setting is higher among patients receiving patient-controlled analgesia (PCA) (approximately 1 in 83 patients) or epidural opioid infusion (approximately 1 in 76) (Rosenfeld et al 2015). Other patient risk factors for respiratory depression in the postsurgical setting include older age, obesity, sleep apnea, and preexisting pulmonary or cardiac disease (The Joint Commission 2012).

Postsurgical opioid use has also been linked to subsequent persistent use (Alam et al 2012). A recent large study of claims data found that approximately 1 in 16 (6%) opioid-naïve patients who underwent surgery and received opioids continued to use opioids 90 days after surgery (Brummett et al 2017). Surprisingly, the incidence of persistent opioid use did not differ among patients undergoing minor (5.9%) or major (6.5%) surgeries, suggesting that many patients are likely continuing opioid therapy for reasons other than the intensity of their pain.

There is widespread recognition of the need for a comprehensive approach to address the opioid epidemic, which includes elements such as proper prescribing, prescription drug monitoring, physician and patient education, and safe disposal, among others. One component of the larger public health strategy is the preferential use of non-opioid pain management strategies in order to reduce patient exposure to opioids and reduce the volume of prescription opioids in the community available for misuse, abuse, and diversion. While opioid analgesics are often a critical component of individual patient pain management plans, it stands to reason that increased utilization of safe and effective non-opioid pain management options that reduced the overall

exposure to opioid analgesics would benefit both patients in postsurgical recovery as well as the general public health.

2.3 Potential Clinical Advantages of EXPAREL as a Nerve Block

Bupivacaine, the API in EXPAREL, has been used for field block/infiltration and nerve block for decades. EXPAREL – a long-acting, opioid-free analgesic – has been used for local infiltration/ field block since its approval by the Food and Drug Administration (FDA) in 2011. Expansion of the current indication for EXPAREL to include nerve block could provide physicians and patients with several clinical advantages.

- First, EXPAREL could provide physicians with a long-acting analgesic option for procedures that are more amenable to nerve block than field block/infiltration, an indication for which EXPAREL has an extensive history of safe and effective use in over 3.5 million patients in the US.
- Second, the analgesic effects of a local anesthetic for nerve block could be prolonged via a single-shot technique without the risks and difficulty of placing one or more continuous nerve block catheters.
- Finally, the use of a long-acting, non-opioid analgesic also has the potential to reduce the exposure of surgical patients to opioids and their associated AEs, as well as reduce the number of opioids available for abuse and diversion in the community.

3 EXPAREL PRODUCT DESCRIPTION AND CLINICAL DEVELOPMENT

Summary

- EXPAREL is a long-acting, non-opioid analgesic containing bupivacaine in a multivesicular liposome suspension, provided as a single-dose injection of 133 mg or 266 mg.
- EXPAREL has been approved since 2011 for infiltration/field block administration into the surgical site to product postsurgical analgesia and has been used in over 3.5 million patients in the US.
- EXPAREL is proposed as a nerve block to produce regional analgesia.
- The efficacy and safety of EXPAREL for regional analgesia was evaluated in a comprehensive clinical development program, including:
  - Two Phase 3 studies which provide the primary evidence of efficacy
  - A safety dataset of 531 patients who received EXPAREL as a nerve block

3.1 Proposed Indication

EXPAREL has been approved by the FDA since October 2011 with an indication for administration into the surgical site to produce postsurgical analgesia (Pacira 2016, USPI).

Pacira is proposing to add an indication for EXPAREL as a nerve block to produce regional analgesia. The proposed indication is as follows:

> **EXPAREL is indicated for infiltration to produce local analgesia and as a nerve block to produce regional analgesia.**

3.2 Treatment Administration and Dosing Regimen

EXPAREL is intended for single-dose administration via infiltration to produce local analgesia and as a nerve block to produce regional analgesia. EXPAREL is available in dosage forms of either 10 mL single-use vial (133 mg bupivacaine free base) or 20 mL single-use vial (266 mg bupivacaine free base), 1.3% (13.3 mg/mL). The recommended dose of EXPAREL for a field block or as a regional nerve block is based on the desired effect for an individual patient taking into account the following factors:

- Duration of analgesia desired
- Dose and volume required for nerve block
- Maximum dose of 266 mg (20 mL)

In addition, the current EXPAREL United States Package Insert (USPI) specifies that "bupivacaine HCl and EXPAREL may be administered simultaneously in the same syringe, and

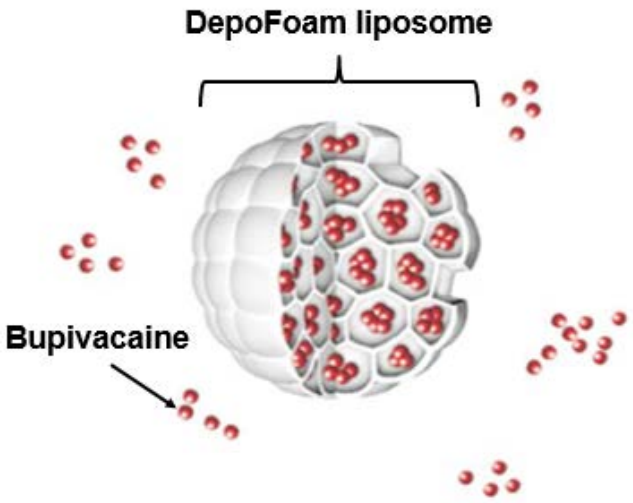
bupivacaine HCl may be injected immediately before EXPAREL as long as the ratio of the milligram dose of bupivacaine HCl solution to EXPAREL does not exceed 1:2" (Pacira 2016, USPI).

3.3 Mechanism of Action

The API in EXPAREL is bupivacaine free base. Bupivacaine, as other local anesthetics, block the generation and the conduction of nerve impulses presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential.

The liposome formulation of EXPAREL is responsible for the extended-release of bupivacaine after injection. EXPAREL consists of microscopic spherical, multivesicular liposomes (DepoFoam® drug delivery system), organized in a honeycomb-like structure comprised of numerous nonconcentric internal aqueous chambers containing bupivacaine (13.3 mg/mL) (Figure 7). Each chamber is separated from adjacent chambers by lipid membranes comprised of naturally occurring or close analogs of endogenous lipids (phospholipids, cholesterol, and triglycerides). Bupivacaine is slowly released from the DepoFoam particles by a complex mechanism involving reorganization of the barrier lipid membranes and subsequent diffusion of the drug over an extended period of time.

Figure 7: Structure of EXPAREL Multivesicular Liposome



3.4 Regulatory History

The FDA approved EXPAREL in October 2011 for single-dose administration into the surgical site via wound infiltration/field block to produce postsurgical analgesia. Since then, EXPAREL has been used to manage pain for more than 3.5 million patients in the US. EXPAREL's original approval was based on Pacira's initial clinical development program, which included 21 clinical studies and 1 observational study. Two of these studies were positive Phase 3 multicenter, randomized, double-blind, placebo-controlled trials, which demonstrated efficacy in visceral (hemorrhoidectomy) and nonvisceral (bunionectomy) pain. The initial development program also

included Phase 1 and Phase 2 studies evaluating EXPAREL as a nerve block for the upper/thoracic and lower extremities.

Following the initial approval, Pacira conducted three additional studies to support an indication for EXPAREL as a nerve block:

- Study 111, a Phase 1 femoral nerve block study in healthy volunteers
- Study 322, a Phase 3 intercostal nerve block study in patients undergoing thoracotomy
- Study 323, a Phase 2/3 femoral nerve block study in patients undergoing total knee arthroplasty (TKA)

Pacira submitted supplemental NDA (sNDA) 022,496/S-009 for an expanded indication as a nerve block in May 2014. FDA issued a complete response letter (CRL) in February 2015 and requested additional data. The key requests from FDA included:

- Evidence of efficacy from an adequate and well-controlled trial in at least one additional setting, since Study 322 did not meet its primary efficacy endpoint
- Additional data characterizing PK through the time to maximum plasma concentration (T_{max})
- Additional analyses of existing cardiac safety data
- Additional data on sensory and motor function to characterize the onset and duration of nerve block

In consultation with the FDA, Pacira designed two additional Phase 3 multicenter, randomized, double-blind, placebo-controlled trials in order to meet the Agency's request for additional data. These trials included:

- Study 326, a Phase 3 femoral nerve block study among patients undergoing TKA
- Study 327, a Phase 3 brachial plexus nerve block study among patients undergoing total shoulder arthroplasty (TSA) or rotator cuff repair (RCR)

Following the conduct of these two trials, Pacira resubmitted the sNDA in October 2017. Currently, EXPAREL is not approved for marketing in any country outside of the US.

3.5 Clinical Studies

The clinical development program of EXPAREL for regional analgesia comprises eight clinical studies: two Phase 1 studies, two Phase 2 studies, and four Phase 3 studies (one was a two-part Phase 2/3 study). These studies were designed in collaboration with FDA to assess the clinical pharmacokinetics, efficacy, and safety of EXPAREL in upper and lower extremities in both small and large nerves (Table 3). Across the eight nerve block studies, a total of 570 individuals received a dose of EXPAREL ranging from 2 mg to 310 mg. Excluding the healthy volunteers enrolled in the Phase 1 studies, a total of 531 patients received EXPAREL as a nerve block for regional analgesia.

The primary studies that support the efficacy of EXPAREL are Study 327 in TSA/RCR and Part 2 of Study 323 in TKA. As the techniques and the principles behind peripheral nerve blockade are similar regardless of the nerve being targeted, the models used in these Phase 3 studies are representative of the majority of blocks currently being performed in the US. Therefore, the efficacy data generated from these two studies are applicable to regional analgesia in general.

Table 3: Summary of Clinical Studies in Regional Analgesia

Study (Study Type) Number of Volunteers/Patients[a]	Nerve Block (Procedure)	Evaluations	EXPAREL Dose
Study 002 (Phase 1) N=36	Partial Ankle (Healthy volunteers)	PK	67, 110, 133, 155 mg
Study 111 (Phase 1) N=14	Femoral (Healthy volunteers)	PD	2, 4, 10, 13, 27, 53, 62, 71, 89, 106, 124 mg
Study 203 (Phase 2) N=58	Ankle (Bunionectomy)	PK	155, 200, 310 mg
Study 211[b] (Phase 2) N=3	Intercostal (Thoracotomy)	PD, PK	67, 133 mg
Study 322 (Phase 3) N=185	Intercostal (Thoracotomy)	Efficacy, Safety, PK	266 mg
Study 323 (Phase 2/3) N=278	Femoral (Total knee arthroplasty)	Efficacy, Safety, PK	Part 1: 67, 133, 266 mg Part 2: 266 mg
Study 326 (Phase 3) N=230	Femoral (Total knee arthroplasty)	Efficacy, Safety, PK	133, 266 mg
Study 327 (Phase 3) N=155	Brachial plexus (Total shoulder arthroplasty / rotator cuff repair)	Efficacy, Safety, PK	133 mg, 266 mg[c]

PK = pharmacokinetics; PD = pharmacodynamics
a. Includes those in EXPAREL, placebo, or bupivacaine HCl groups.
b. Only three patients were enrolled (two EXPAREL and one bupivacaine HCl) before the study was terminated by the Sponsor; no PK or PD data are available from the study.
c. Fifteen patients were enrolled in the 266 mg group before this treatment group was terminated by the Sponsor.

In addition, two investigator-initiated trials evaluated the efficacy of EXPAREL admixed with bupivacaine HCl in comparison to bupivacaine HCl in upper and lower extremity nerve block studies. These studies provide additional efficacy results for the expanded indication and relevant information on EXPAREL when coadministered with bupivacaine HCl.

Safety data were pooled from all six Phase 2 and 3 studies to form the primary safety dataset of EXPAREL for regional analgesia. The pooled regional analgesia safety population includes 888 patients (531 EXPAREL, 357 placebo).

4 CLINICAL PHARMACOLOGY

Summary

- The pharmacokinetics (PK) of bupivacaine after administration of EXPAREL as a nerve block have been evaluated in six studies at doses ranging from 67 mg to 310 mg of bupivacaine.
- Two nerve block studies assessed the PK of both EXPAREL (75-350 mg) and bupivacaine HCl (75-125 mg). Key findings include:
  - The bioavailability of bupivacaine from EXPAREL and bupivacaine HCl is comparable.
  - All EXPAREL doses had a lower initial C_{max} relative to bupivacaine HCl within 1 hour of injection.
  - Plasma concentrations decreased rapidly after T_{max} (30 min) with bupivacaine HCl and were lower than EXPAREL after 24 hours.
  - Plasma bupivacaine concentrations with EXPAREL persisted and formed a pronounced later peak that gradually tapered through approximately 96 hours.
- Multiple-dose studies showed a linear relationship between the dose of EXPAREL and bupivacaine PK parameters.
- Bupivacaine absorption varied depending on the location of the nerve block. Greater C_{max} and AUC and longer T_{max} and $t_{1/2}$ were observed for femoral nerve blocks compared to brachial plexus nerve blocks.
- Population PK analyses demonstrated no effects on PK from factors such as mild or moderate renal impairment, mild hepatic impairment, BMI, race, and ethnicity. Effects of age and sex were observed for C_{max}; however, the effects were not clinically meaningful and do not necessitate dose adjustments.

4.1 Overview of Clinical Pharmacology Program

The PK of EXPAREL when administered as a nerve block have been examined in six studies, one in healthy volunteers and five in patients undergoing various surgical procedures at doses ranging from 67 mg to 310 mg of bupivacaine (free base) (Table 4). All studies were randomized double-blind studies, and all but the study in healthy volunteers were multicenter.

Studies 002 and 203 characterized the PK of EXPAREL relative to bupivacaine HCl. Studies 323 and 326 collected PK data on EXPAREL when administered as a femoral nerve block, and Study 327 collected PK data in the brachial plexus model. Pharmacokinetic results from Study 322 were confounded by study drug administration factors, as discussed in Section 5.5, and will, therefore, not be discussed here.

All EXPAREL doses are expressed in terms of bupivacaine free base. For reference, the conversion between bupivacaine free base and bupivacaine HCl equivalent is:

0.886 mg bupivacaine free base = 1.0 mg bupivacaine HCl equivalent

Table 4: Clinical Pharmacology Studies in Regional Analgesia

Study (Study Type)	Nerve Block (Procedure)	Dosage[a]	Subjects Included in PK Assessments
Study 002 (Phase 1)	Partial Ankle (Healthy volunteers)	EXPAREL 67 mg	6
		EXPAREL 110 mg	6
		EXPAREL 133 mg	6
		EXPAREL 155 mg	6
		Bupivacaine HCl 75 mg	12
Study 203 (Phase 2)	Ankle (Bunionectomy)	EXPAREL 155 mg	12
		EXPAREL 200 mg	12
		EXPAREL 310 mg	14
		Bupivacaine HCl 125 mg	20
Study 322 (Phase 3)	Intercostal (Thoracotomy)	EXPAREL 266 mg	25
Study 323 Part 1 (Phase 2)	Femoral (Total knee arthroplasty)	EXPAREL 67 mg	18
		EXPAREL 133 mg	19
		EXPAREL 266 mg	21
Study 326 (Phase 3)	Femoral (Total knee arthroplasty)	EXPAREL 133 mg	23
		EXPAREL 266 mg	23
Study 327 (Phase 3)	Brachial plexus (Total shoulder arthroplasty / rotator cuff repair)	EXPAREL 133 mg	12
		EXPAREL 266 mg	12

a. EXPAREL dose expressed in terms of bupivacaine free base.

4.2 Pharmacokinetic Characteristics

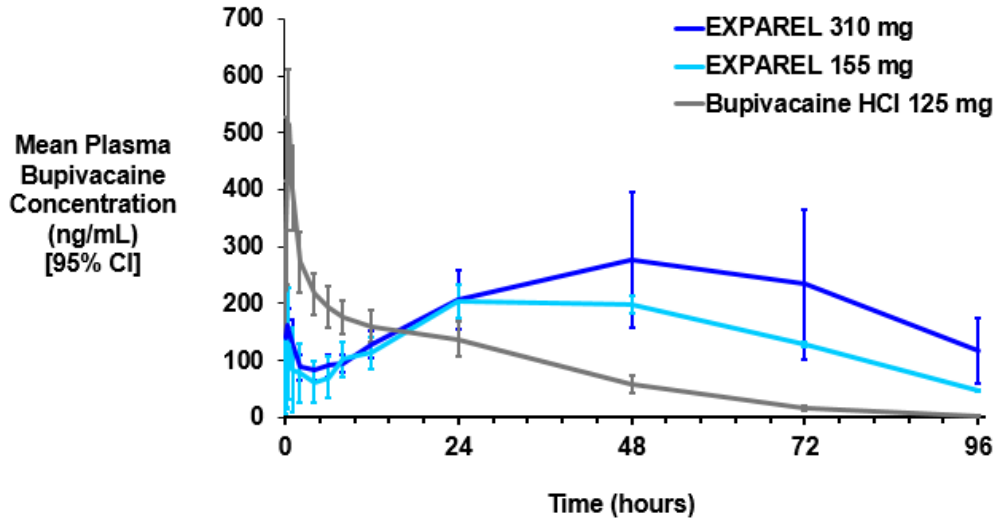
In evaluating the PK of EXPAREL, it is important to note that the PK of local anesthetics are less closely associated with analgesic efficacy than the PK of systemic analgesic agents (eg, opioids) given that their analgesic effect is based on their local availability at a specific anatomical location rather than their systemic concentration. However, PK may provide useful information with regard to safety and is less useful for in determining the onset and duration of analgesia.

Overall, the PK studies demonstrated that administration of EXPAREL results in systemic plasma levels of bupivacaine which can persist for 120 hours after a nerve block. The rate and linear extent of absorption are controlled by the vascularity of the administration site and total dose administered.

4.2.1 *EXPAREL Versus Bupivacaine HCl in Regional Analgesia*

Results from Study 203 (ankle block in patients undergoing bunionectomy) showed that relative to nerve block with conventional bupivacaine HCl, the absorption of bupivacaine following EXPAREL nerve blockade was gradual and sustained through approximately 96 hours. The initial peak bupivacaine concentration (C_{max}) was lower after administration of EXPAREL (regardless of dose) than after administration of an equivalent dose of bupivacaine HCl (linearly extrapolated), as shown in Figure 8. Unlike conventional bupivacaine HCl, EXPAREL nerve block was associated with pronounced later peaks observed approximately 24 to 48 hours after administration, with gradual tapering of plasma concentrations through 96 hours. The extent of systemic exposure to bupivacaine (AUC_{inf}) was consistent between corresponding doses of EXPAREL and bupivacaine HCl (ie, EXPAREL 200 mg and linearly extrapolated bupivacaine HCl 225 mg). The elimination half-life ($t_{1/2}$) of EXPAREL was 31-67 hours and 3-4-fold longer compared to bupivacaine HCl; this is attributed to the extended release of bupivacaine from EXPAREL's multivesicular liposome formulation.

Figure 8: Mean Plasma Bupivacaine Concentration with EXPAREL and Bupivacaine HCl After Administration by Nerve Block in Patients Undergoing Bunionectomy (Study 203)



The dose equivalent of bupivacaine HCl 125 mg is 111 mg EXPAREL.

4.2.2 *Pharmacokinetics of Phase 3 Dosing Regimens*

In response to the FDA's request to fully characterize the PK of EXPAREL following single-injection nerve blocks, Pacira conducted Studies 327 and 326 to collect PK data over a longer duration (at regular intervals through 120 hours and at Days 7 and 10). Studies 327 and 326 sufficiently characterized the clinical pharmacologic profile of EXPAREL as a nerve block and confirmed that safety outcomes through T_{max} (ie, 48-49 hours for brachial plexus block and 66-74 hours for femoral block) and resolution of the nerve block were successfully captured in the studies.

Pharmacokinetic parameters from Studies 327 and 326, the Phase 3 TSA/RCR and TKA studies, are shown in Table 5 and Table 6, respectively. These studies showed a linear relationship between the dose of EXPAREL and bupivacaine C_{max}, T_{max}, and AUC. The variability across studies for the same dose may be due in part to between-patient or study-to-study variability. In general, C_{max}, T_{max}, and $t_{1/2}$ appear to be slightly higher and longer in blockade of the femoral nerve.

Table 5: Pharmacokinetic Parameters of EXPAREL After Brachial Plexus Nerve Block (Study 327)

Mean (Standard Deviation)	EXPAREL 133 mg N=12	EXPAREL 266 mg N=12
C_{max}, ng/mL	207 (137)	469 (194)
T_{max}, hours[a]	48	49
AUC_{0-t}, hour*ng/mL	11,469 (8,528)	28,566 (13,322)
AUC_{0-inf}, hour*ng/mL	12,204 (8,641)	28,696 (13,408)
$t_{1/2}$, hours	9.5 (2.9)	13.6 (5.3)

AUC_{0-t} = area under the plasma concentration-versus-time curve from time 0 to the time of the last quantifiable concentration; AUC_{inf} = area under the plasma concentration-versus-time curve from time 0 extrapolated to infinity; C_{max} = maximum plasma concentration; T_{max} = time to reach C_{max}; $t_{1/2}$ = apparent terminal elimination half-life
a. Median reported for T_{max}

Table 6: Pharmacokinetic Parameters of EXPAREL After Femoral Nerve Block (Study 326)

Mean (Standard Deviation)	EXPAREL 133 mg N=23	EXPAREL 266 mg N=23
C_{max}, ng/mL	411 (148)	743 (348)
T_{max}, hours[a]	66	74
AUC_{0-t}, hour*ng/mL	22,848 (9,078)	46,911 (20,000)
AUC_{0-inf}, hour*ng/mL	23,609 (10,436)	48,900 (20,149)
$t_{1/2}$, hours	14.2 (10.3)	19.1 (18.3)

AUC_{0-t} = area under the plasma concentration-versus-time curve from time 0 to the time of the last quantifiable concentration; AUC_{inf} = area under the plasma concentration-versus-time curve from time 0 extrapolated to infinity; C_{max} = maximum plasma concentration; T_{max} = time to reach C_{max}; $t_{1/2}$ = apparent terminal elimination half-life
a. Median reported for T_{max}

4.2.3 *Population PK Modeling*

A population PK model of bupivacaine following administration of EXPAREL for regional analgesia was developed to more thoroughly analyze the PK data across the six nerve block studies (4,020 quantifiable bupivacaine concentrations from 464 patients) and characterize the effects of potential covariate factors.

The model demonstrated that bupivacaine concentrations following EXPAREL nerve block were described by a linear two-compartment model with fast and slow absorption routes. The slower

absorption route was associated with a median T_{max} of 32-75 hours and higher dose-linear C_{max} relative to the early peak, which occurred at a median T_{max} of 0.5-0.75 hours. Furthermore, there was no effect as a result of mild or moderate renal impairment, mild hepatic impairment, race or ethnicity. Minor effects on C_{max} were observed with other patient factors.

- Older age was associated with higher C_{max}. Relative to a 55 year-old patient, an 80 year-old patient had a 33% higher C_{max} and a 30 year-old patient had a 39% lower C_{max}.
- Females had higher C_{max} values (26%) compared to males.

The modest differences in C_{max} are not expected to be clinically meaningful with regard to safety, given that the C_{max} observed in all subgroups were lower than the C_{max} achieved with bupivacaine HCl. Furthermore, there was no significant effect of any covariate on exposure, the most clinically relevant PK parameter for efficacy, so dose adjustments are not necessary. The effect of age on PK profile is addressed in the current EXPAREL USPI, which states: “In clinical studies, differences in various pharmacokinetic parameters have been observed between elderly and younger patients” (Pacira 2016, USPI).

5 CLINICAL EFFICACY

Summary

- Pacira conducted four Phase 3 randomized, placebo-controlled, double-blind, multicenter studies to evaluate the efficacy of EXPAREL for regional analgesia.
  - The studies assessed cumulative pain intensity (AUC of pain intensity scores) and opioid medication use over a period of 48 or 72 hours.
  - Two trials successfully demonstrated the efficacy of EXPAREL when administered as a nerve block in the upper extremities (prior to TSA/RCR) and in the lower extremities (prior to TKA).
- Study 327, a brachial plexus nerve block study in TSA/RCR, demonstrated that EXPAREL 133 mg was efficacious for regional nerve block in an upper extremity while also reducing the requirement for opioid rescue medication for postsurgical pain control.
  - A significant reduction in cumulative pain intensity through 48 hours was observed with EXPAREL relative to the placebo group ($p < 0.0001$).
  - EXPAREL was associated with a 77% reduction in the mean total opioid medication use ($p < 0.001$) and a longer time to first opioid use ($p < 0.0001$).
- Study 322, an intercostal nerve block study in thoracotomy, did not meet the primary efficacy endpoint (cumulative pain intensity through 72 hours). PK data indicate that the nerve block was not properly administered, so the efficacy of EXPAREL as a nerve block could not be meaningfully evaluated in this study.
- Study 323, a femoral nerve block study in TKA, demonstrated that EXPAREL 266 mg provided efficacious regional analgesia while also reducing the requirement for opioid rescue medication for postsurgical pain control.
  - Cumulative pain intensity through 72 hours was significantly reduced with EXPAREL relative to placebo ($p < 0.0001$).
  - EXPAREL was associated with a 24% reduction in total opioid medication use ($p = 0.002$).
- Study 326, a femoral nerve block study in TKA, did not achieve statistical significance for the primary endpoint. Further investigation of the data showed that several factors, including infiltration of the posterior capsule in both EXPAREL and placebo groups and study site effects, reduced the study's statistical power.
- Two supportive investigator-initiated studies demonstrated that EXPAREL 133 mg when admixed with bupivacaine HCl led to a significant reduction in post-procedure pain and use of opioid medications or supplemental local anesthesia following wrist and ankle nerve blocks compared to bupivacaine HCl alone.
- Overall, the efficacy of EXPAREL as a nerve block was demonstrated in two adequate and well-controlled trials in upper and lower extremities and in large and small nerves that are representative of most nerve blocks performed in the US.

5.1 Phase 3 Clinical Study Design

5.1.1 *Overview of Pivotal Studies for Regional Analgesia*

The efficacy of EXPAREL as a regional analgesic was evaluated in four Phase 3 studies designed to be representative of nerve blockades in both upper and lower extremities: one in TSA or RCR, one in thoracotomy, and two in TKA. All four studies were Phase 3, multicenter, randomized, double-blind, placebo-controlled trials designed to evaluate the magnitude and duration of the analgesic effect achieved following single-dose injection with EXPAREL as a nerve block in adult patients. These studies were designed in consultation with the FDA. The key aspects of the EXPAREL Phase 3 studies are shown in Table 7 and are further detailed below. Appendix 1 provides details on the schedule of study procedures and assessments.

Table 7: Characteristics of Phase 3 Nerve Block Studies

Study Characteristic	Study 327	Study 322	Study 323 (Part 2)	Study 326
Nerve block	Brachial plexus (interscalene or supraclavicular)	Intercostal (index nerve, nerve above, and nerve below)	Femoral	Femoral
Surgery Type	TSA/RCR	Thoracotomy	TKA	TKA
Treatment Groups	EXPAREL 133 mg Placebo	EXPAREL 266 mg Placebo	EXPAREL 266 mg Placebo	EXPAREL 133 mg EXPAREL 266 mg Placebo
Number of Patients[a]	N=140	N=185	N=183	N=230
Region	US and Western Europe	US and Eastern Europe	US	US and Western Europe
Primary Endpoint	48-hour AUC of VAS for pain	72-hour AUC of NRS-R for pain	72-hour AUC of NRS-R for pain	72-hour AUC of VAS for pain
	Rank of Secondary Endpoints			
Total opioid use	1	1	1	1
% opioid-free	2	Not ranked	Not ranked	2
Time to first opioid use	3	2	2	3

AUC = area under the curve; RCR = rotator cuff repair; TKA = total knee arthroplasty; TSA = total shoulder arthroplasty; VAS = visual analog scale
a. Efficacy analysis population

5.1.2 *Study Designs*

5.1.2.1 *Total Shoulder Arthroplasty/Rotator Cuff Repair (Study 327)*

Study 327 was a brachial plexus nerve block study in patients undergoing either primary unilateral TSA or RCR with general anesthesia. Patients were randomized in a 1:1 ratio to receive a single dose of EXPAREL 133 mg (10 mL expanded with 10 mL normal saline) or placebo (20 mL normal saline), administered as a brachial plexus (interscalene or supraclavicular) block under ultrasound guidance 1 hour prior to the surgical procedure.

Both the 133 mg and 266 mg dose of EXPAREL were initially selected for Study 327. A planned interim PK assessment of Study 327 was conducted after approximately 15 patients had been enrolled in October 2016. Based on these interim results and emerging literature supporting the adequacy of the 133 mg dose for total shoulder arthroplasty (Vandepitte et al, 2016), Pacira made an administrative protocol revision in November 2016 to stop further enrollment in the 266 mg group. Results from the 15 patients treated with the 266 mg dose are included in the safety analyses but not the efficacy analyses.

5.1.2.2 *Thoracotomy (Study 322)*

Study 322 was an intercostal regional analgesia study in patients undergoing thoracotomy for a noninfectious indication under general anesthesia. EXPAREL 266 mg (20 mL) or placebo (20 mL normal saline) was divided into three equal doses in three syringes and administered to each of three nerve segments (index nerve, nerve above, and nerve below). Study drug (EXPAREL or placebo) was administered immediately prior to wound closure under direct visualization by the surgeon using the surgeon's normal and usual technique.

5.1.2.3 *Total Knee Arthroplasty (Study 323)*

Study 323 was a Phase 2/3 femoral regional analgesia study in patients undergoing primary unilateral TKA under general or spinal anesthesia. The study included 2 independent parts:

- Part 1 of the study was designed to evaluate three dose levels of EXPAREL compared to placebo. An unblinded dose selection committee was charged with reviewing safety and efficacy results for each dose and selecting a single therapeutic dose of EXPAREL to be tested in Part 2 of the study. Patients in Part 1 were randomized in a 1:1:1:1 ratio to receive a single-dose injection of one of four treatments:
    - EXPAREL 266 mg (20 mL)
    - EXPAREL 133 mg (10 mL of EXPAREL plus 10 mL of normal saline)
    - EXPAREL 67 mg (5 mL of EXPAREL plus 15 mL of normal saline)
    - Placebo (20 mL of normal saline)
- Part 2 of the study randomized patients in a 1:1 ratio to placebo or EXPAREL 266 mg, the dose selected by the dose selection committee based on efficacy and safety results from Part 1 of the study (see Section 5.6).

Part 1 results were not included in evaluation of Part 2 (ie, patients enrolled in Part 1 were not included in the analysis of Part 2 [Phase 3] study results).

In both phases, either EXPAREL or placebo was administered as a single-dose femoral nerve block under ultrasound guidance. Study treatment was administered 1-2 hours before the surgical procedure. At the conclusion of the block, a femoral nerve catheter was left in place for delivery of post-surgical rescue pain medication. Additionally, a PCA pump was established prior to the completion of the surgery (see Section 5.1.5 for details).

5.1.2.4 *Total Knee Arthroplasty (Study 326)*

Similar to Study 323, Study 326 was a femoral regional analgesia study in patients undergoing primary unilateral TKA under general or spinal anesthesia. In Study 326, patients were randomized 1:1:1 to EXPAREL 266 mg (20 mL), EXPAREL 133 mg (10 mL expanded with 10 mL normal saline), or placebo (20 mL normal saline). EXPAREL or placebo was administered as a single-dose femoral nerve block under ultrasound guidance. Study treatment was administered 1-2 hours before the surgical procedure.

The femoral nerve arising from L2, L3, and L4 supplies motor to the anterior thigh as well as sensory to the knee joint. Nerve block of the femoral nerve results in motor block of the quadriceps muscles and sensory block of all but the posterior aspect of the knee. Branches of the sciatic nerve in L4, L5, S1, S2, and S3 which divide into the common peroneal and tibial nerves before reaching the knee are missed by a femoral nerve block. This was addressed in Study 326 by having the surgeon inject 8 mL of bupivacaine HCl (0.5%) diluted with 8 mL normal saline as a periarticular infiltration to the posterior capsule (8 mL medially and 8 mL laterally behind the medial and lateral condyles) before placement of the prosthesis. This additional active treatment was provided to both EXPAREL and placebo patients. (Note: the additional infiltration with bupivacaine HCl was not provided in Study 323). Rescue medications consisted of oral or IV opioids only and use of PCA or continuous nerve block postsurgery was not permitted (see Section 5.1.5 for details).

5.1.3 ***Enrollment Criteria***

The four Phase 3 studies included similar key enrollment criteria:

Inclusion

- Male or female adults (≥18 years of age) and scheduled to undergo the procedure corresponding to each trial
- ASA physical status of 1, 2, or 3
- Demonstrated normal motor function (only Study 327 [score of 5 on the Lovett scale for biceps, wrist, and thumb movement] and Study 323 [able to walk 20-meters unassisted, with the optional use of a 4-legged walker])
- Sensitivity (to cold, pinprick, and light touch [Studies 327 and 326] or to cold only [Studies 322 and 323])

Exclusion

- Planned concurrent surgical procedure
- Concurrent painful physical condition that required analgesic treatment (eg, NSAID or opioid) in the postsurgical period for pain not strictly related to the surgery
- Long-acting opioid medication, NSAID (except for aspirin), or dexmedetomidine within 3 days of surgery, and opioid medication of any kind within 24 hours of surgery

- Systemic glucocorticosteroids, selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, gabapentin, pregabalin, or duloxetine within 1 month of study (or, for some medications, within 3 days of study [Study 322])
- Contraindications to any pain-control agents planned for surgical or postsurgical use (ie, bupivacaine, hydromorphone, etc.)
- Suspected or known history of drug or alcohol abuse within the previous 1-2 years

5.1.4 *Perioperative Medications*

In addition to the study treatment (EXPAREL or placebo), the medications in Table 8 were administered as part of standard perioperative care.

Table 8: Perioperative Medications

Perioperative Time Point	Medications Allowed
Pre-operatively	• Low-dose aspirin for cardioprotection • Acetaminophen/paracetamol (≤ 1,000 mg orally or IV every 8 hours for a maximum total daily dose of 3,000 mg) • Midazolam (1-2 mg) (only Studies 327 and 326)
Intraoperatively	• Short acting opioids (ie, fentanyl, sufentanil, or remifentanil)
Post-operatively	• Prophylactic antiemetics (ie, single-dose ondansetron, metoclopramide, or 10 mg dexamethasone IV), at the investigator's discretion

IV = intravenous

5.1.5 *Rescue Pain Medications*

In order to assess the true effect of EXPAREL nerve block, no analgesic agents (including NSAIDs) outside of the protocol-specified rescue medications were permitted through 72 (Studies 327, 323, and 322) or 108 hours (Study 326). The following rescue medications were allowed post-surgery:

- Study 327: To reflect the current standard of care of postsurgical multimodal therapy, all patients received cyclobenzaprine (a single dose of 10 mg orally or as needed) at the investigator's discretion and acetaminophen/paracetamol (up to 1,000 mg orally or IV every 8 hours for a maximum total daily dose of 3,000 mg), unless contraindicated. Oral, immediate-release oxycodone (initiated at 5-10 mg every 4 hours or as needed) was administered upon request for pain control. If a patient could not tolerate oral medication, IV morphine (2.5 to 5 mg) or hydromorphone (0.5 to 1 mg) was permitted every 4 hours or as needed. Patient-controlled analgesia was not permitted.
- Study 322: A step-wise approach included an initial single IV bolus of fentanyl 100 mcg. If insufficient, PCA-administered morphine or hydromorphone bolus, intramuscular opioid (morphine, ≤10 mg every 4 hours) injection, or oral immediate-release oxycodone (≤10 mg every 4 hours) was administered on an as-needed basis.

- Study 323: A step-wise approach included an initial single IV bolus of hydromorphone 0.5 mg. If needed, morphine or hydromorphone was administered as a bolus using PCA pump at a dose and lockout interval consistent with the site's standard practice; or, if tolerated, oral immediate-release oxycodone (≤10 mg every 4 hours) was administered on an as-needed basis. If still insufficient, a femoral nerve block of bupivacaine HCl (0.125%) at a rate of 8 mL per hour for up to 12 hours was administered.
- Study 326: Same as Study 327.

5.1.6 *Efficacy Endpoints*

The primary efficacy endpoint in all Phase 3 studies was the AUC of the pain intensity scores, a measure of cumulative pain, from the first pain assessment obtained after surgery through 48 (TSA/RCR study) or 72 hours (TKA and thoracotomy studies).

Across the four Phase 3 studies, pain intensity was measured at baseline (prior to nerve block) and at pre-specified time points and immediately prior to administration of rescue pain medication using similar unipolar scales with consistent anchors. In Studies 327 and 326, pain was assessed using a 10-cm VAS, anchored at 0 cm (no pain) and 10 cm (worst possible pain). In Studies 322 and 323, pain at rest was assessed using the 11-point NRS scale (NRS-R), anchored at 0 (no pain) and 10 (worst possible pain). The NRS-R can only take on integer values (eg, 0, 1, 2) while the VAS can take on any numeric value to the nearest tenths place (eg, 5.2, 6.8, 7.0).

Secondary efficacy endpoints were assessed through 48 hours in the TSA/RCR study and 72 hours in the TKA and thoracotomy studies:

- Total postsurgical opioid consumption (in IV morphine equivalents)
- Percentage of opioid-free patients (tertiary endpoint in Studies 322 and 323)
- Time to first opioid rescue

The primary and secondary efficacy endpoints were analyzed using the efficacy analysis population which included all randomized patients who received study drug and underwent the planned surgery.

5.1.6.1 *Statistical Analyses*

For all studies, the AUC of pain intensity was derived using the trapezoidal rule on all pain scores obtained after surgery including those collected prior to rescue medication and those recorded at unscheduled times. Pain scores were adjusted for use of rescue medication based on a windowed worst observation carried forward (wWOCF) imputation procedure. Under the wWOCF approach, the worst pain intensity score prior to the use of a pain medication was carried forward for a duration based on the half-life of the rescue pain medication, as shown in Table 9. (If a worse pain score was recorded during the window, it would not be replaced.)

Table 9: Imputation Windows for Rescue Medication

Medication	Route	Window used for Imputation
Oxycodone, acetaminophen-oxycodone	PO, IM, IV, SC	6 hours
Morphine	IV, PO, SC	4 hours
Hypdromorphone	IV	2 hours
	PO, IM, SC	4 hours
Hydrocodone	PO	6 hours
Fentanyl	IV, PO, IM	
Hydrocodone, hydrocodone-acetaminophen	PO	
Codeine, acetaminophen-codeine	PO	
Tramadol	PO	

IM = intramuscular; IV = intravenous; PO = oral; SC = subcutaneous

In Studies 322 and 323, the primary efficacy endpoint was evaluated using analysis of covariance (ANCOVA) controlling for baseline NRS-R pain intensity score. In Studies 326 and 327, the primary efficacy endpoint was evaluated using analysis of variance (ANOVA) controlling for age, weight, and height. Missing data were handled using last observation carried forward (LOCF) in Studies 322 and 323 and multiple imputation in Studies 326 and 327.

Secondary efficacy endpoints were ranked in order of clinical importance and analyzed using a hierarchical fixed-sequence stepwise testing procedure in order to maintain each study's respective overall Type-I error rate (order shown in Table 7). Postsurgical opioid consumption was log-transformed and evaluated using ANOVA model with the same covariates as the primary efficacy endpoint analysis. The percentage of opioid-free patients was evaluated using a Cochran-Mantel-Haenszel (CMH) test. The time to first opioid rescue medication use was evaluated using the log-rank test.

5.2 Patient Disposition

Patient disposition was similar in the EXPAREL and placebo groups in all four Phase 3 regional analgesia studies (Table 10). Study completion rates were generally higher in Studies 327 and 326 (>95%) than Studies 322 and 323 (~80-85%). The reasons for study discontinuation were similar in the EXPAREL and placebo groups.

Table 10: Patient Disposition for Phase 3 Studies

	Study 327			Study 322		Study 323 (Part 2)		Study 326		
n (%)	EXPAREL 266 mg N=15	EXPAREL 133 mg N=69	Placebo N=71	EXPAREL 266 mg N=94	Placebo N=91	EXPAREL 266 mg N=92	Placebo N=91	EXPAREL 133 mg N=75	EXPAREL 266 mg N=76	Placebo N=79
Randomized	15	69	72	96	95	99	97	76	77	79
Efficacy Analysis Population	-	69	71	94	91	92	91	75	76	79
Completed Study	15 (100)	68 (99)	71 (100)	82 (87)	74 (81)	82 (89)	82 (90)	75 (100)	73 (96)	74 (94)
Discontinued Study	0	1	0	14	21	17	15	1	4	5
Death	0	0	0	2	4	0	0	0	0	0
Adverse Event	0	0	0	2	4	0	0	0	1	1
Lack of Efficacy	0	0	0	8	10	2	2	0	0	0
Lost to Follow-up	0	0	0	0	0	2	0	0	0	0
Withdrew Consent	0	0	0	0	2	3	3	0	3	4
Other	0	1[a]	0	2[b]	1[c]	10[d]	10[e]	1[f]	0	0

a. Withdrawn by the principal investigator
b. Patients were not treated (surgery aborted, 1; did not meet exclusion criteria, 1)
c. Patient was not treated (procedure qualification changed)
d. Patients were not treated (surgery not completed, 4; treatment unavailable, 1; disqualified for taking prohibited treatments, 2), disqualified for protocol deviation (1), withdrawn by investigator (1), withdrew because of lack of efficacy (1)
e. Patients were not treated (did not undergo surgery as scheduled, 2; positive urine drug test, 1; no reason given, 1), discharged before the 72-hour planned hospitalization period (2), disqualified because of different primary surgery (1), disqualified for taking prohibited treatment (1), withdrew because of lack of efficacy (2)
f. Patient cancelled the operation

5.3 Patient Demographic and Baseline Characteristics

Demographic and baseline characteristics were similar in the EXPAREL and placebo groups in all Phase 3 studies (Table 11). The majority of patients were white across studies while the proportion of males was slightly higher and the mean age was slightly lower in the TSA/RCR and thoracotomy studies (64%-68% male; mean age of all patients 58-61 years) compared to the TKA studies (33%-52% male; mean age of all patients 64-66 years). More than 50% of patients were ASA Class 2 across all treatment groups, except for the EXPAREL group in Study 323 (Part 2), where the majority of patients (51%) were ASA Class 3.

Approximately three-quarters of patients were from the US in Study 327. Study 322 enrolled patients almost exclusively outside of the US and Study 323 was enrolled entirely in the US. Patient enrollment in Study 326 was approximately evenly split between patients from the US and outside the US.

Table 11: Patient Demographics and Baseline Characteristics in Phase 3 Studies

	Study 327		Study 322		Study 323 (Part 2)		Study 326		
n (%)	EXPAREL 133 mg N=69	Placebo N=71	EXPAREL 266 mg N=94	Placebo N=91	EXPAREL 266 mg N=92	Placebo N=91	EXPAREL 133 mg N=75	EXPAREL 266 mg N=76	Placebo N=79
Age, Mean (SD)	61 (10)	59 (9)	58 (13)	59 (13)	66 (10)	64 (9)	65 (7)	66 (9)	65 (9)
Sex, n (%)									
Female	25 (36)	23 (32)	30 (32)	31 (34)	52 (57)	57 (63)	36 (48)	43 (57)	53 (67)
Male	44 (64)	48 (68)	64 (68)	60 (66)	40 (43)	34 (37)	39 (52)	33 (43)	26 (33)
Race, n (%)[a]									
Black/African American	13 (19)	15 (21)	0	0	15 (16)	14 (15)	8 (11)	5 (7)	12 (15)
White	53 (77)	54 (76)	94 (100)	91 (100)	75 (82)	76 (84)	66 (88)	69 (91)	67 (85)
Other/Missing	2 (3)	2 (3)	0	0	2 (2)	2 (2)	1 (1)	1 (1)	0
Hispanic/Latino	3 (4)	5 (7)	4 (4)	3 (3)	8 (9)	9 (10)	2 (3)	2 (3)	2 (3)
Region, n (%)									
Outside US[b]	17 (25)	18 (25)	92 (98)	88 (97)	0	0	37 (49)	38 (50)	39 (49)
US	52 (75)	53 (75)	2 (2)	3 (3)	92 (100)	91 (100)	38 (51)	38 (50)	40 (51)
ASA Status, n (%)									
1	15 (22)	14 (20)	32 (34)	24 (26)	7 (8)	3 (3)	11 (15)	9 (12)	10 (13)
2	36 (52)	37 (52)	48 (51)	50 (55)	38 (41)	48 (53)	41 (55)	41 (54)	46 (58)
3	18 (26)	20 (28)	14 (15)	17 (19)	47 (51)	40 (44)	23 (31)	26 (34)	23 (29)

ASA = American Society of Anesthesiologists; SD = standard deviation; US = United States

a. Patients may be in more than one category

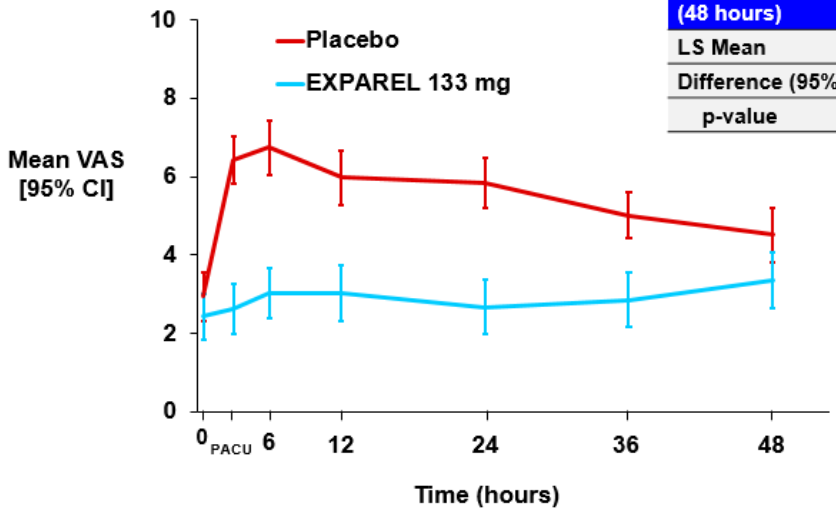
b. Belgium and Denmark (Study 327 and Study 326); Bulgaria, Czech Republic, Georgia, and Poland (Study 322)

5.4 Study 327 Results

5.4.1 *Primary Endpoint*

The primary endpoint of total pain through 48 hours after TSA or RCR was significantly lower for EXPAREL than placebo ($p < 0.0001$). The least squares (LS) mean difference in AUC of VAS pain intensity scores between the EXPAREL group (136) and the placebo group (254) was -118. The mean VAS pain intensity scores remained at approximately 2 to 3 on the 10-cm VAS scale in the EXPAREL group throughout the study compared to mean VAS scores of approximately 5 to 7 in the placebo group (Figure 9).

Figure 9: Pain Intensity Scores Through 48 Hours (Study 327)



AUC of VAS (48 hours)	EXPAREL 133 mg N=69	Placebo N=71
LS Mean	136	254
Difference (95% CI)	-118 (-151, -84)	
p-value	< 0.0001	

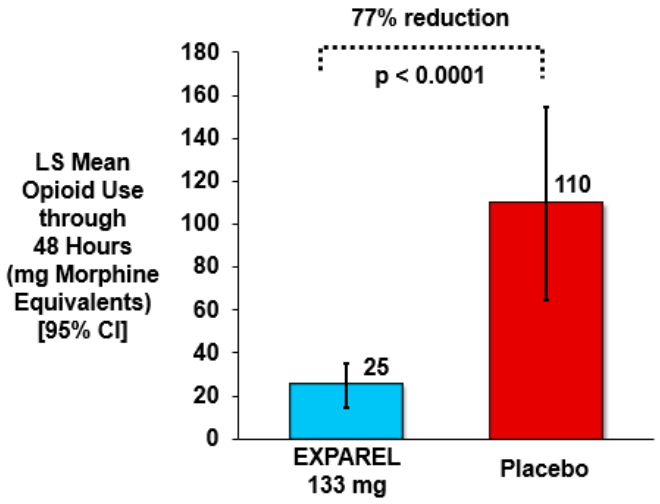
PACU = post-anesthesia care unit

5.4.2 *Secondary Endpoints*

Total Opioid Consumption

EXPAREL was associated with a significant reduction (77%) in the mean total amount of opioids used by patients, post-surgery. As shown in Figure 10, the LS mean morphine equivalents of opioids consumed through 48 hours was 25 mg in the EXPAREL group compared to 110 mg in the placebo group ($p = 0.0001$). Opioid use was lower in the EXPAREL group in all 24-hour time intervals throughout the study.

Figure 10: Opioid Rescue Medication Used Through 48 Hours (Study 327)



LS Mean Opioid Use (mg Morphine Equivalents)		
	EXPAREL 133 mg	Placebo
Time Period	N=69	N=71
0-24 hr	9	63
24-48 hr	7	32
48-72 hr	8	26

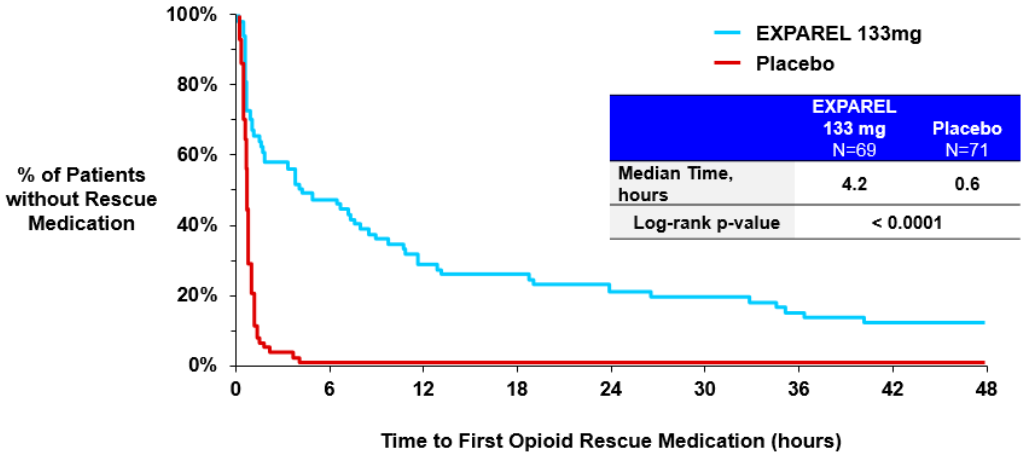
Percentage of Opioid-Free Patients

Significantly more patients in the EXPAREL group were opioid-free (did not require any rescue opioids) through 48 hours after surgery, compared to the placebo group (9/69 [13%] vs 1/71 [1%]; p = 0.008).

Time to First Opioid Rescue

EXPAREL was also associated with a longer time to first opioid use compared to placebo. The median time to first use was 35 minutes following surgery for placebo-treated patients compared to 4 hours for EXPAREL-treated patients (p < 0.0001; Figure 11).

Figure 11: Time to First Opioid Rescue (Study 327)



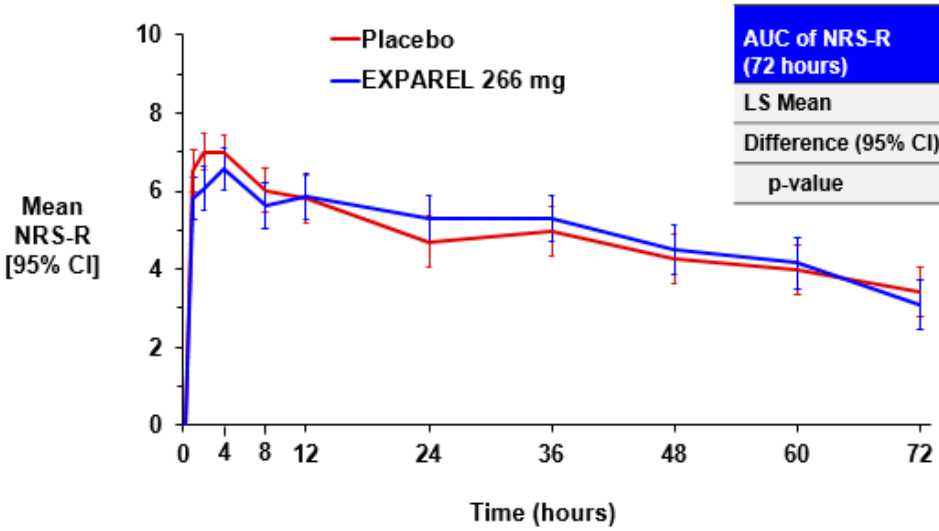
	EXPAREL 133 mg N=69	Placebo N=71
Median Time, hours	4.2	0.6
Log-rank p-value	< 0.0001	

Overall, the primary and secondary endpoints in Study 327 demonstrate that EXPAREL is efficacious for regional nerve block in an upper extremity while also reducing postoperative opioid use.

5.5 Study 322 Results

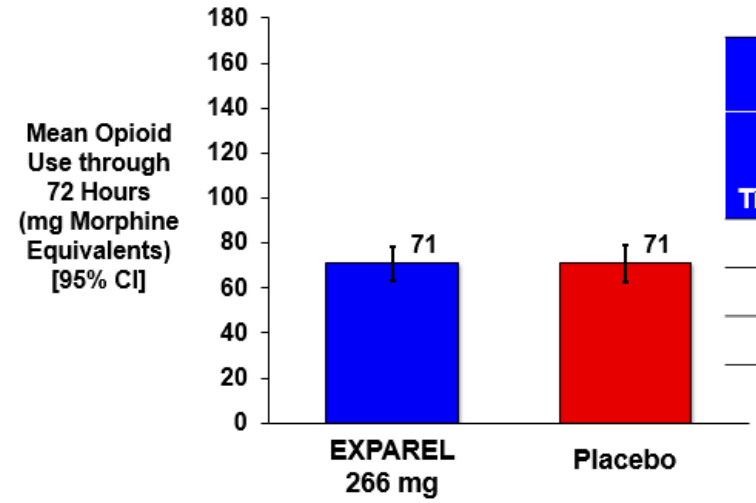
In Study 322, the primary efficacy endpoint of cumulative pain intensity after thoracotomy was not met. There was no statistically significant difference in pain intensity scores through 72 hours with EXPAREL compared to placebo (Figure 12). The secondary endpoints, total opioid consumption through 72 hours (Figure 13) and the time to first opioid rescue medication use (Figure 14), were also similar in the EXPAREL and placebo groups.

Figure 12: Pain Intensity Scores Through 72 Hours (Study 322)



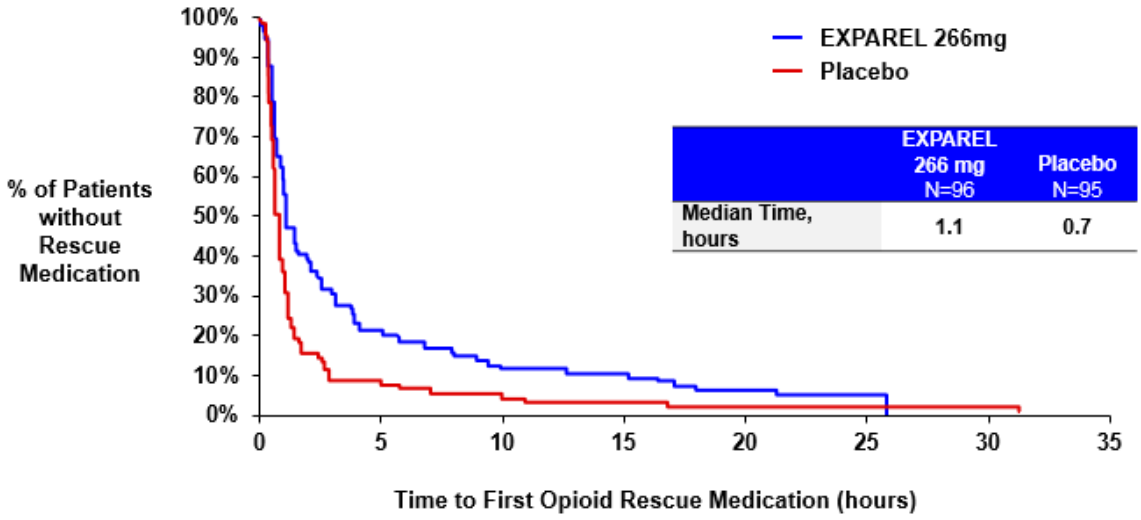
AUC of NRS-R (72 hours)	EXPAREL 266 mg N=96	Placebo N=95
LS Mean	472	459
Difference (95% CI)	13 (-31, 57)	
p-value	0.56	

Figure 13: Opioid Rescue Medication Used Through 72 Hours (Study 322)



Mean Opioid Use (mg Morphine Equivalents)		
Time Period	EXPAREL 266 mg N=94	Placebo N=91
0-24 hr	36	40
24-48 hr	21	19
48-72 hr	14	12

Figure 14: Time to First Opioid Rescue (Study 322)



Pacira conducted an in-depth assessment of factors that may have impacted the efficacy outcomes and identified that the primary issue was the administration of the block. The study drug was delivered by the surgeon to the intercostal nerve via instillation rather than injection with ultrasound guidance, which led to substantial variability in retention of the study drug. Optimal placement and retention of the analgesic within the intercostal musculature was likely not achieved.

This explanation is supported by PK data collected during the study. The median time to maximum concentration (T_{max}) was 1 hour compared to 49-75 hours in the other studies evaluating the 266 mg dose. This suggests that in Study 322, EXPAREL was absorbed and cleared very quickly, consistent with administration into a highly vascular field. Thus, the lack of efficacy in Study 322 appears to have resulted from the administration of the drug in such a manner that a successful nerve block was not achieved. As a result, the efficacy of EXPAREL as a regional nerve block cannot be meaningfully evaluated in this study.

5.6 Study 323 – Part 1 Results

Table 12 shows the results of the efficacy endpoints evaluated in Part 1 of Study 323. For the primary efficacy endpoint, both the 133 mg and 266 mg dose of EXPAREL resulted in statistically significant reductions in cumulative pain intensity following TKA relative to placebo, with an LS mean difference in 72-hour AUC of -103 and -94 ($p = 0.024$ and $p = 0.039$), respectively. The difference between the EXPAREL 67 mg group and the placebo group was not statistically significant ($p = 0.95$). The 266 mg dose also showed favorable results for time to first opioid rescue.

Table 12: Efficacy Endpoint Results (Study 323 – Part 1)

Endpoint Parameter	EXPAREL 67 mg N=22	EXPAREL 133 mg N=24	EXPAREL 266 mg N=24	Placebo N=24
AUC of NRS-R pain intensity through 72 hours				
LS Mean (SE)	533 (33)	427 (32)	436 (32)	531 (32)
LS Mean Difference (95% CI)	3 (-88, 94)	-103 (-192, -14)	-94 (-184, -5)	-
p-value vs placebo	0.95	0.024	0.039	-
Total opioid consumption through 72 hours, mg morphine equivalents				
Geometric LS Mean	101	81	95	111
Geometric LS Ratio (95% CI)	0.90 (0.6, 1.3)	0.73 (0.5, 1.1)	0.85 (0.6, 1.3)	-
p-value vs placebo	0.62	0.11	0.41	-
Time to first opioid rescue, hours				
Median (First, Third Quartiles)	0.5 (0.3, 0.7)	0.4 (0.3, 0.7)	1.3 (0.4, 2.4)	0.4 (0.3, 0.6)
p-value[a]	0.19	0.34	0.0004	-

AUC=area under the curve; LS=least squares; NRS-R=numeric rating scale at rest; SE=standard error
a. Log-rank test

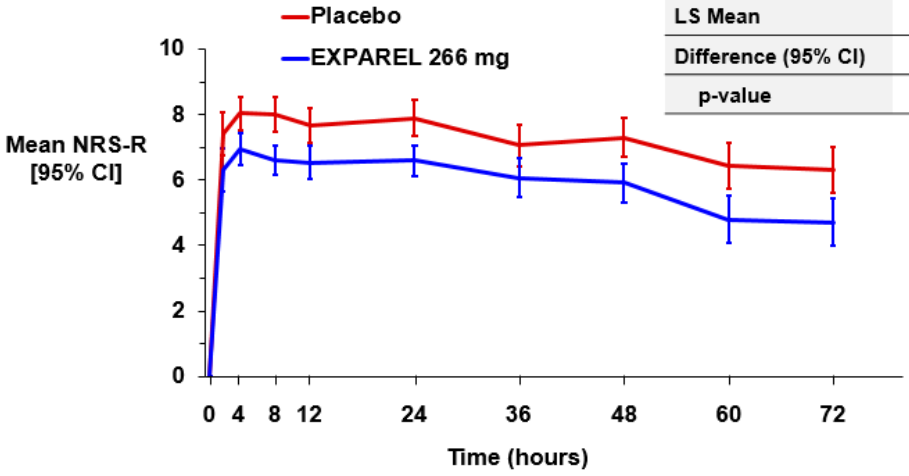
Based on these results, as well as the demonstration of similar safety across dose groups, the independent Unblinded Dose Selection Committee concluded that the 266 mg dose should be moved forward for further testing in Part 2 of Study 323. (Note: Regarding safety, the 266 mg dose did not appear to pose a greater risk to the patients than the 133 mg dose. There were no perioperative falls within 72 hours of study drug administration, and the percentages of patients who could perform the 20-meter walk test were similar between the EXPAREL and placebo groups.)

5.7 Study 323 – Part 2 Results

5.7.1 *Primary Endpoint*

The primary efficacy endpoint in Part 2 of Study 323 was met. Cumulative pain through 72 hours following TKA was significantly lower for EXPAREL than placebo ($p < 0.0001$). The LS mean AUC of NRS-R pain intensity scores was 419 in the EXPAREL group and 516 in the placebo group, resulting in a treatment difference of -97. The mean pain intensity was approximately 2 points lower on the NRS-R scale after surgery in the EXPAREL group, and the benefit was maintained through 72 hours (Figure 15).

Figure 15: Pain Intensity Scores Through 72 Hours (Study 323 – Part 2)

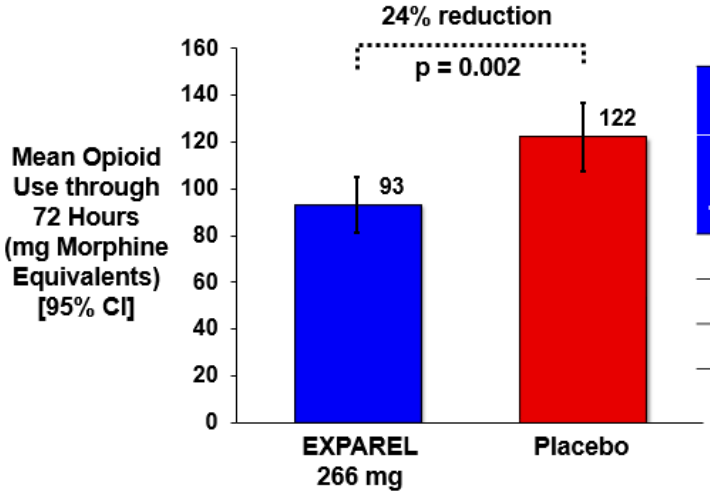


AUC of NRS-R (72 hours)	EXPAREL 266 mg N=92	Placebo N=91
LS Mean	419	516
Difference (95% CI)	-97 (-144, -49)	
p-value	< 0.0001	

5.7.2 *Secondary Endpoints*

Over 72 hours post-surgery, the EXPAREL group consumed on average 93 mg of opioid rescue pain medications while control patients consumed 122 mg (Figure 16). Thus, EXPAREL was associated with a 24% reduction in the total use of opioids (p = 0.002).

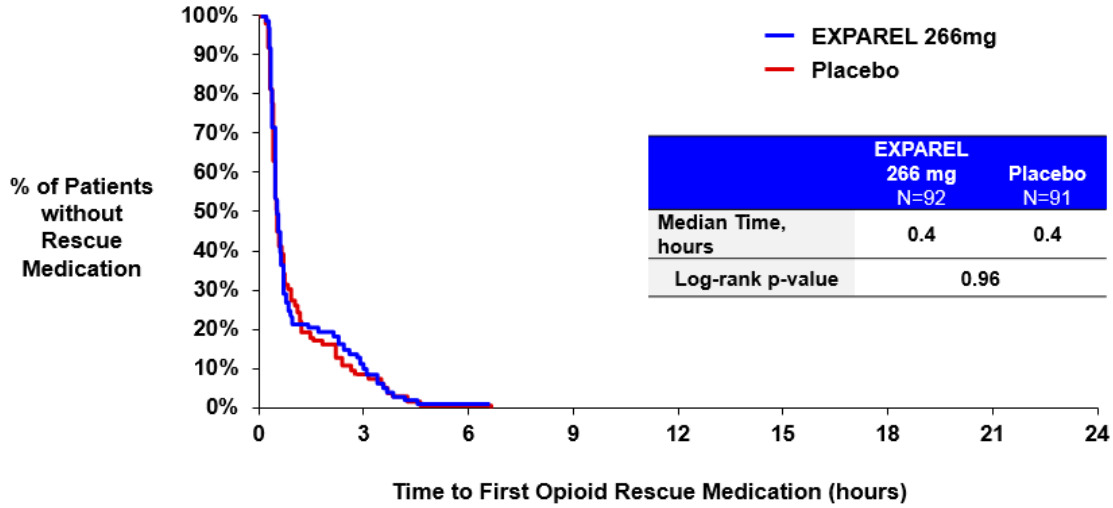
Figure 16: Opioid Rescue Medication Used Through 72 Hours (Study 323 – Part 2)



Mean Opioid Use (mg Morphine Equivalents)		
Time Period	EXPAREL 266 mg N=92	Placebo N=91
0-24 hr	56	69
24-48 hr	24	35
48-72 hr	13	19

The time to first opioid rescue was similar between groups (median = 0.4 hours for EXPAREL and placebo; p = 0.96; Figure 17). The lack of a difference in timing may be attributed to post-procedure pain from the posterior region of knee, which is not covered by a femoral nerve block. This area was not anesthetized during the surgery despite being within the surgical field and, therefore, potentially necessitated pain control following the procedure. The percentage of patients free from opioid rescue medication was not a ranked secondary endpoint in Study 323; all patients in both groups received at least 1 rescue medication, although fewer patients in the EXPAREL group required all lines of rescue medications (8% vs 19%).

Figure 17: Time to First Opioid Rescue (Study 323 – Part 2)



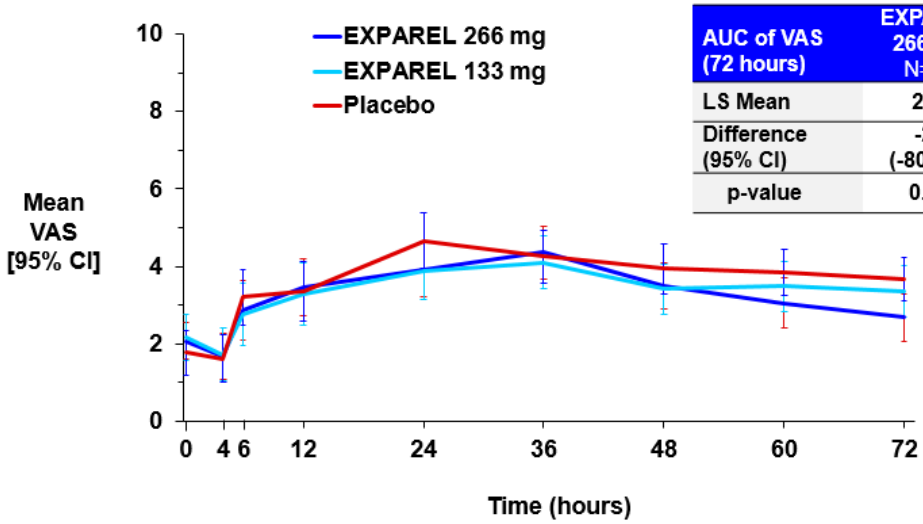
	EXPAREL 266 mg N=92	Placebo N=91
Median Time, hours	0.4	0.4
Log-rank p-value	0.96	

Overall, Study 323 demonstrated that EXPAREL 266 mg is efficacious as a regional analgesic in reducing postsurgical pain in the lower extremities while also reducing the use of opioid medication.

5.8 Study 326 Results

In Study 326, EXPAREL 133 mg and EXPAREL 266 mg did not demonstrate a significant reduction in cumulative pain intensity in the 72 hours following TKA compared to placebo (Figure 18).

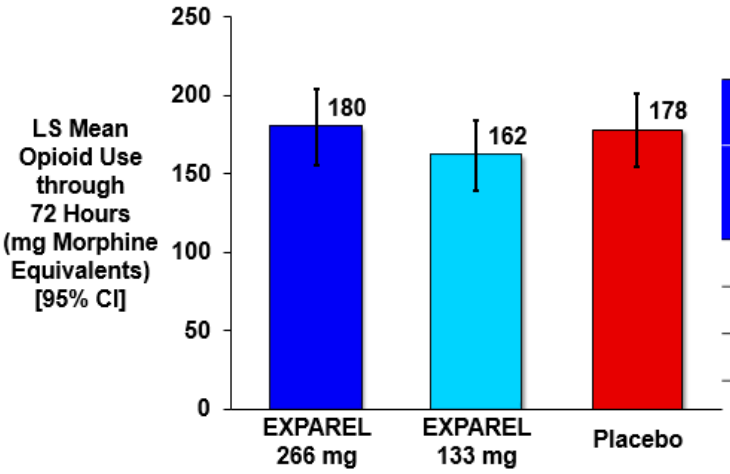
Figure 18: Pain Intensity Scores Through 72 Hours (Study 326)



AUC of VAS (72 hours)	EXPAREL 266 mg N=76	EXPAREL 133 mg N=75	Placebo N=91
LS Mean	251	260	280
Difference (95% CI)	-29 (-80, 23)	-20 (-72, 32)	-
p-value	0.27	0.45	-

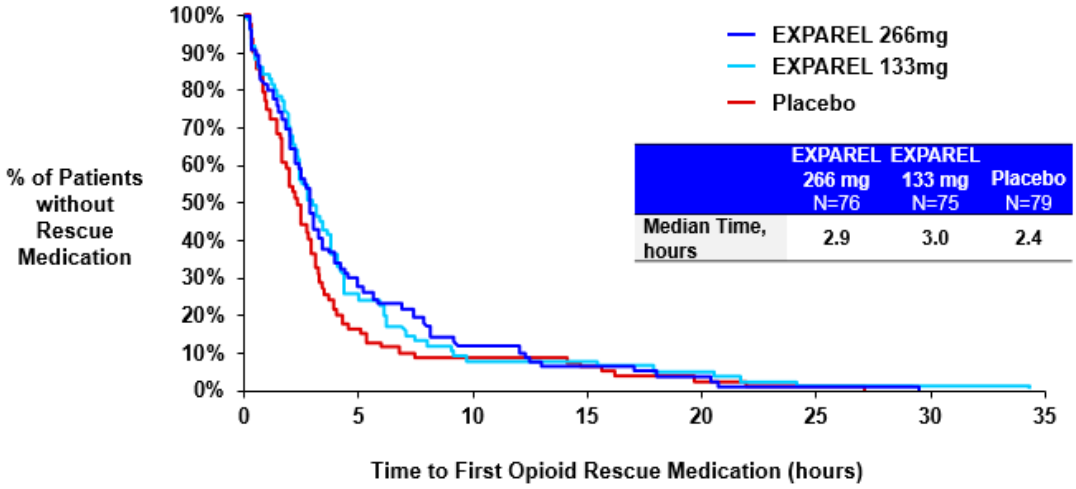
The mean total amount of rescue opioid consumption through 72 hours was similar in all treatment groups (Figure 19). All patients used rescue medication at least once; the median time to first use of opioid rescue was similar in all treatment groups (Figure 20).

Figure 19: Opioid Rescue Medication Used Through 72 Hours (Study 326)



LS Mean Opioid Use (mg Morphine Equivalents)			
	EXPAREL 266 mg	EXPAREL 133 mg	Placebo
Time Period	N=76	N=75	N=79
0-24 hr	60	48	67
24-48 hr	52	52	43
48-72 hr	22	19	12

Figure 20: Time to First Opioid Rescue (Study 326)



	EXPAREL 266 mg N=76	EXPAREL 133 mg N=75	Placebo N=79
Median Time, hours	2.9	3.0	2.4

Pacira thoroughly evaluated the potential factors that may have influenced the incongruence in efficacy findings between the TKA studies, Studies 326 and 323, including differences in study design, study conduct, site effects, and PK. The key findings from this evaluation are provided below.

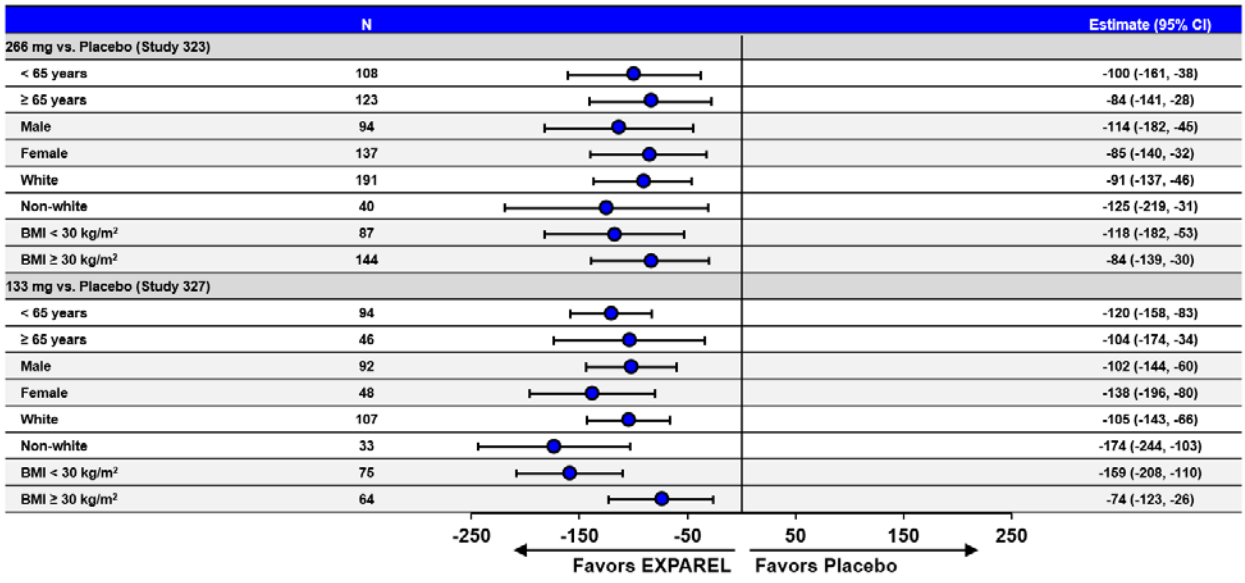
- In terms of study design, all patients (both EXPAREL and placebo) in Study 326 received a posterior capsule infiltration with bupivacaine HCl. Therefore, the placebo group in Study 326 received a component of active therapy, which was not the case in Study 323. This may have contributed to the lower pain scores across all groups in Study 326 (ie, both EXPAREL and placebo cumulative pain scores were approximately 40-50% lower in Study 326 than Study 323). Since the sample size of Study 326 was predicated on the results of Study 323, the marked difference in overall pain scores reduced the study's statistical power to detect a treatment difference.

- In terms of study conduct and site effects, the largest enrolling site in Study 326 (enrolling 47% of patients in the study) had substantially lower pain scores relative to the rest of the study (AUC of VAS: 152 vs 392 in the placebo groups). Upon further review, this site provided more opioid rescue medications than other sites in the study, regardless of the pain scores reported by patients. Excluding this single center from the analysis, the relative treatment effect for the 266 mg dose was consistent with the prior TKA study.

5.9 Subgroup Analyses

Subgroup analyses of the AUC of pain intensity scores were conducted for the positive pivotal Phase 3 studies (327 and 323). In general, similar results were obtained across subgroups based on age, sex, race, and body mass index (BMI; Figure 21).

Figure 21: Subgroup Analysis of AUC Pain Intensity (Studies 323 [Parts 1 and 2 Combined] and 327)



5.10 Efficacy in Supportive Studies

Results from two investigator-initiated trials were submitted to the FDA to provide additional support for the use of EXPAREL as a nerve block. These trials evaluated the efficacy of EXPAREL when admixed with bupivacaine HCl for regional analgesia in an upper and a lower extremity procedure. Both investigator-initiated trials were blinded, active-controlled, randomized clinical trials conducted at a single site in Belgium.

In clinical practice, EXPAREL may be admixed with bupivacaine HCl (as described in Section 3.2) to achieve a higher degree of immediate regional analgesia than produced by EXPAREL alone. Combined administration with bupivacaine HCl is described in the EXPAREL USPI for infiltration/field block and is expected to be relevant for a regional analgesia indication.

5.10.1 ***Study 1601***

Study Design

Study 1601 evaluated EXPAREL in adult patients undergoing Dupuytren's contracture release. Patients were randomized in a 1:1 ratio to receive one of two single-dose treatments:

- EXPAREL 133 mg (10 mL) admixed with bupivacaine HCl 25 mg (5 mL) (total 15 mL)
- Bupivacaine HCl 75 mg (15 mL)

Half of each treatment was administered as a nerve block to the ulnar nerve while the other half was placed as a median nerve block at least 30 minutes before collagenase clostridium histolyticum (CCH) injection. The study drug was administered under ultrasound guidance and with nerve stimulation and opening injection pressure monitoring to ensure that the anesthetic was deposited precisely in the tissue plane between the superficial and deep flexors of the forearm. All patients received standardized postoperative pain treatment with NSAIDS (ie, diclofenac [75 mg BID] and paracetamol [1,000 mg every 6 hours {q6h}]). In case of breakthrough pain, tramadol 50 mg was allowed up to four times per day.

The efficacy endpoints were:

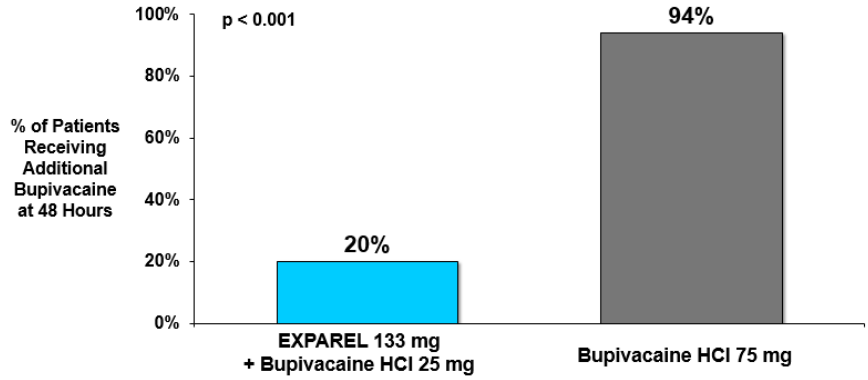
1) The need for additional local anesthetic (bupivacaine HCl) during finger manipulations to rupture the cords during the second phase of treatment for Dupuytren's contracture release 48 hours after CCH injections. Typically, this procedure is a few minutes in duration but extremely painful, requiring administration of sedation, local nerve block, or brief general anesthesia.
2) Patient-reported worst pain over the first 72 hours, as assessed using the modified Brief Pain Inventory-short form
3) Persistence of sensory block in the hand over the first postoperative week

A total of 32 patients were randomized 1:1 to EXPAREL admixed with bupivacaine HCl or bupivacaine HCl alone. All patients completed the study. Demographics and other baseline characteristics were similar in both groups. Most of the patients were male (88% in each group) and all patients were white.

Results

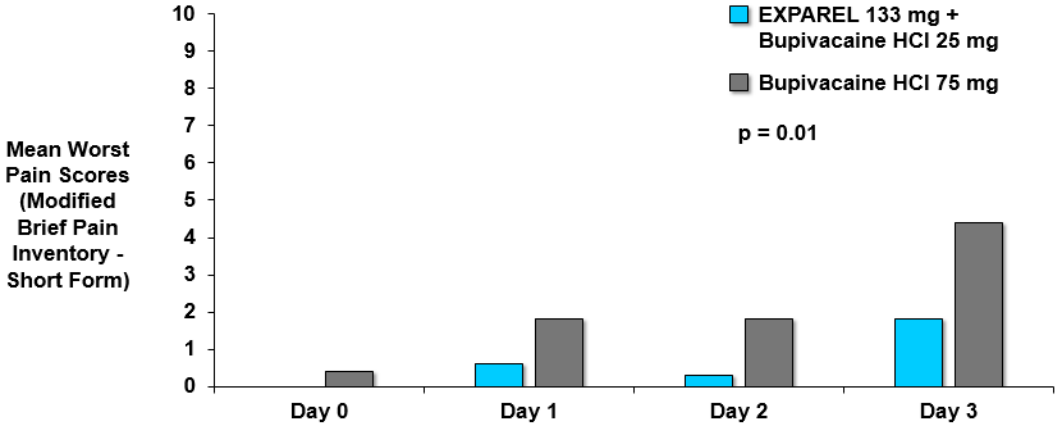
Significantly fewer patients in the EXPAREL plus bupivacaine HCl group required additional local anesthetic to undergo finger manipulations at 48 hours compared with the bupivacaine HCl alone group. Additional bupivacaine HCl was required by 94% of the bupivacaine HCl alone group versus 20% of the EXPAREL plus bupivacaine HCl group ($p < 0.001$; Figure 22).

Figure 22: Patients Requiring Local Anesthetic for Finger Manipulation 48 Hours after Ulnar and Median Nerve Block for CCH Injections (Study 1601)



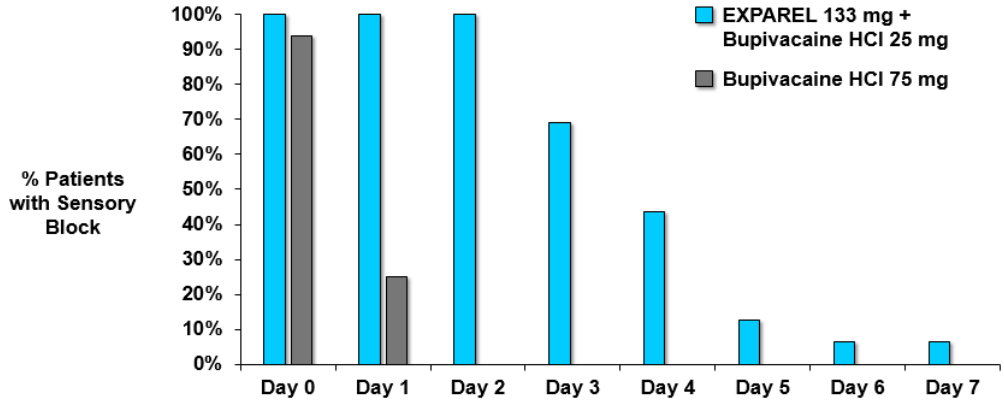
Using repeated-measures analysis, patient-reported worst pain through Day 3 after nerve block was significantly lower (p = 0.01) in the EXPAREL plus bupivacaine HCl group compared with the bupivacaine HCl alone group (Figure 23).

Figure 23: Worst Pain Scores Through 72 Hours (Study 1601)



Approximately 68% and 44% of patients treated with EXPAREL plus bupivacaine HCl reported sensory block at Days 3 and 4, respectively. No patients in the bupivacaine HCl alone group reported persistence of sensory block in the hand after Day 1 (Figure 24).

Figure 24: Proportion of Patients with Sensory Block Through Day 7 (Study 1601)



5.10.2 ***Study 1602***

Study Design

Study 1602 evaluated EXPAREL admixed with bupivacaine HCl in adult patients undergoing scarf osteotomy to correct severe hallux valgus deformity under either ultrasound-guided ankle nerve block or under general anesthesia. Patients were randomized in a 1:1:1 ratio to one of three groups:

- EXPAREL 133 mg (10 mL) admixed with bupivacaine HCl 25 mg (5 mL) (total 15 mL or 7.5 mL per nerve)
- Bupivacaine HCl 75 mg (total 15 mL or 7.5 mL per nerve)
- General anesthesia with propofol 8.0 mcg/mL target-controlled infusion and fentanyl 3 mcg/kg followed by N_2O 50% and propofol 3.0-4.0 mcg/mL target-controlled infusion, remifentanil infusion

Injections with either EXPAREL plus bupivacaine or bupivacaine alone were administered to the distal tibial and deep peroneal nerves 30 minutes before surgery. Ultrasound guidance with nerve stimulation and opening injection pressure monitoring were utilized to ensure precise placement of the anesthetic. All groups received multimodal post-procedural analgesia consisting of diclofenac 75 mg BID and acetaminophen/paracetamol [1,000 mg q6h]. Postsurgical rescue medication was tramadol 50 mg up to four times per day.

The efficacy endpoints were:

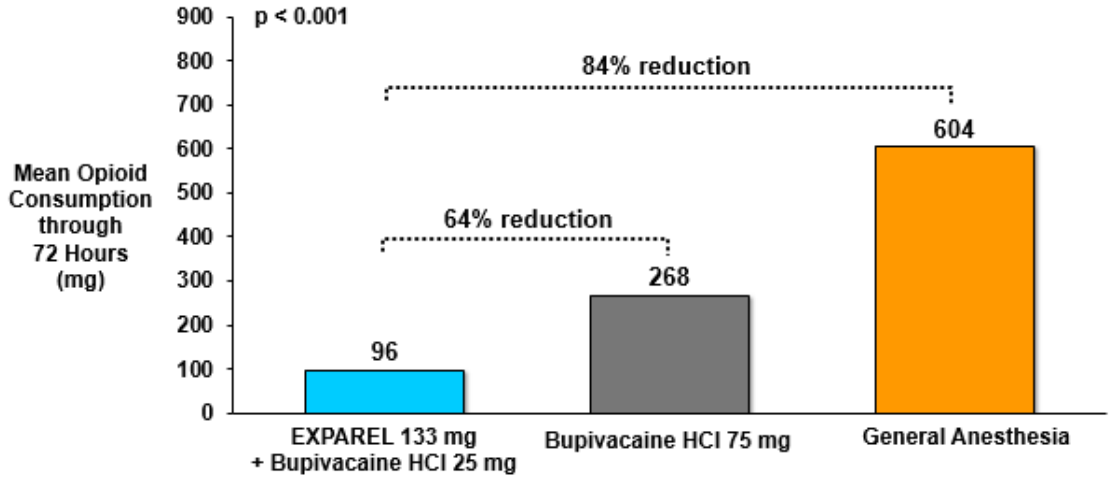
1) Opioid consumption in the first postoperative week
2) Patient-reported worst pain over the first 72 hours, as assessed using the modified Brief Pain Inventory-short form
3) Persistence of sensory block in the foot over the first postoperative week

A total of 40 patients were randomized into Study 1602, 12 to EXPAREL plus bupivacaine HCl, 14 to bupivacaine HCl alone, and 14 to general anesthesia. Most patients in each of the groups completed the study, with the exception of one patient in the bupivacaine HCl alone group (withdrawal by patient) and two patients in the general anesthesia group (change in surgical scope and withdrawal by patient). Demographics and baseline characteristics were similar across the groups in Study 1602. Most of the patients were female (>98%) and white (>93%).

Results

During the first postoperative week, the EXPAREL plus bupivacaine HCl group used 64% fewer opioids than the bupivacaine HCl alone group (96 mg vs 268 mg) and 84% fewer than the general anesthesia group (96 mg vs 604 mg) ($p < 0.001$; Figure 25).

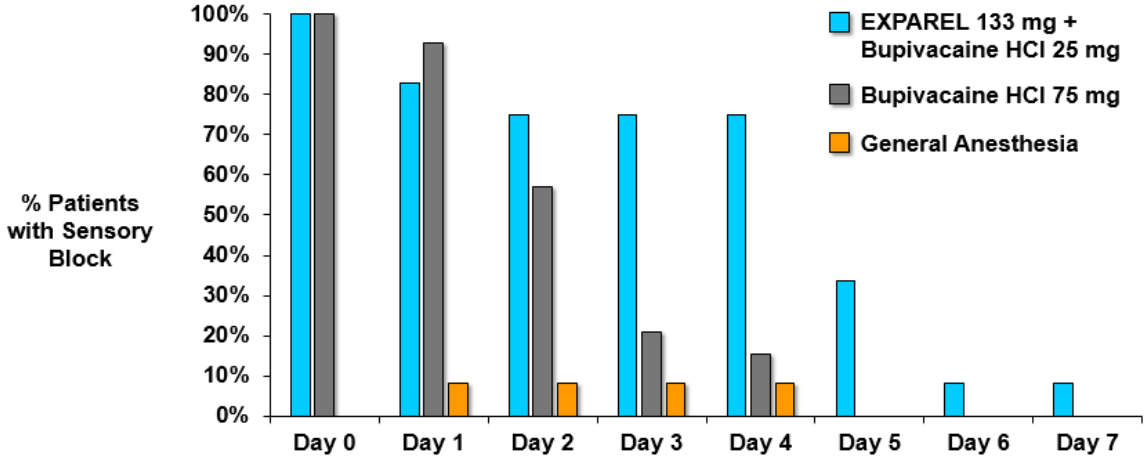
Figure 25: Opioid Use Through 72 Hours (Study 1602)



Using repeated-measures analysis, patient-reported worst pain over the first 72-hour postoperative interval was significantly lower in the EXPAREL plus bupivacaine HCl group compared with the bupivacaine HCl alone and general anesthesia groups (p = 0.003).

Sensory block in the foot persisted through Day 4 in more than 70% of patients in the EXPAREL plus bupivacaine HCl group. The percentage of patients in the bupivacaine HCl alone group with sensory block was more than 90% through Day 1 and fell to approximately 20% by Day 3. Few patients in the general anesthesia group reported sensory block at any time point (Figure 26).

Figure 26: Proportion of Patients with Sensory Block in Foot Through Day 7 (Study 1602)



5.11 Efficacy Conclusions

The clinical development program explored the single-dose administration of EXPAREL 133 mg and 266 mg as a nerve block for regional analgesia in upper and lower extremities and in small and large nerves, which is representative of most of the nerve blocks performed in the US. The Phase 3 studies demonstrated that EXPAREL provides effective control of post-procedural pain for several days and reduces the use of opioids in the postsurgical setting. While Study 322 and Study 326 did not produce positive findings, due to either confounding factors in either treatment

administration or study site effects, the performance of EXPAREL was characterized in two adequate and well-controlled Phase 3 studies in accordance with FDA guidance for approval of a new indication of an analgesic. These efficacy findings were also supported by two randomized, active-controlled investigator-initiated trials in different upper and lower extremity procedures.

Study 327 demonstrated the efficacy of EXPAREL 133 mg nerve block for the management of acute pain following TSA or RCR and Study 323 demonstrated the efficacy of EXPAREL 266 mg nerve block in the management of acute pain following TKA. Both studies also measured significant reductions in the use of opioids after surgery. In these studies, the efficacy profile of EXPAREL was consistent across age, sex, race, and BMI.

The value of prolonged analgesia with EXPAREL over current bupivacaine HCl nerve blocks was demonstrated in the investigator-initiated trials, Studies 1601 and 1602. Both studies demonstrated that EXPAREL admixed with bupivacaine HCl provided superior pain control compared to bupivacaine HCl alone as a nerve block and reduced the need for subsequent use of opioid medications or supplemental local anesthetics.

Overall, the totality of the clinical data demonstrates that both proposed doses of EXPAREL can be expected to provide meaningful pain relief and reduce the need for opioids in the postsurgical setting.

6 CLINICAL SAFETY

Summary

- The EXPAREL safety database includes 2,047 individuals exposed to EXPAREL across 29 clinical studies, 531 of whom were patients who received EXPAREL as a nerve block in 6 Phase 2 and Phase 3 studies.
- The safety profile of EXPAREL as a nerve block is consistent with the known safety profile of EXPAREL for infiltration/field block.
- The incidence of adverse events (AEs), serious adverse events (SAEs), severe AEs, and AEs leading to discontinuation were similar for the EXPAREL and placebo groups across the pooled nerve block studies.
- There were 6 deaths reported in the pooled nerve block studies (2 patients receiving EXPAREL 266 mg and 4 patients receiving placebo). All deaths occurred in Study 322 among patients undergoing thoracotomy most often for lung cancer.
- Local anesthetic systemic toxicity is a rare, potentially life-threatening complication associated with inadvertent intravascular injection of a local anesthetic leading to very high local anesthetic plasma concentrations sufficient to cause severe CNS and cardiac events such as seizures and cardiovascular collapse. No apparent cases of local anesthetic systemic toxicity were reported in any of the EXPAREL clinical studies. The results of a comprehensive analysis of the global clinical safety database and pre-clinical studies indicate that EXPAREL has a favorable safety margin for local anesthetic systemic toxicity compared to bupivacaine HCl due to the liposome-bound nature (and slow release) of bupivacaine in EXPAREL.
- The only new safety concern identified in the nerve block studies was a higher incidence of falls with EXPAREL after TKA. In order to address this safety risk, Pacira is proposing that the product label reflect that EXPAREL is not recommended for use as a femoral nerve block when early mobilization and ambulation is part of the patient's recovery plan.
- Electrocardiographic results and the incidence of cardiac disorders showed no clinically significant concerns after administration of EXPAREL.
- Safety data from the clinical development program and postmarketing experience in over 3.5 million patient demonstrate that the safety profile of EXPAREL is favorable for the proposed expanded indication for nerve block.

6.1 Treatment Exposure

A total of 2,047 individuals were exposed to EXPAREL across 29 clinical studies. The primary focus of the safety evaluation for EXPAREL as a nerve block comprises the 6 Phase 2 and Phase 3 nerve block studies, which included 531 patients exposed to EXPAREL and 357 patients exposed to placebo (Table 13).

Given the substantial differences between the procedures evaluated in the studies, the adverse event profile across the studies are somewhat different. First, all safety data are shown pooled across all four Phase 3 studies. In addition, Study 326 safety data are shown separately because it is the only Phase 3 nerve block study that included both 133 mg and 266 mg doses and enabled inspection of a dose-response relationship.

Table 13: Summary of Exposure in Nerve Block Studies

Type of Study Study Number	EXPAREL			Placebo
	133 mg	266 mg	Any Dose	
Phase 2				
Study 203[a]	-	-	38	0
Study 211[b]	1	-	2	0
Study 323 (Part 1)[c]	24	24	70	24
Phase 3				
Study 322	-	94	94	91
Study 323 (Part 2)	-	92	92	92
Study 326	75	76	151	79
Study 327[d]	69	15	84	71
TOTAL	169	301	531	357

a. Study 203 randomized individuals in a 1:1:1 ratio to 155, 200, or 310 mg EXPAREL.
b. Study 211 randomized individuals in a 1:1:1 ratio to 67 or 133 mg EXPAREL or bupivacaine HCl. Only three patients were enrolled (two EXPAREL and one bupivacaine HCl) before the study was terminated by Pacira.
c. Part 1 of Study 323 randomized patients in a 1:1:1:1 ratio to EXPAREL 67, 133, 266 mg, or placebo; 22 patients received EXPAREL 67 mg.
d. Fifteen patients were randomized to 266 mg prior to a protocol amendment.

6.2 Adverse Events

The incidence of AEs, SAEs, severe AEs, and AEs leading to discontinuation were similar for the EXPAREL and placebo groups across the pooled nerve block studies (Table 14). There were six deaths reported (2 EXPAREL 266 mg, 4 placebo), all of which occurred in Study 322 (thoracotomy). None of the deaths was assessed by the investigator as related to study drug.

Table 14: Overall Summary of AEs in the Phase 3 Nerve Block Studies

Number (%) of Patients with Any:	Pooled Nerve Block Studies			Study 326		
	EXPAREL 133 mg (N=169)	EXPAREL 266 mg (N=301)	Placebo (N=357)	EXPAREL 133 mg (N=75)	EXPAREL 266 mg (N=76)	Placebo (N=79)
AE	153 (91%)	260 (86%)	299 (84%)	73 (97%)	74 (97%)	76 (96%)
Serious AE	9 (5%)	30 (10%)	29 (8%)	5 (7%)	8 (11%)	6 (8%)
Severe AE	5 (3%)	19 (6%)	28 (8%)	3 (4%)	3 (4%)	2 (3%)
AE Leading to Study Discontinuation	0	3 (1%)	7 (2%)	0	0	1 (1%)
AE Leading to Death	0	2 (<1%)	4 (1%)	0	0	0

The most frequently occurring AEs (incidence of ≥ 5% in any of the pooled EXPAREL dose groups) with a higher (≥ 2%) incidence compared to placebo are shown in Table 15. The AE profile was consistent with what would be expected following a surgical procedure. Anemia was the only AE that was notably higher with 266 mg than 133 mg; however, the incidence of anemia in the 266 mg group was similar to placebo in both the pooled nerve block studies as well as Study 326 which allows for a randomized comparison between the two EXPAREL doses.

Table 15: AEs Occurring in ≥ 5% of Patients with a ≥ 2 % Higher Incidence in Either EXPAREL Group vs Placebo in Pooled Nerve Block Studies

AE Preferred Term	Pooled Nerve Block Studies			Study 326		
	EXPAREL 133 mg (N=169)	EXPAREL 266 mg (N=301)	Placebo (N=357)	EXPAREL 133 mg (N=75)	EXPAREL 266 mg (N=76)	Placebo (N=79)
Any AE	153 (91%)	260 (86%)	299 (84%)	73 (97%)	74 (97%)	76 (96%)
Pyrexia	36 (21%)	70 (23%)	64 (18%)	23 (31%)	18 (24%)	22 (28%)
Constipation	29 (17%)	66 (22%)	68 (19%)	12 (16%)	16 (21%)	15 (19%)
Motor dysfunction	35 (21%)	35 (12%)	37 (10%)	34 (45%)	35 (46%)	34 (43%)
Headache	14 (8%)	10 (3%)	10 (3%)	4 (5%)	2 (3%)	0
Anemia	2 (1%)	18 (6%)	13 (4%)	1 (1%)	6 (8%)	5 (6%)

6.2.1 *Serious Adverse Events*

The percentages of patients with a SAE in the pooled EXPAREL 133 mg and 266 mg groups were 5% and 10%, respectively, compared to 8% in the pooled placebo groups. The higher incidence of SAEs in the pooled 266 mg group compared to the pooled 133 mg group was driven by the thoracotomy study (13% EXPAREL 266 mg and 10% placebo), which had the highest SAE rates of any study, consistent with the invasiveness of the procedure and the patient population (ie, patients undergoing surgery for lung cancer). There were no dose-related relationships observed in Study 326. Pyrexia and post-procedural hematoma were the only

individual SAEs that occurred at an incidence of ≥ 1% in any of the pooled treatment groups. None of the SAEs in any study was considered by the study investigators to be related to the study drug.

Table 16: SAEs Occurring in ≥ 2 Patients in the Pooled EXPAREL Groups

	Pooled Nerve Block Studies			Study 326		
SAE Preferred Term	**EXPAREL 133 mg (N=169)**	**EXPAREL 266 mg (N=301)**	**Placebo (N=357)**	**EXPAREL 133 mg (N=75)**	**EXPAREL 266 mg (N=76)**	**Placebo (N=79)**
Any SAE	9 (5%)	30 (10%)	29 (8%)	5 (7%)	8 (11%)	6 (8%)
Pyrexia	0	4 (1%)	1 (<1%)	0	0	0
Post-procedural hematoma	3 (2%)	1 (<1%)	0	3 (4%)	1 (1%)	0
Anemia	0	2 (<1%)	2 (<1%)	0	0	0
Pneumonia	1 (<1%)	2 (<1%)	2 (<1%)	0	0	0
Myocardial infarction	0	3 (1%)	1 (<1%)	0	0	0
Urinary tract infection	0	3 (1%)	0	0	0	0
Atrial fibrillation	1 (<1%)	1 (<1%)	2 (<1%)	1 (1%)	1 (1%)	1 (1%)
Cardiac arrest	0	2 (<1%)	2 (<1%)	0	0	0
Wound dehiscence	0	1 (<1%)	1 (<1%)	0	0	0
Motor dysfunction	0	2 (<1%)	0	0	2 (3%)	0
Cellulitis	1 (<1%)	0	0	1 (1%)	0	0

6.2.2 *Deaths*

There were 6 deaths reported in the pooled nerve block studies (2 patients receiving EXPAREL 266 mg and 4 patients receiving placebo). All deaths occurred in Study 322 (thoracotomy). None of the deaths was assessed by the investigator as related to the study drug (Table 17). Patient narratives for these deaths are provided in Appendix 2.

Table 17: Deaths by Patient in Pooled Nerve Block Studies

Study	Patient ID	Treatment	Age/Race/ Sex	Fatal AE Preferred Terms	Relationship to Study Drug
322	301-0006	EXPAREL 266 mg	73/W/M	Cardiac arrest Cardiac failure acute Heart injury	Unrelated
322	503-0020	EXPAREL 266 mg	72/W/M	White blood cell count increased Renal failure Cardiac arrest	Unrelated
322	201-0001	Placebo	63/W/M	Acute kidney injury Respiratory failure Coma uremic	Unrelated
322	202-0005	Placebo	40/W/M	Myocardial infarction	Unrelated
322	506-0002	Placebo	71/W/M	Pneumonia Sepsis Renal failure Cardiac arrest	Unrelated
322	506-0017	Placebo	75/W/M	Pneumothorax	Unrelated

M = male; W = white

6.2.3 *AEs Leading to Study Discontinuation*

Three patients who received EXPAREL 266 mg and seven patients who received placebo had AEs leading to study discontinuation. (No patients who received EXPAREL 133 mg had an AE leading to discontinuation.) The AEs leading to discontinuation for EXPAREL patients were post-procedural hemorrhage, confusional state, and bronchial obstruction. The AEs leading to discontinuation for placebo patients were delirium (n=2), pneumonia, post-procedural hemorrhage, pneumothorax, respiratory depression, and respiratory failure. None of the AEs leading to study discontinuation were considered by the investigator as related to the study drug.

6.3 Adverse Events of Special Interest

6.3.1 *Local Anesthetic Systemic Toxicity*

Local anesthetic systemic toxicity is a rare, serious adverse reaction resulting from very high systemic plasma concentrations of local anesthetic. Local anesthetic systemic toxicity may occur when a local anesthetic is accidentally injected intravascularly, is absorbed very rapidly in a highly vascular area, or is used in excess of the maximum dose (Dewaele et al 2017). Local anesthetic systemic toxicity typically occurs within minutes of injection of the local anesthetic (Vasques 2015). The incidence of local anesthetic systemic toxicity has been reported as 0.7-1.8 per 10,000 epidurals and 2.0-2.8 per 10,000 peripheral nerve blocks with non-liposomal local anesthetics (El Boghdadly et al 2016).

Local anesthetic systemic toxicity is characterized by the rapid onset and progression of a constellation of escalating CNS and cardiovascular symptoms. Early cardiovascular signs and symptoms are known to include hypertension and tachycardia, followed by later symptoms

which can include peripheral vasodilation, hypotension, cardiac conduction defects, sinus bradycardia or atrioventricular (AV) blocks, and cardiac arrest. Early CNS effects may include paraesthesia, restlessness, tinnitus, muscle twitching, or dizziness followed by later symptoms which can include tonic-clonic seizure, unconsciousness, and respiratory arrest. Treatment of local anesthetic systemic toxicity may include airway management, seizure suppression agents, management of cardiac dysrhythmias, and lipid emulsion therapy.

At the request of FDA, Pacira performed a search of pre-specified Preferred Terms (PTs) related to local anesthetic effects to conservatively assess the risk of local anesthetic systemic toxicity and the potential for a delayed onset of local anesthetic systemic toxicity due to the slow-release properties of EXPAREL. During the sNDA review process, FDA identified additional AEs of interest for Studies 326 and 327 that were not included in the pre-specified list, which were also evaluated by Pacira.

The limitations of this approach should be acknowledged. Many of the events identified are either common effects of local anesthetics or common clinical events associated with surgery (Vaporciyan 2004; Hague 2005; Sohn 2009). In addition, local anesthetic systemic toxicity is a very rare event, and a search of individual PTs is highly sensitive with extremely low specificity.

The percentages of patients reporting any pre-specified terms or any of the additional FDA terms are presented in Table 18. Overall, the frequencies of the pre-specified terms (22% vs 25%) and the additional FDA terms (35% vs 35%) were similar in the pooled EXPAREL and placebo groups. None of the events identified in the pre-specified search or in the search of FDA's additional terms was consistent with a local anesthetic systemic toxicity event.

Table 18: Summary of Patients with AEs Associated with Local Anesthetic Effects in Pooled Nerve Block Studies

	Pooled Nerve Block Studies			
AE Preferred Term	**EXPAREL 133 mg (N=169)**	**EXPAREL 266 mg (N=301)**	**All EXPAREL (N=531)**	**Placebo (N=357)**
Any Pre-specified Term	32 (19%)	75 (25%)	116 (22%)	91 (25%)
Any Pre-specified Term or Additional FDA Term	65 (38%)	99 (33%)	173 (33%)	126 (35%)

The plasma levels commonly associated with local anesthetic systemic toxicity in the scientific literature have been reported as greater than 2,000 ng/mL (Jorfeldt 1968; Knudsen 1997; Bardsley 1998). All bupivacaine plasma concentrations were below this level in the EXPAREL nerve block studies with the exception of one plasma PK sample in Study 322. Patient 202-0001, a 47 year-old white male with sinus tachycardia on the baseline ECG had a plasma bupivacaine concentration of 2,090 ng/mL approximately 30 minutes after administration of EXPAREL 266 mg. The bupivacaine level rapidly dropped to 759 ng/mL within the next 20 minutes and remained below 800 ng/mL for the duration of the study. The plasma concentrations were consistent with inadvertent intravascular administration of EXPAREL, however no AEs were

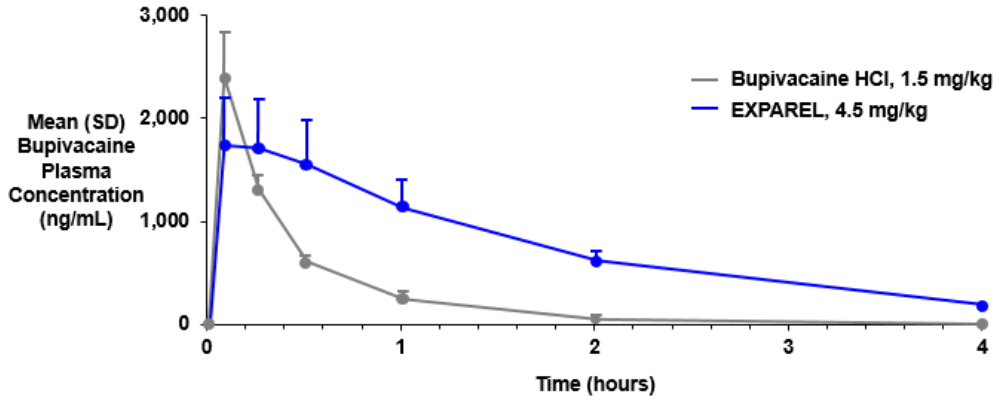
reported for this patient. Post-hoc review of the patient's Holter recording showed tachycardia beginning the day after surgery during which plasma bupivacaine concentrations ranged from 64 to 272 ng/mL. Given the patient's baseline cardiac findings, the tachycardia was not considered to represent an effect of EXPAREL.

In collaboration with the FDA, Pacira has also conducted a review of all suspected cases of local anesthetic systemic toxicity associated with EXPAREL, regardless of type of administration, in its global safety database, which includes cases identified in the scientific literature or through spontaneous reporting from the time of marketing until May 2017. Using the modified criteria recommended by FDA, Pacira identified 63 cases in the postmarketing safety database where local anesthetic systemic toxicity could not be ruled out. Given the 3 million exposures at the time of the assessment, and assuming that each of the cases was definitive, the reported rate of local anesthetic systemic toxicity with EXPAREL would be approximately 0.2 per 10,000 patients, which is lower than the reported rate for epidural and nerve blocks with other local anesthetic agents (0.7-1.8 per 10,000 epidurals and 2.0-2.8 per 10,000 peripheral nerve blocks).

Pacira also conducted a series of pre-clinical studies to evaluate the comparative safety and PK of EXPAREL and bupivacaine HCl after intravascular (IV or intra-arterial [IA]), epidural, and intrathecal administration in dogs. Detailed results of these studies can be found in the primary peer-reviewed publication (Joshi et al 2015). Key findings of these studies include:

- **IV/IA administration**: The maximum dose level at which no meaningful adverse events were observed was several-fold higher with EXPAREL than for bupivacaine HCl (IV: 4.5 mg/kg vs 0.75 mg/kg; IA: 1.5 mg/kg vs 0.1 mg/kg). Adverse clinical signs included transient convulsions, lying on side, and decreased muscle tone. The maximum plasma bupivacaine levels following IV administration of EXPAREL were similar to a threefold *lower* dose of bupivacaine HCl (4.5 mg/kg and 1.5 mg/kg; Figure 27).
- **Epidural administration**: EXPAREL was well tolerated up to the maximum dose tested (40 mg) with less motor blockade than bupivacaine HCl 15 mg and no evidence of spinal cord damage. The maximum plasma bupivacaine levels following epidural administration of EXPAREL were similar to a threefold *lower* dose of bupivacaine HCl (40 mg vs 15 mg).
- **Intrathecal administration**: EXPAREL 40 mg was not associated with significant adverse events and resulted in less motor blockade than bupivacaine HCl 15 mg.

Figure 27: Bupivacaine Concentrations Following Intravascular Administration of EXPAREL and Bupivacaine HCl in Dogs (Joshi et al 2015)



Overall, the comprehensive evaluation of the global clinical database and postmarketing data did not suggest a local anesthetic systemic toxicity safety signal for EXPAREL. Additionally, pre-clinical data suggest that the likelihood of very high circulating bupivacaine levels is lower with EXPAREL than with bupivacaine HCl due to the liposome-bound nature of bupivacaine in EXPAREL.

6.3.2 *Falls*

More falls were reported for patients in the EXPAREL groups (n=12; 2%) than the placebo group (n=1, <1%) in the nerve block studies. The incidence of falls was comparable in the 133 mg (n=4, 2%) and 266 mg (n=8, 3%) groups. All falls among EXPAREL patients in the nerve block program occurred in the TKA studies; the single fall among placebo patients occurred in the TSA/RCR study.

The incidence of falls in the clinical program for EXPAREL is similar to the reported incidence among TKA patients in general. A recent paper reviewing 191,570 TKA patients in 400 acute care hospitals reported that the incidence of in-patient falls was between 1% and 2% regardless of the anesthesia used (ie, general, neuraxial, combined general and neuraxial, or peripheral nerve block) (Memtsoudis et al 2014).

Given that EXPAREL is a long-acting analgesic, and to minimize the risk of falls, Pacira is proposing to incorporate the following statement in the label for EXPAREL: “EXPAREL is not recommended for use as a femoral nerve block if early mobilization and ambulation is part of the patient’s recovery plan.” However, it should be noted that there may be cases when early ambulation is not part of a patient’s recovery plan (eg, lower extremity trauma, tumor removal, deformity correction, amputation) and, in such cases, a long-lasting femoral nerve block could be clinically appropriate.

6.3.3 *Sensory and Motor Function*

Sensory and motor function loss and return were assessed in Studies 326 and 327. Sensation loss was defined as the absence of sensation (ie, cold, pinprick, or light touch) in the proximal or distal part of innervated dermatomes that express the lateral femoral cutaneous nerve (L2/L3)

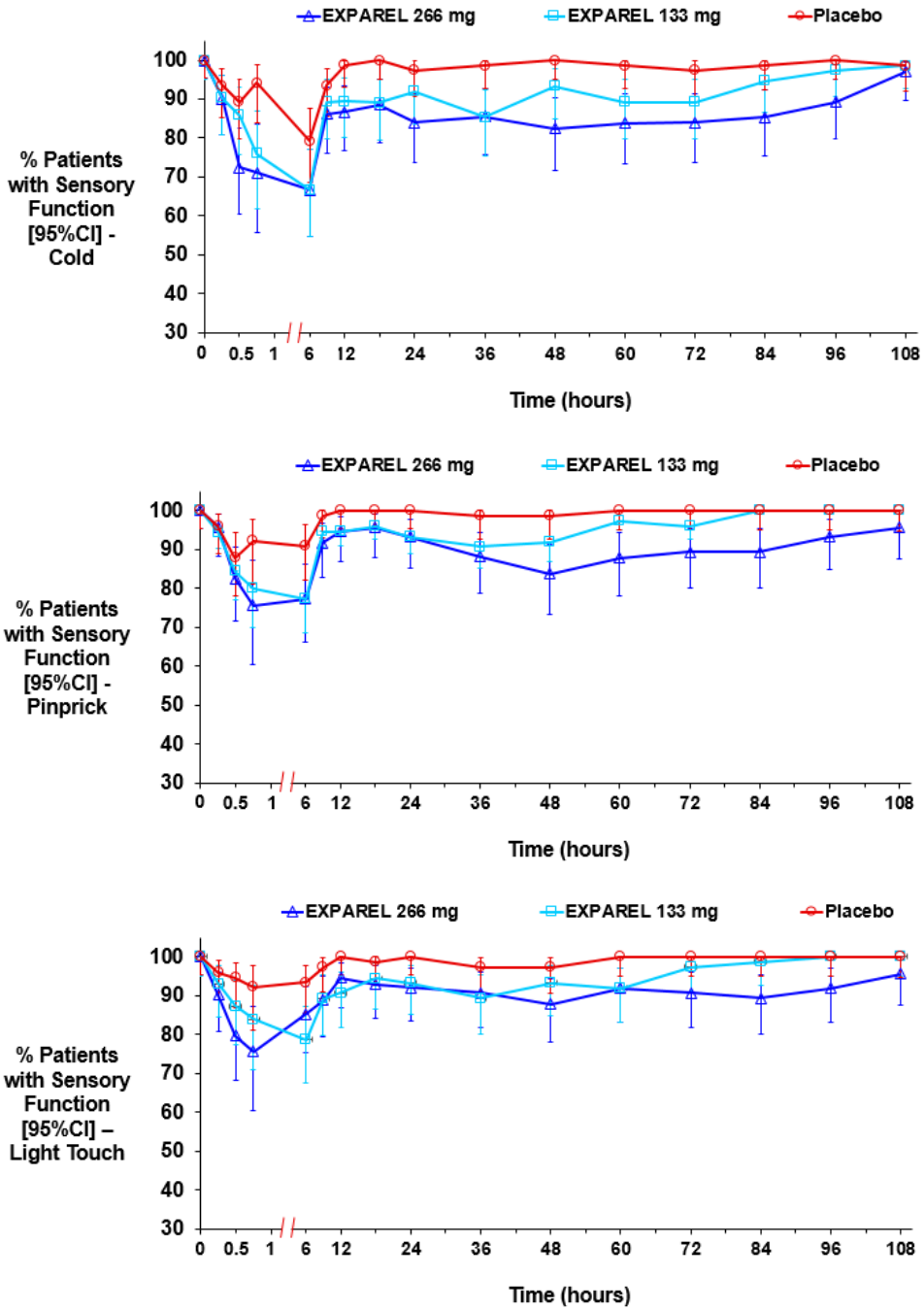
and saphenous nerve (L4) in Study 326, and in the distal part of the innervated dermatomes (musculocutaneous, median, ulnar, radial, or axillary) in Study 327. Motor function was assessed by measuring the change from baseline in knee flexion (active and passive) and extension (active and passive) in Study 326 and by evaluating thumb abduction (radial nerve), thumb adduction (ulnar nerve), thumb opposition (median nerve), and elbow flexion (musculocutaneous nerve) in Study 327.

In both studies, sensory and motor function were present at baseline and, as expected, patients receiving a nerve block experienced a loss of such function as the nerve block took effect and regained function as the effect of the block wore off.

In Study 326, sensory function of the thigh and foot in EXPAREL-treated patients was comparable to placebo by 48 hours in the 133 mg group and 72-84 hours in the 266 mg group (thigh shown in Figure 28).

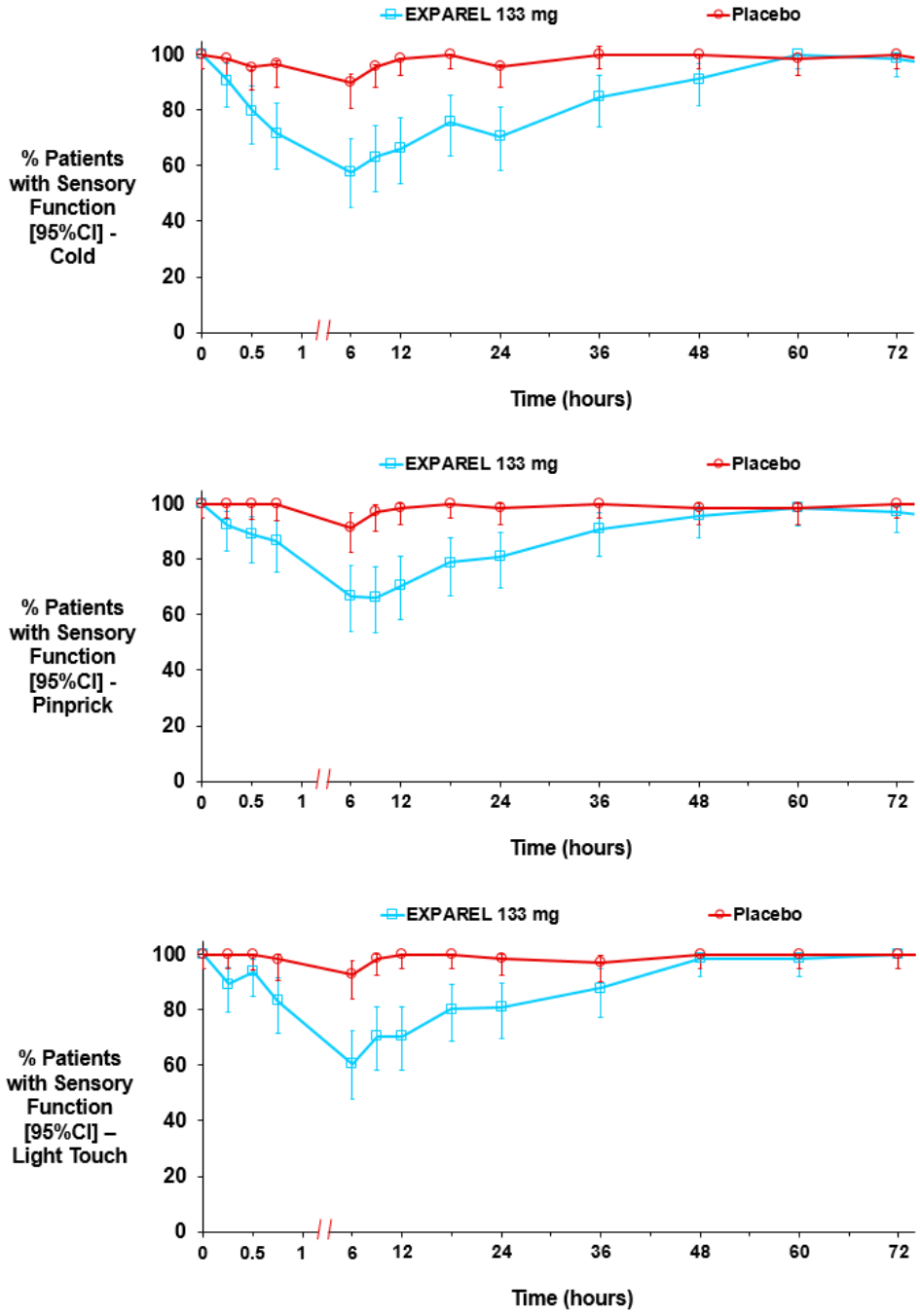
In the assessment of motor function in Study 326, return to function was affected by the nature of the surgery and the presence of a large postoperative bandage used to stabilize the knee. Another confounding factor that may have inhibited patients' willingness to perform the function test was the pain experienced while performing range of motion. However, with these limitations, the proportion of EXPAREL-treated patients who completed extension-flexion motor function test was comparable to placebo at 9-12 hours in the 133 mg group and at 12-18 hours in the 266 mg group. Also, as expected with local anesthetics, motor block occurs later and returns sooner and is dose dependent while sensory block occurs sooner and returns later.

Figure 28: Time Course of Sensory Loss and Return in the Thigh (Study 326)



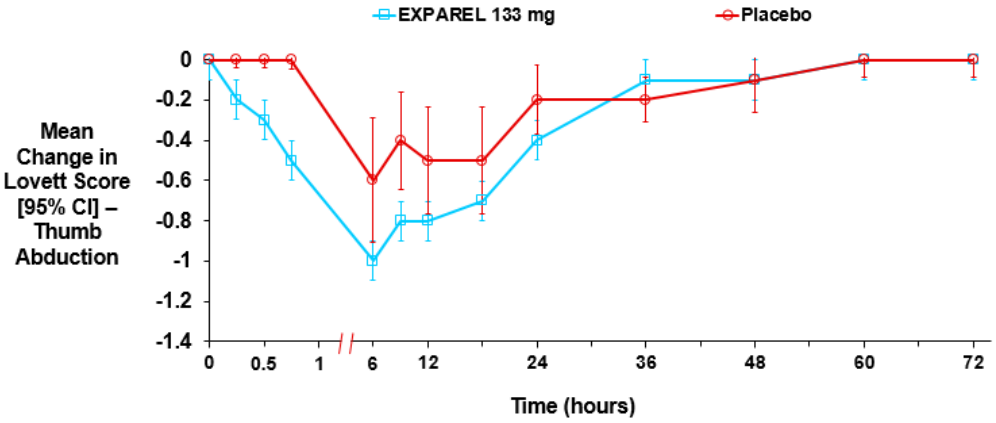
In Study 327, return of sensory function in the EXPAREL groups was comparable to placebo by 48 hours for the 133 mg dose (Figure 29).

Figure 29: Time Course of Sensory Loss and Return for the Shoulder (Study 327)



In the assessment of motor function (elbow and thumb abduction) in Study 327, return to function was affected by patients' willingness to perform the elbow function test due to the pain experienced while performing range of motion. However, with these limitations, the pattern for completion of the motor function test was comparable to placebo at approximately 24 hours in the 133 mg group (Figure 30). As expected and consistent with the nature of the surgery, motor function returned before sensory function.

Figure 30: Time Course of Motor Function Loss and Return (Study 327)



6.4 Cardiovascular Safety

In Studies 322 (thoracotomy) and 323 (TKA) all patients underwent Holter monitoring beginning approximately 1 hour prior to the start of surgery and continuing for up to a total of 72 hours. In order to satisfy data requests from the FDA, the Holter recordings from these studies have undergone substantial review and analysis to address the following aspects of the cardiac safety of EXPAREL:

- Bradycardia and tachycardia as related to local anesthetic systemic toxicity and the assessment of potentially clinically significant abnormal vital signs (see Section 6.4.1)
- FDA-specified "arrhythmias of interest" identified upon retrospective review of the Holter recordings and the impact, if any, of these retrospectively identified events on the established safety profile of EXPAREL (see Section 6.4.2)

Pacira contracted with eResearch Technologies, Inc (ERT) to conduct a full investigation and analysis of the Holter recordings collected in these studies, including:

- A review of each patient's Holter recording to identify any episodes of bradycardia (heart rate ≤ 50 bpm) or tachycardia (heart rate ≥ 100 bpm)
- A review of each patient's Holter recording to identify any FDA-specified arrhythmias of interest
- An independent review of the totality of collected Holter recordings for all patients.

6.4.1 *Tachycardia and Bradycardia*

Upon review of the Holter recordings and investigator-reported AEs, tachycardia was identified during the retrospective review of the Holter recordings far more often than it was reported as an AE by the study investigators and events were generally supraventricular in nature. Overall, retrospective and reported tachycardias were as frequent in the placebo-treated patients as those receiving EXPAREL and were much more often recorded/reported in the thoracotomy study than the TKA study (Table 19).

Bradycardia occurred much less frequently than tachycardia, was reported much less frequently as an AE by the study investigators, and was identified in the retrospective review of Holter recordings only in the thoracotomy study. Bradycardia was reported/recorded at a similar incidence for patients treated with EXPAREL (any dose) and those receiving placebo and more often in the thoracotomy study than the TKA study (Table 19).

Table 19: Incidence of Patients with Tachycardia and/or Bradycardia Reported as AEs or Identified in Retrospective Review Holter Recordings (Studies 322 [Thoracotomy] and 323 [TKA])

	EXPAREL			
Study	**67 mg**	**133 mg**	**266 mg**	**Placebo**
Tachycardia				
322				
Investigator Reported	NA	NA	3/94 (3%)	2/91 (2%)
Retrospective Identification	NA	NA	60/94 (64%)	65/91 (71%)
323				
Investigator Reported	0/22 (0%)	0/24 (0%)	5/116 (4%)	6/116 (5%)
Retrospective Identification	0/22 (0%)	1/24 (4%)	2/116 (2%)	1/116 (1%)
Bradycardia				
322				
Investigator Reported	NA	NA	3/94 (3%)	0/91 (0%)
Retrospective Identification	NA	NA	5/94 (5%)	3/91 (3%)
323				
Investigator Reported	1/22 (5%)	0/24 (0%)	1/116 (1%)	2/116 (2%)
Retrospective Identification	0/22 (0%)	0/24 (0%)	0/116 (0%)	0/116 (0%)

NA=Not applicable; TKA=Total knee arthroplasty

6.4.2 *FDA-Specified Arrhythmias of Interest*

In consultation with the FDA, arrhythmias of interest to be identified during review of the Holter recordings included ventricular and supraventricular arrhythmic events (including non-sustained and sustained ventricular tachycardia), Torsade de Pointes, ventricular fibrillation, atrial fibrillation, atrial flutter, Mobitz Type I (Wenckebach) and Mobitz Type II second-degree AV blocks, 2:1 AV block, high grade AV block, complete heart block, and sinus pause > 3 seconds.

Table 20 presents the arrhythmias of interest that were reported as adverse events or were identified in the retrospective review of the Holter recordings.

Table 20: FDA-Specified Arrhythmias of Interest Reported as AEs or Identified in Retrospective Review of the Holter Recordings (Studies 322 [Thoracotomy] and 323 [TKA])

Arrhythmia of Interest	EXPAREL			
Study	67 mg	133 mg	266 mg	Placebo
Non-sustained ventricular tachycardia (Holter review only/no investigator-reported AEs)				
322	NA	NA	19/95 (20%)	19/92 (21%)
323	3/23 (13%)	2/24 (8%)	16/120 (13%)	13/116 (11%)
Sustained supraventricular tachycardia (Holter review only/no investigator-reported AEs)				
322	NA	NA	1/95 (1%)	2/92 (2%)
323	0/23 (0%)	0/24 (0%)	2/120 (2%)	1/116 (<1%)
Ventricular fibrillation (Holter review only/no investigator-reported AEs)				
322	NA	NA	1/94 (1%)	0/91 (0%)
323	0/22 (0%)	0/24 (0%)	0/116 (3%)	0/116 (0%)
Atrial fibrillation				
322				
Investigator Reported	NA	NA	2/94 (2%)	7/91 (8%)
Holter Identified	NA	NA	13/94 (14%)	12/921 (13%)
323				
Investigator Reported	0/22 (0%)	0/24 (0%)	0/116 (0%)	0/116 (0%)
Holter Identified	2/22 (9%)	0/24 (0%)	4/116 (3%)	5/116 (4%)
Atrial flutter				
322				
Investigator Reported	NA	NA	0/94 (0%)	0/91 (0%)
Holter Identified	NA	NA	2/95 (2%)	3/92 (3%)
323				
Investigator Reported	0/22 (0%)	0/24 (0%)	0/116 (0%)	0/116 (0%)
Holter Identified	0/22 (0%)	0/24 (0%)	0/116 (0%)	3/116 (3%)
Mobitz Type I (Holter review only/no investigator-reported AEs)				
322	NA	NA	3/94 (3%)	4/91 (4%)
323	3/22 (14%)	1/24 (4%)	4/116 (3%)	1/116 (1%)
Mobitz Type II (Holter review only/no investigator-reported AEs)				
322	NA	NA	2/94 (2%)	1/91 (1%)
323	0/22 (0%)	0/24 (0%)	1/116 (<1%)	2/116 (2%)

Arrhythmia of Interest	EXPAREL			
Study	67 mg	133 mg	266 mg	Placebo
2:1 AV Block (Holter review only/no investigator-reported AEs)				
322	NA	NA	3/94 (3%)	5/91 (5%)
323	1/22 (5%)	1/24 (4%)	2/116 (2%)	3/116 (3%)
High Grade AV Block (Holter review only/no investigator-reported AEs)				
322	NA	NA	0/95 (0%)	2/92 (2%)
323	1/23 (4%)	0/24 (0%)	0/120 (0%)	1/116 (1%)
Complete Heart Block (Holter review only/no investigator-reported AEs)				
322	NA	NA	2/95 (2%)	0/92 (0%)
323	0/23 (0%)	0/24 (0%)	0/120 (0%)	1/116 (1%)
Sinus Pause >3 seconds (Holter review only/no investigator-reported AEs)				
322	NA	NA	2/95 (2%)	2/92 (2%)
323	0/22 (0%)	0/24 (0%)	0/116 (0%)	2/116 (0%)
Torsade de Pointes (no identified or reported events)				
322	NA	NA	0/94 (0%)	0/91 (0%)
323	0/22 (0%)	0/24 (0%)	0/116 (0%)	0/116 (0%)

AE=Adverse event; AV= atrioventricular; NA=Not applicable; TKA=Total knee arthroplasty

Overall, there were more electrocardiographic findings in the thoracotomy study (Study 322) and more reported symptoms in the TKA study (Study 323). Cardiac events of major concern such as high-grade heart block, bradyarrhythmias, ventricular tachycardias or ectopy, non-sinus supraventricular tachycardia, and atrial fibrillation, were temporary, uncommon, and evenly observed among EXPAREL and placebo patients in the two studies. Importantly, with regard to FDA's request for assessment of ventricular and supraventricular arrhythmic events, including non-sustained and sustained ventricular tachycardia:

- There were no findings of sustained ventricular tachycardia in any of the Holter recordings for either study.
- Non-sustained ventricular tachycardia was identified only by retrospective review of the Holter recordings and was not reported as AEs by the study investigators in real time.
- Non-sustained ventricular tachycardia was identified in the Holter recordings for a similar proportion of patients in the EXPAREL groups and the placebo groups, with no evidence of a dose response among the EXPAREL groups.
- Of the total 72 patients for whom non-sustained ventricular tachycardia was identified on the Holter review, 90% had no reported cardiac-related AEs. Of the seven patients (four EXPAREL and three placebo patients) with cardiac-related reported AEs, none of the reported events coincided with the recorded non-sustained ventricular tachycardia.

- A total of six patients (three treated with EXPAREL 266 mg and three treated with placebo) showed sustained supraventricular tachycardia on the retrospective review of the Holter recordings. None of these patients had reported cardiac-related AEs that coincided with the recorded sustained supraventricular tachycardia. Sustained ventricular tachycardia was identified only by retrospective review of the Holter recordings and was not reported as AEs by the study investigators in real time.

Addition of the cardiac events identified post-study with Holter recordings to those reported by the investigators increased the numbers of events overall. However, the overall balance between treatment groups did not change, and no new differences in cardiac safety were observed between EXPAREL and placebo.

6.5 Safety by Subgroups

There were no clinically relevant differences in the proportion of patients with AEs, severe AEs, SAEs, or AEs of special interest by age, sex, ethnicity, race, or ASA class. As would be expected, the proportion of patients with AEs, severe AEs, and AEs of special interest was higher among patients with baseline ASA class 3 or 4 than those with a baseline ASA class 1 or 2. However, no differences were noted between the treatment groups.

6.6 Postmarketing Data

EXPAREL was approved by the US FDA in October 2011 for administration into the surgical site to produce postsurgical analgesia. EXPAREL has not been approved and is not marketed anywhere else in the world. Therefore, all the postmarketing experience to date comes from use of the product in the US. Based on internal sales data and the assumption that one sold vial of EXPAREL represents one treated patient, over 3.5 million patients have received EXPAREL in the postmarketing setting to date.

On an ongoing basis, Pacira's Pharmacovigilance/Medical group reviews the medical/scientific literature for abstracts/articles describing adverse experience reports with EXPAREL. In addition, AEs are also collected via company hotlines or email from healthcare professionals, consumers, and company representatives including license partners/company affiliates.

Since US approval of EXPAREL, Pacira has prepared and provided to FDA 14 Periodic Adverse Drug Experience Reports (PADERs). As of October 2016 (the last completed PADER), the most frequently occurring postmarketing adverse events captured in the global safety database were hypoesthesia (n=22 cases), hypotension (n=18), pain (n=18), drug ineffective (n=14), nausea (n=13), bradycardia (n=13), labeled drug-drug interaction medication error (n=11), peroneal nerve palsy (n=11), and erythema (n=11). All postmarketing adverse events are assumed to be at least possibly related to EXPAREL. The most frequently occurring serious unlisted events were bradycardia (n=5), cardiac arrest (n=4), and hypotension (n=4).

Review of these events against the current approved labeling for EXPAREL has not identified any new safety concerns and no changes to the product labeling have been required for safety reasons since initial approval.

6.7 Safety Conclusions

Results of the clinical program demonstrate that EXPAREL is safe and well tolerated when administered as a single-injection nerve block to produce regional analgesia. No clinically meaningful differences were noted in the safety profile of EXPAREL compared with its well-established safety in the current approved indication. Its favorable safety profile as a nerve block is further supported by its well-known profile in the approved indication with more than 3.5 million exposures in the US.

7 CLINICAL SUMMARY

EXPAREL demonstrated efficacy in two pivotal Phase 3 clinical studies, which satisfies the FDA draft guidelines requiring two positive trials for an analgesic intended for general acute pain. As the controlled-release and mechanism of action of bupivacaine following nerve block are the same regardless of anatomical location and surgery type, EXPAREL can be expected to provide effective pain relief in any nerve block setting. The efficacy of EXPAREL was demonstrated in both lower extremity as well as upper extremity surgeries, in both smaller and larger nerves. These surgeries are representative of most of the nerve blocks currently being used in the US. Lastly, in the positive EXPAREL nerve block studies, there were no significant differences in treatment effect across patient subgroups, supporting the use of EXPAREL across different patient populations.

Clinical studies also showed that EXPAREL is safe for its intended use as a nerve block. The safety profile of EXPAREL was generally similar to that observed in the prior studies with infiltration/field block. The safety profile of EXPAREL is also supported by its use in over 3.5 million patients in the US. Furthermore, the API in EXPAREL, bupivacaine, has been used extensively as a nerve block across the world for 6 decades.

Adverse events with EXPAREL are consistent with the use of a local anesthetic as a nerve block. The potential for local anesthetic systemic toxicity associated with inadvertent IV injection of any local anesthetic is rare. The reported rate of local anesthetic systemic toxicity with conventional local anesthetics when used as a peripheral nerve block is 2.0-2.8 per 10,000 patients (El Boghdadly et al 2016). The totality of data from the clinical database, postmarketing database, and preclinical studies suggest that EXPAREL poses no greater risk for local anesthetic systemic toxicity compared to bupivacaine HCl. For EXPAREL, the reported rate of cases where local anesthetic systemic toxicity could not be ruled out is 0.2 per 10,000 patients, which represents a lower reported rate than with conventional local anesthetics. This is consistent with pre-clinical findings which showed that intravascular injection of EXPAREL did not lead to plasma bupivacaine concentrations identified in the literature as associated with cardiotoxicity or neurotoxicity, presumably due to the liposome-bound nature of bupivacaine in the formulation.

The benefit-risk profile of EXPAREL as a nerve block is further enhanced by its opioid-sparing potential. A key contributor to the ongoing opioid crisis has been the prescription of opioids to treat postsurgical pain, as there is a clear association between the duration of postsurgical opioid medication use and persistent opioid use (Brummett et al 2017). While the public health response to the opioid epidemic requires a comprehensive and multifactorial approach including appropriate prescribing, prescription drug monitoring programs, and physician and patient education, among others, one of the components is a reduced reliance on opioid analgesics and the utilization of non-opioid pain medications when medically appropriate.

Numerous studies have shown that EXPAREL reduces exposure to opioids (Gorfine et al 2011; Golf et al 2011; Smoot et al 2012; Lieblich et al 2017; Mont et al 2017). In surgeries ranging

from knee replacements to hemorrhoidectomy, third molar removal, and cesarean sections – the benefits of a single administration of EXPAREL for local analgesia included a reduction in opioid consumption. The reduction in the use of opioid medications with EXPAREL in Studies 327 and 323 as well as the investigator-initiated studies indicate that a decrease in opioid consumption is a likely benefit when EXPAREL is used as a nerve block.

Given the comparability of benefit-risk profiles in the currently-approved indication for infiltration/field block and the proposed indication for nerve block, as well as the important role that EXPAREL is currently playing in postsurgical multimodal pain management, the approval of EXPAREL for use in a regional analgesia setting is justified on the basis of the clinical program and would provide a valuable treatment option for patients who would benefit from a long-acting non-opioid analgesic.

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APPENDIX 1 – SCHEDULE OF STUDY PROCEDURES AND ASSESSMENTS

Study	Type of Procedure	Duration of Procedure (hr)	Timing of Study Drug Administration of	Assessments	Timing of Postsurgical Assessments
322	Thoracotomy	Total n 185 Mean 2.0 StDev 0.9 Min 0.6 Median 2.0 Max 6.5	Immediately prior to surgical wound closure	Timing of assessments was based on the end of surgery	
				Vital signs	1,12,24,48,72 hr
				Neurological assessment	15,30 min; 1,2,4,8,12,18,24,30,36,42,48,60,72 hr
				Holter recording	Start 1 hr prior to surgery; run for a total 72 hours
				Sensory assessment	2,4,12,24,36,48,60,72 hr
				Numeric Rating Scale at Rest (pain assessment)	1,2,4,8,12,24,36,48,60,72 hr; Day 12
				Numeric Rating Scale with Activity (pain assessment)	24,48,72 hr; Day 12
				PK (specific sites only)	15,30 min; 1,2,4,8,12,24,36,48,60, 72 hr
				Overall benefit of analgesia score	24,48,72 hr
				Subject satisfaction with pain control	72hr; Days 12 and 30
				AEs/Concomitant Meds	Through Day 30

Study	Type of Procedure	Duration of Procedure (hr)	Timing of Study Drug Administration of	Assessments	Timing of Postsurgical Assessments
323	TKA	Total n 277 Mean 1.5 StDev 0.6 Min 0.6 Median 1.4 Max 3.8	Within 2 hours prior to surgery	Timing of assessments was based on the end of surgery	
				Numeric Rating Scale at Rest (pain assessment)	2, 4, 8, 12, 24, 36, 48, 60, 72 hr; request for 1st rescue pain med
				Numeric Rating Scale with Activity (pain assessment)	2, 4, 8, 12, 24, 36, 48, 60, 72 hr; request for 1st rescue pain med
				Time of first opioid use	
				Opioid use	Through 72 hr
				Sensory (cold) test	When patient wakes up, 2, 4, 12, 24, 36, 48, 60, and 72 hours after surgery, or until the patient's sensitivity to cold is demonstrated on two consecutive evaluations.
				Overall benefit of analgesia score	24, 48, 72 hr
				Subject satisfaction	72 hr, Day 30
				Opioid-related AEs	Through 72 hr
				PK draw	15 min, 30 min, and 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 hours after the beginning of study drug administration
				Vital Signs	0.5, 1, 2 hr
				Neurological assessment	15 minutes, 30 minutes, and 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 60, and 72 hr
				ECG	Approximately 1 hour before surgery for a total of total of 72 hours
				Motor assessment	24, 72 hr, Day 30
				Physician satisfaction of return of sensory/motor	72 hr, Day 30
				AEs/Concomitant Meds	Through Day 30

Study	Type of Procedure	Duration of Procedure (hr)	Timing of Study Drug Administration of	Assessments	Timing of Postsurgical Assessments
326	TKA	Total n 230 Mean 1.3 StDev 0.3 Min 0.6 Median 1.3 Max 2.5	At least 1 hr prior to surgery	Timing of assessments was based on the beginning of the nerve block.	
				Visual Analog Scale (pain assessment)	Arrival at post-anesthesia care unit (PACU), every15min in PACU, prior to PACU discharge; 6, 12, 24, 36, 48, 60, 72, 84, 96, 108 hr; immediately prior to rescue pain meds through 108 hours
				Opioid medications	Through 108 hr
				Overall benefit of analgesia score	24, 72 hr and Day 10
				Subject satisfaction with pain control	24, 72 hr, Day 10
				Discharge readiness	24, 36, 48, 60, 72, 84, 96 hrs or until discharge ready
				Unscheduled phone calls	Through Day 10
				PK draws (patients assigned to 1 of 2 draw schedules)	Schedule 1: 24, 56, 68, 80, and 108 hr Schedule 2: 48, 60, 76, 96 hr, and Day 6.
				Clinical labs	Day 10
				Vital signs	Every 5 min during performance of the block and up to 30 minutes after the end of the injection, every 15 min until entering the operating room; arrival at PACU; at 6, 9, 12, 24, 36, 48, 56, 60, 64, 68, 72, 76, 80, 84, 96, 108 hr; Days 6 and 10
				ECG	Arrival at PACU; 6, 9, 12, 24, 36, 48, 56, 60, 64, 68, 72, 76, 80, 84, 96, 108 hr; Days 6 and 10
				Neurological assessment	Arrival at PACU; 6, 9, 12, 24, 36, 48, 56, 60, 64, 68, 72, 76, 80, 84, 96, 108 hr; Days 6 and 10

Study	Type of Procedure	Duration of Procedure (hr)	Timing of Study Drug Administra-tion of	Assessments	Timing of Postsurgical Assessments
				Sensory assessment	15, 30, 45 min prior to operating room (OR); discharge from PACU; 6, 9, 12, 18, 24, 36, 48, 60, 72, 84, 96, 108 hr; hospital discharge - Day 6 or Day 10 if necessary
				Motor assessment	15, 30, 45 min prior to OR; discharge from PACU; 6, 9, 12, 18, 24, 36, 48, 60, 72, 84, 96, 108 hr; hospital discharge - Day 6 or Day 10 if necessary
				AEs/Concomitant Meds	Through Day 30

Study	Type of Procedure	Duration of Procedure (hr)	Timing of Study Drug Administration of	Assessments	Timing of Postsurgical Assessments
327	TSA/RCR	Total n 155 Mean 1.3 StDev 0.8 Min 0.3 Median 1.1 Max 4.1	At least 1 hr prior to surgery	Timing of assessments was based on the beginning of the nerve block	
				Visual Analog Scale (pain assessment)	Arrival at PACU, every15min while in PACU, prior to PACU discharge; at 6, 12, 24, 36, 48, 60, and 72 hr; immediately prior to administration of rescue pain meds through 72 hours
				Opioid meds	Through 72 hr
				Overall benefit of analgesia score	24, 72 hr, Day 10
				Subject satisfaction	24, 72 hr, Day 10
				Discharge readiness	12, 24, 36, 48, 60, 72 hr or until discharge ready
				Unscheduled phone calls	Through Day 10
				PK draws (patients assigned to 1 of 2 draw schedules)	Schedule 1: 12, 24, 40, 52, 72 hr Schedule 2: 24, 36, 48, and 60 hr, hospital discharge
				Clinical labs	Day 10
				Vital signs	Every 5min during block through 30 minutes after, every15 min until entering OR; arrival at PACU; at 6, 9, 12, 24, 36, 40, 44, 48, 52, 56, 60, and 72 hr; Days 5 and 10.
				ECG	Arrival at PACU; at 6, 9, 12, 24, 36, 40, 44, 48, 52, 56, 60, and 72 hr; Days 5 and 10
				Neurological assessment	Arrival at PACU; at 6, 9, 12, 24, 36, 40, 44, 48, 52, 56, 60, 72 hr; Days 5 and 10

Study	Type of Procedure	Duration of Procedure (hr)	Timing of Study Drug Administra-tion of	Assessments	Timing of Postsurgical Assessments
				Sensory assessment	15, 30, 45 min prior to OR; prior to discharge from PACU; at 6, 9, 12, 18, 24, 36, 48, 60, and 72 hrs – Day 5, 10, 29 if necessary
				Motor assessment	15, 30, 45 min prior to OR; prior to discharge from PACU; at 6, 9, 12, 18, 24, 36, 48, 60, and 72 hrs – Day 10, 29 if necessary
				AEs/Concomitant Meds	Through Day 30

AE=adverse events; ECG=electrocardiogram; Max=maximum; Meds=medications; Min-minimum; OR=Operating room; PACU=Post-anesthesia care unit; PK=pharmacokinetics; RCR=rotator cuff repair; StDev=standard deviation; TKA=total knee arthroplasty; TSA=total shoulder arthroplasty

APPENDIX 2 – DEATH NARRATIVES

Patient 301-0006 (EXPAREL 266 mg)

Patient 301-0006, a 73 year-old white male, ASA class 1, experienced SAEs of cardiac arrest, cardiac failure acute, and heart injury beginning the same day he underwent posterolateral thoracotomy and received study drug (EXPAREL).

The patient's medical history included left lung carcinoma, chronic cardiac insufficiency, and lower limb varices. His surgical history included appendectomy, tumor excision (left forearm), and reoperation on tumor excision (left forearm). Prior and concomitant medications included heparin-fraction sodium salt, diazepam, beta-lactamase inhibitors, propofol, atracurium besilate, sufentanil citrate, atropine sulfate, neostigmine bromide, aminophylline, sufentanil citrate, pipercuronium bromide, atropine, sodium bicarbonate, nitrazepam, calcium gluconate, sodium chloride, insulin, fentanyl, glucose, and omeprazole.

The patient underwent surgery (left-sided pneumonectomy with pericardial resection and lymphadenectomy) on (b) (6) from 08:42 to 10:51 and received EXPAREL 266 mg at 10:25. Holter monitoring began at 07:33 on (b) (6) and continued until 17:45 on (b) (6).

Following surgery, he received first rescue pain medication (fentanyl 100 mcg IV) at 13:21 (NRS-R 8 prior to first rescue) followed by 1 dose of morphine (10 mg IM) at 15:42. No other pain medication was reported. Total postoperative opioid consumption was 20 mg morphine equivalents.

He experienced cardiac arrest on the day of surgery ((b) (6)), which occurred as a consequence of a cardiac puncture sustained during the surgical procedure. Cardiopulmonary resuscitation was performed and he received epinephrine, suxamethonium chloride, etomidate, and amiodarone. He was also treated with noradrenalin and received "massive volume substitution." Upon transfer to the ICU, he experienced "bleeding from his chest tubes" and was "reoperated on." It was during the second surgery that the pericardial rupture was identified. Despite additional medicinal treatment and repeated resuscitation "with direct and indirect heart massage," the patient died on (b) (6). The cause of death was reported as "acute exacerbation of chronic cardiac insufficiency."

An unscheduled blood sample collected 8.75 hours after study drug administration showed a bupivacaine plasma concentration of 462 ng/mL.

Patient 503-0020 (EXPAREL 266 mg)

Patient 503-0020, a 72 year-old white male, ASA class 3, experienced SAEs of white blood cell (WBC) count increased, renal failure, and cardiac arrest beginning 1 day after undergoing posterolateral thoracotomy and receiving study drug (EXPAREL).

The patient underwent surgery on (b) (6) from 12:50 to 14:10 and received EXPAREL 266 mg at 13:35. Holter monitoring began at 11:41 on (b) (6) and continued until 06:47 on (b) (6). Prior to surgery, the patient was experienced a nonserious event of mild elevated fibrinogen. The event resolved (with sequelae, not otherwise specified) without treatment.

Following surgery, he received first rescue pain medication (fentanyl 100 mcg IV) at 14:45 (NRS-R 9 prior to first rescue) followed by 9 doses of morphine (5-10 mg) from (b) (6) to (b) (6) No other pain medication was reported. Total postoperative opioid consumption was 80 mg morphine equivalents.

On the day after surgery, he experienced nonserious, moderate dizziness. The event was treated the following day (b) (6) with nicergoline and was considered resolved (with sequelae, not otherwise specified) on (b) (6). Also on the day after surgery, he was diagnosed with a serious elevation in white blood cells, which was not treated and was attributed to "the subject's post operative status."

On the morning of postoperative day 3 (b) (6), renal failure was suspected and a gastroscopy was performed (results not reported). The patient experienced a cardiac arrest at 06:51 and resuscitation (epinephrine and dopamine) was unsuccessful. He was pronounced dead at (b) (6) The cardiac arrest was attributed to "suspected renal insufficiency" and not related to study treatment. The renal insufficiency was also not considered to be related to study treatment "but due to an unknown reason." The 3 serious events – elevated WBCs, cardiac arrest and renal failure – were all reported with a fatal outcome. No autopsy results were provided.

No bupivacaine concentration data are available for this patient.

The ECG extracted on post-procedure day 1 at the time of the event of dizziness was interpreted by the independent reviewing cardiologist as being normal and showing sinus tachycardia. Of the triplicate ECGs comprising the patient's baseline, one was interpreted as normal and two were interpreted as abnormal showing "intraventricular conduction defect." Review of all Holter recordings for this patient identified a single event of tachycardia beginning on post-procedure day 2 and lasting for almost 24 hours. The patient experienced a fatal cardiac arrest just after the Holter monitoring ended.

This patient experienced a complicated course following surgery. Review of the reported adverse events and concomitant medications suggests that the patient may have developed disseminated intravascular coagulation (DIC; treatment with enoxaparin) and began to bleed (adverse event of haematochezia and treatment with esomeprazole magnesium and etamsilate). In response to the bleeding, the attending physicians performed a gastroscopy. The DIC ultimately lead to renal failure. (caused by cellular fragments in the glomeruli) and the subsequent cardiac arrest. The dizziness that was reported as an adverse event and the tachycardia that was noted on the review of the Holter were likely due to hypovolemia/hypovolemic shock secondary to the hemorrhaging.

Patient 201-0001 (Placebo)

Patient 201-0001, a 63 year-old white male, ASA class 3, experienced SAEs of respiratory failure, coma uremic, and renal failure acute after undergoing posterolateral thoracotomy and receiving study drug (placebo).

The patient's medical history included lung cancer, COPD, chronic respiratory failure, arterial hypertension, ischemic heart disease, mitral regurgitation, tricuspid regurgitation, nephrolithiasis, myasthenia gravis, and thymectomy. Prior and concomitant medications included pyridostigimine, seretide, bisoprolol, nadroparin, and cefoperazone/sulbactam.

On (b) (6), the patient underwent posterolateral thoracotomy and receive placebo study drug. On (b) (6) he experienced respiratory failure and was discontinued from the study due to this SAE. Treatment included ventilatory support. On (b) (6), the patient experienced acute renal failure and uremic coma. On (b) (6), the patient died. An autopsy was not performed. The outcome for each of the three SAEs was fatal.

The Investigator assessed the events of respiratory failure, acute renal failure, and uremic coma as severe in intensity and unrelated to study drug.

Patient 202-0005 (Placebo)

Patient 202-0005, a 40 year-old white male, ASA class 2, experienced an SAE of myocardial infarction 9 days after undergoing posterolateral thoracotomy and receiving study drug (placebo).

His medical history included lung cancer and right inguinal hernia repair. His surgical history included appendectomy. Prior and concomitant medications included fentanyl.

On (b) (6), the patient underwent posterolateral thoracotomy and received placebo study drug. On (b) (6), he experienced a myocardial infarction. Treatment included cardiopulmonary resuscitation (CPR). On (b) (6), the patient died.

The Investigator assessed the event of myocardial infarction as severe in intensity and unrelated to study drug.

Patient 506-0002 (Placebo)

Patient 506-0002, a 71 year-old white male, ASA class 2, experienced SAEs of pneumonia, sepsis, renal failure, and cardiac arrest after undergoing posterolateral thoracotomy and receiving study drug (placebo).

His medical history included right lung nonmicrocellular cancer, shoulder trauma, arterial hypertension, rheumatoid arthritis, and nausea. His surgical and procedural history included shoulder surgery and endobronchial ultrasound biopsy. Prior and concomitant medications included pantoprazole, chloroquine phosphate, bisoprolol, perindopril, fentanyl, ondansetron, midazolam, ambroxol hydrochloride, sultamicillin, lidocaine hydrochloride, propofol,

cisatracurium besilate, ephedrine hydrochloride, atropine, dopamine, neostigmine, metoclopramide, cefuroxime, insulin, and potassium chloride.

On (b) (6), the patient underwent posterolateral thoracotomy and received placebo study drug. He subsequently experienced SAEs of pneumonia ((b) (6)), sepsis (onset unspecified), renal failure ((b) (6)), and cardiac arrest ((b) (6)). The patient was discontinued from the study due to the pneumonia. Treatment included nitrazepam, heparin sodium, imipenem, amikacin sulfate, furosemide, colistin, sulperazon, mechanical ventilation, renal replacement therapy, and resuscitation. On (b) (6), the patient died. An autopsy was not performed. The outcome for each of the SAEs was fatal.

The Investigator assessed each of the SAEs as severe in intensity and unrelated to study drug.

Patient 506-0017 (Placebo)

Patient 506-0017, a 75 year-old white male, ASA class 2, experienced SAEs of pneumothorax and cardiac arrest 3 days after undergoing posterolateral thoracotomy and receiving study drug (placebo).

His medical history included nodular lesions of both lungs, right lung tumor, varices of the left lower limb, benign prostatic hyperplasia, and benign adenoma. His surgical history included umbilical hernia repair. Prior and concomitant medications included terazosin hydrochloride, omega 3 acids, midazolam, propofol, cisatracurium besilate, fentanyl, cefuroxime, enoxaparin sodium, ambroxol hydrochloride, ciprofloxacin, and clonazepam.

On (b) (6), the patient underwent posterolateral thoracotomy and received placebo study drug. On (b) (6), he experienced SAEs of pneumothorax and cardiac arrest. The patient was discontinued from the study due to the pneumothorax. He underwent a tracheostomy, CPR, and drainage of the pneumothorax. Treatment medications included norepinephrine bitartrate, epinephrine, atropine, and sodium bicarbonate. The cardiac arrest resolved on (b) (6). On (b) (6), the patient died due to the pneumothorax. An autopsy was not performed.

The investigator assessed cardiac arrest and pneumothorax as severe in intensity and unrelated to study drug.