Clinical Study Protocol
Amendment 2

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of Brachial Plexus Block with EXPAREL for Postsurgical Analgesia in Subjects Undergoing Total Shoulder Arthroplasty or Rotator Cuff Repair

Protocol No.:	402-C-327
EudraCT No.:	2015-005228-24
IND No.:	69,198
Study Phase:	Phase 3
Study Drug:	EXPAREL® (bupivacaine liposome injectable suspension)
Date:	14 November 2016 (Amendment 2) 15 February 2016 (Amendment 1) 24 November 2015 (Original)
Investigator(s) or Study Site(s):	Multicenter study in the US and Europe
Sponsor:	Pacira Pharmaceuticals, Inc. 5 Sylvan Way Parsippany, NJ 07054 Telephone: (973) 254-3560

1. SIGNATURE PAGE

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2. SYNOPSIS

Name of Sponsor/Company: Pacira Pharmaceuticals, Inc. 5 Sylvan Way Parsippany, NJ 07054 (973) 254-3560	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: EXPAREL (bupivacaine liposome injectable suspension)		
Name of Active Ingredient: Bupivacaine, 1.3%, 13.3 mg/mL		

Title of Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of Brachial Plexus Block with EXPAREL for Postsurgical Analgesia in Subjects Undergoing Total Shoulder Arthroplasty or Rotator Cuff Repair.

Principal Investigator(s): To be determined

Study Center(s): Multicenter study in the US and Europe

Publications (Reference): None

Objectives:

Primary Objective: The primary objective of this study is to evaluate the magnitude and duration of the analgesic effect achieved following single-dose injection brachial plexus block with EXPAREL in subjects undergoing primary unilateral total shoulder arthroplasty or rotator cuff repair.

Secondary Objectives: The secondary objectives of this study are to assess the efficacy, safety, and pharmacokinetic (PK) profiles of EXPAREL, as well as the onset and duration of sensory and motor function blockade, following administration for analgesia in subjects undergoing primary unilateral total shoulder arthroplasty or rotator cuff repair.

Methodology: This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study in approximately 120 adult subjects undergoing primary unilateral total shoulder arthroplasty or rotator cuff repair with general anesthesia.

Screening

Subjects will be screened within 30 days prior to study drug administration. During the screening visit, which must take place at least 1 day prior to surgery, subjects will be assessed for past or present neurologic, cardiac, and general medical conditions that in the opinion of the investigator would preclude them from study participation. After the informed consent form (ICF) is signed, the patient's eligibility for participation in the study will be confirmed and demographic and baseline characteristics will be recorded. A medical history, surgical history, neurological assessment, sensory and motor function assessments, physical examination, 12-lead electrocardiogram (ECG), vital sign measurements, urine drug screen, blood alcohol test, clinical laboratory tests (hematology, chemistry, and urinalysis), and urine pregnancy test for women of childbearing potential will be conducted.

Day of Surgery

On Day 0, eligible subjects will be randomized in a 1:1 ratio to receive a single dose of either EXPAREL 133 mg in 10 mL expanded in volume with 10 mL of normal saline for a total volume of 20 mL or placebo 20 mL. Subjects may receive acetaminophen/ paracetamol 1000 mg orally (PO) or intravenously (IV) every 8 hours (q8h) (maximum total daily dose of 3000 mg) prior to surgery. Study drug (EXPAREL or placebo) will be administered in a blinded manner via an ultrasound guided single-dose brachial plexus block at least 1 hour prior to surgery. A confirmatory photo of the ultrasound nerve block needle placement will be taken. The type of brachial plexus block (i.e., interscalene or supraclavicular) will be documented. The use of opioids (other than ultrashort-acting opioids [i.e., fentanyl, sufentanil, or remifentanil]), acetaminophen/paracetamol, ketorolac, or other non-steroidal anti-inflammatory drugs (NSAIDs), and local anesthetics other than the study drug will not be permitted intraoperatively, except for emergency use to treat an adverse event (AE).

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Subjects will be required to remain at the hospital facility through 72 hours.

Postsurgical Rescue Medication

Subjects should only receive rescue medication upon request for pain control, as needed. Postsurgical rescue medication will consist of PO immediate-release oxycodone (initiating at 5-10 mg every 4 hours [q4h] or as needed [PRN]). If a subject cannot tolerate PO medication, IV morphine (2.5-5 mg) or hydromorphone (0.5-1 mg) may be administered q4h or PRN. **Patient-controlled analgesia (PCA) is not permitted**. Postsurgically, all subjects will receive acetaminophen/paracetamol up to 1000 mg PO or IV q8h unless contraindicated. The total daily dose of acetaminophen/paracetamol should not exceed 3000 mg.

No other analgesic agents, including NSAIDs, are permitted through 72 hours (postsurgical Day 3). After 72 hours, the analgesic regimen may be adjusted for each subject individually as deemed appropriate by the physician responsible for the postsurgical care.

Postsurgical Assessments

Postsurgical assessments will include:

- Pain intensity scores using a 10-cm visual analog scale (VAS; Appendix 1)
- Total postsurgical opioid consumption
- Overall benefit of analgesia score (OBAS) questionnaire (Appendix 2)
- Subject satisfaction with overall analgesia using a 5-point Likert scale (Appendix 3)
- Neurological assessment (Appendix 4)
- Sensory function assessment (as measured by cold, pinprick, and light touch testing; Appendix 5)
- Motor function assessment (Appendix 6)
- Discharge readiness (Appendix 7)
- Unscheduled phone calls or office visits related to pain
- 12-lead ECGs (ECGs must be read within 2 hours)
- Vital sign measurements
- Clinical laboratory tests (hematology, chemistry, and urinalysis; Appendix 8)

At timepoints when multiple assessments coincide, the pain intensity assessment will be conducted first and the blood draw for PK analysis will be conducted second, as applicable.

Adverse events will be recorded from the time the ICF is signed through postsurgical Day 29. If a cardiac or neurological AE of special interest (AESI), fall, or serious AE (SAE) occurs during the study, an unscheduled PK blood sample must be collected. In addition, a 12-lead ECG, vital signs, and any appropriate clinical laboratory tests must be conducted. If conducted, the ECG must be read within 2 hours.

Cardiac AESIs include chest pain (angina, myocardial infarction), abnormal/irregular heart rate (bradycardia, tachycardia, extrasystoles), and shortness of breath requiring intervention. Neurologic AESIs include altered mental status/altered sensorium, rigidity, dysarthria, seizure, tremors, metallic taste, tinnitus, perioral numbness, visual disturbance, severe or worsening dizziness, and dizziness beyond 72 hours postdose. Additionally, the following events are of special interest if they persist or occur beyond 72-hours postdose: hyperesthesia, muscular twitching, and tingling/paresthesia.

Follow-up visits will be scheduled for all subjects on postsurgical Days 5 and 10. A follow-up phone call will be made on postsurgical Day 29 to all subjects who received study drug to assess for AEs.

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Methodology (Cont.):

Pharmacokinetic Assessment

A population PK analysis will be utilized to limit the number of blood draws. A total of 7 PK samples will be collected from each subject for this study. All subjects will have PK samples taken at baseline and upon arrival at the post-anesthesia care unit (PACU). An additional 5 blood samples will be collected at the assigned time windows, spanning from 12 hours postdose to hospital discharge. There are two PK collection sequences for this study and a subject can only be randomized to one sequence. The PK schedule sequence will be indicated for each subject at the time of randomization and will also be noted on the randomization confirmation. Subjects in Sequence 1 will have samples taken at 12, 24, 40, 52, and 72 hours. Subjects in Sequence 2 will have samples taken at 24, 36, 48, and 60 hours, and at hospital discharge.

Blood samples for PK analysis may be drawn using a properly maintained indwelling cannula (PICC line) at the discretion of the Investigator. Blood samples will be collected from all subjects to maintain the treatment double-blind.

Interim PK Analysis

A blinded interim PK analysis was completed after 13 subjects completed the assessments through postsurgical Day 10. All of the plasma samples from the subjects who received EXPAREL were analyzed and the plasma samples from the subjects randomized to placebo were analyzed through the 24-hour timepoint. Enrollment continued while the interim PK data were analyzed. The goal of this blinded analysis was to determine the appropriateness of the PK timepoints selected and make recommendations to keep, remove, or revise them in order to fully characterize the PK profile.

The results of this analysis showed a median time to maximum plasma concentration (T_{max}) of 48 hours for the 133 mg EXPAREL group and a median T_{max} of 60 hours for the 266 mg EXPAREL group. These data informed the changes to the PK collection schedule contained in this protocol amendment.

In addition, the safety assessment timepoints, including the neurological exam, vital signs, and ECG were adjusted based on the initial interim PK data; a confirmatory blinded PK interim analysis will be conducted once 30 subjects have completed the assessments through postsurgical Day 10.

Number of Subjects (Planned): Approximately 120 subjects (50 subjects randomized to EXPAREL 133 mg, 50 subjects randomized to placebo, and any subjects enrolled under the original protocol and randomized to EXPAREL 266 mg) are planned for enrollment in this study in order to have at least 94 evaluable subjects in the EXPAREL 133 mg and placebo treatment groups.

Eligibility Criteria:

Inclusion Criteria:

1. Male or female, at least 18 years of age at screening.
2. Scheduled to undergo primary unilateral total shoulder arthroplasty or rotator cuff repair.
3. Subjects scheduled for rotator cuff repair must have a magnetic resonance imaging (MRI) with a reading confirming a tear of at least 1 cm.
4. American Society of Anesthesiologists (ASA) physical status 1, 2, or 3.

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5. Female subject must be surgically sterile; or at least 2 years postmenopausal; or have a monogamous partner who is surgically sterile; or practicing double-barrier contraception; or practicing abstinence (must agree to use double-barrier contraception in the event of sexual activity); or using an insertable, injectable, transdermal, or combination oral contraceptive approved by the Food and Drug Administration (FDA) for greater than 2 months prior to screening and commit to the use of an acceptable form of birth control for the duration of the study and for 30 days after completion of the study.
6. Able to demonstrate normal motor function (by obtaining a 5 on the Lovett Scale when exhibiting biceps, wrist, and thumb movement) and sensory function (by exhibiting sensitivity to cold, pinprick, and light touch) in the location where sensory function will be measured throughout the study: 2 cm superior to the coracoid process on the skin overlying the acromioclavicular joint.
7. Able to provide informed consent, adhere to the study visit schedule, and complete all study assessments.

Exclusion Criteria:

1. Currently pregnant, nursing, or planning to become pregnant during the study or within 1 month after study drug administration.
2. Planned concurrent surgical procedure.
3. Concurrent painful physical condition that may require analgesic treatment (such as an NSAID or opioid) in the postsurgical period for pain that is not strictly related to the shoulder surgery and which may confound the postsurgical assessments (e.g., significant pain from other joints, chronic neuropathic pain).
4. History of hypersensitivity or idiosyncratic reaction to amide-type local anesthetics.
5. Smoking history of greater than 25 pack-years.
6. Contraindication to any one of the following: bupivacaine, oxycodone, morphine, or hydromorphone.
7. Use of any of the following medications within the times specified before surgery: long-acting opioid medications or NSAIDs (except for low-dose aspirin used for cardioprotection) within 3 days, or any opioid medication within 24 hours.
8. Initiation of treatment with any of the following medications within 1 month of study drug administration or if the medication(s) are being given to control pain: selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin (Lyrica®), or duloxetine (Cymbalta®). If a subject is taking one of these medications for a reason other than pain control, he or she must be on a stable dose for at least 1 month prior to study drug administration.
9. Current use of systemic glucocorticosteroids within 1 month of enrollment in this study.
10. Use of dexmedetomidine HCl (Precedex®) within 3 days of study drug administration.
11. History of impaired kidney function, emphysema or other chronic respiratory disease, rheumatoid arthritis, coagulopathy, or loss of sensation in extremities.
12. Impaired kidney function (e.g., serum creatinine level >2 mg/dL [176.8 µmol/L] or blood urea nitrogen level >50 mg/dL [17.9 mmol/L]) or impaired liver function (e.g., serum aspartate aminotransferase [AST] level >3 times the upper limit of normal (ULN) or serum alanine aminotransferase [ALT] level >3 times the ULN.
13. Uncontrolled anxiety, psychiatric, or neurological disorder that might interfere with study assessments.
14. Any chronic neuromuscular deficit effecting the peripheral nerves or muscles of the surgical extremity.
15. Any chronic condition or disease that would compromise neurological or vascular assessments.

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16. Malignancy in the last 2 years, with the exception of non-metastatic basal cell or squamous cell carcinoma of the skin or localized carcinoma in situ of the cervix.
17. Suspected or known history of drug or alcohol abuse within the previous year.
18. Body weight <50 kg (110 pounds) or a body mass index >44 kg/m^2.
19. Previous participation in an EXPAREL study.
20. Administration of an investigational drug within 30 days or 5 elimination half-lives of such investigational drug, whichever is longer, prior to study drug administration, or planned administration of another investigational product or procedure during the subject's participation in this study.

Test Product, Dose, Mode of Administration, and Lot Number:

Name: EXPAREL (bupivacaine liposome injectable suspension)

Active ingredient: Bupivacaine 1.3%, 13.3 mg/mL

Dosage: Single dose of 133 mg (10 mL) expanded in volume with 10 mL of normal saline for a total volume of 20 mL

Lot number: To be determined

Mode of administration: Preoperative brachial plexus block

Reference Product, Dose, Mode of Administration, and Lot Number:

Name: Placebo (normal saline)

Active ingredient: Not applicable

Dosage: 20 mL

Lot number: Commercial product to be provided by Pacira

Mode of administration: Preoperative brachial plexus block

Duration of Subject Participation in Study:

Participation will begin at the signing of the ICF. No more than 30 days should pass between signing of the ICF and the administration of study drug. The time from study drug administration through the end of participation is 30 ± 3 days. Therefore, subjects may participate in the study for up to 63 days.

Efficacy Assessments:

The following efficacy measurements will be assessed at the times specified *after the beginning of the brachial plexus block with study drug*:

- Pain intensity scores using the VAS at baseline (on Day 0 prior to the nerve block and prior to any premedication); upon arrival at the PACU, every 15 minutes while in the PACU, and prior to PACU discharge; at 6, 12, 24, 36, 48, 60, and 72 hours; and immediately prior to each administration of rescue pain medication through 72 hours (see Appendix 1).
- Date, time of administration, and amount of all opioid rescue medication taken through 72 hours.
- The OBAS questionnaire at 24 and 72 hours, and on postsurgical Day 10 (see Appendix 2).
- Subject satisfaction with overall analgesia (using a 5-point Likert scale) at 24 and 72 hours, and on postsurgical Day 10 (see Appendix 3).

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- Discharge readiness at 12, 24, 36, 48, 60, and 72 hours or until the subjects is determined to be discharge ready, whichever occurs first (see Appendix 7).
- Unscheduled phone calls or office visits related. to pain after discharge through postsurgical Day 10

Efficacy Endpoints:

The efficacy endpoints listed below will be assessed based on the efficacy measurements conducted at the times specified *after the beginning of the brachial plexus block with study drug*.

Primary Endpoint:

The primary endpoint is the area under the curve (AUC) of the VAS pain intensity scores through 48 hours.

Secondary Endpoints:

The following secondary endpoints will be analyzed in the following order:

- Total postsurgical opioid consumption (in IV morphine equivalents) through 48 hours.
- Percentage of opioid-free subjects through 48 hours.
- Time to first opioid rescue through 48 hours.

Tertiary Endpoints:

- The AUC of the VAS pain intensity scores through 12, 24, and 72 hours.
- The AUC of the VAS pain intensity scores from 24-48 and 48-72 hours.
- VAS pain intensity scores at each assessed timepoint.
- Proportion of subjects who are pain free (defined as a VAS pain intensity score of ≤1.5 without prior rescue medication use) at each assessed timepoint.
- Sum of the pain intensity scores (SPIS) through 24, 48, and 72 hours.
- SPIS from 24-48 and 48-72 hours.
- Total opioid consumption in IV morphine equivalents through 24 and 72 hours.
- Total opioid consumption in IV morphine equivalents from 24-48 and 48-72 hours.
- Percentage of opioid-free subjects through 24 and 72 hours.
- The OBAS total score at 24 and 72 hours, and postsurgical Day 10.
- Subject satisfaction with overall analgesia (using a 5-point Likert scale) at 24 and 72 hours, and postsurgical Day 10.
- Proportion of subjects meeting Modified Postanesthesia Discharge Scoring System (MPADSS) criteria for discharge readiness at 12, 24, 36, 48, 60, and 72 hours.
- Number of unscheduled phone calls or office visits related to pain after discharge through postsurgical Day 10.

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Pharmacokinetic Assessments:
A population PK analysis will be utilized to limit the number of blood draws. A total of 7 PK samples for each subject will be collected for this study. All subjects will have PK samples taken at baseline and upon arrival at the PACU. An additional 5 blood samples will be collected at the assigned time windows shown in Table 2, spanning from 12 hours postdose to 72 hours. There are two PK collection sequences for this study and a subject can only be randomized to one sequence. The PK schedule sequence will be indicated for each subject at the time of randomization and will also be noted on the randomization confirmation. Subjects in Sequence 1 will have samples taken at 12, 24, 40, 52, and 72 hours. Subjects in Sequence 2 will have samples taken at 24, 36, 48, and 60 hours, and at hospital discharge.

Pharmacokinetic Endpoints:
The following PK parameters will be determined:

- AUC from time 0 to the last collection time after drug administration ($AUC_{0\text{-}tlast}$).
- Area under the plasma curve-versus-time curve from time 0 extrapolated to infinity after drug administration ($AUC_{0\text{-}\infty}$).
- Maximum plasma concentration (C_{max}).
- Time to maximum plasma concentration (T_{max}).
- The apparent terminal elimination rate constant (λ_z).
- The apparent terminal elimination half-life ($t_{1/2el}$).

Safety Assessments:
The following safety measurements will be conducted at the specified timepoints *after the beginning of the brachial plexus block with study drug*:

- Clinical laboratory tests (hematology, chemistry, and urinalysis) at baseline (on Day 0 prior to the nerve block) and on postsurgical Day 10 (see Appendix 8).
- Vital signs (resting heart rate and blood pressure) at baseline (on Day 0 prior to the nerve block); every 5 minutes during performance of the block and up to 30 minutes after the end of the injection and then every 15 minutes until entering the operating room (OR); upon arrival at the PACU; at 6, 9, 12, 24, 36, 40, 44, 48, 52, 56, 60, and 72 hours; and on postsurgical Days 5 and 10.
- 12-lead ECG recordings at baseline (on Day 0 prior to the nerve block); upon arrival at the PACU; at 6, 9, 12, 24, 36, 40, 44, 48, 52, 56, 60, and 72 hours; and on postsurgical Days 5 and 10. Note: The ECG must be read within 2 hours.
- Neurological assessment at baseline (on Day 0 prior to the nerve block); upon arrival at the PACU; at 6, 9, 12, 24, 36, 40, 44, 48, 52, 56, 60, 72 hours; and on postsurgical Days 5 and 10 (see Appendix 4).

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- Sensory function assessment (as measured by cold, pinprick, and light touch testing) will be assessed at baseline (on Day 0 prior to the nerve block); at approximately 15, 30, and 45 minutes prior to the OR; prior to discharge from the PACU; at 6, 9, 12, 18, 24, 36, 48, 60, and 72 hours (see Appendix 5). If on postsurgical Day 5 there is a sensory deficit, the sensory deficit will be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent sensory deficit. The sensory function will be further assessed on postsurgical Day 10. If the sensory deficit persists on postsurgical Day 10, the subject is to return for unscheduled visit(s) at the Investigator's discretion through postsurgical Day 29 or until the sensory function has returned to baseline, whichever occurs first.
- Degree of motor nerve block (biceps, wrist, and thumb movement) will be assessed at baseline (on Day 0 prior to the nerve block); at approximately 15, 30, and 45 minutes prior to the OR; prior to discharge from PACU; at 6, 9, 12, 18, 24, 36, 48, 60, and 72 hours (see Appendix 6). If on postsurgical Day 5 there is a motor deficit, the motor deficit will be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent motor deficit. The degree of motor nerve block will be further assessed on postsurgical Day10. If the motor deficit persists on postsurgical Day 10, the subject is to return for unscheduled visit(s) at the Investigator's discretion through postsurgical Day 29 or until the motor function has returned to baseline, whichever occurs first.
- Adverse events from the time the ICF is signed through postsurgical Day 29

Safety Endpoints:

The following safety endpoints will be assessed based on the safety measurements conducted at the specified timepoints:

- Change from baseline in clinical laboratory data at each assessed timepoint.
- Change from baseline in vital sign data (resting heart rate and blood pressure) at each assessed timepoint.
- Change from baseline in ECG data at each assessed timepoint.
- Summary of neurological assessments (proportion of subjects who are oriented, and proportion of subjects who have any of the neurologic events).
- Cold sensation at each assessed timepoint.
- Pinprick sensation at each assessed timepoint.
- Light touch sensation at each assessed timepoint.
- Change from baseline in motor function (biceps, wrist, and thumb movement) at each assessed timepoint.
- Incidence of treatment-emergent AEs (TEAEs) and SAEs through postsurgical Day 29.

Statistical Methods:

A comprehensive statistical analysis plan (SAP) will be developed for this study. Demographic and baseline characteristics will be summarized descriptively by treatment group. Efficacy data will be summarized by treatment group. EXPAREL will be compared with placebo using analysis of variance (ANOVA) with treatment and site as the main effects for the primary efficacy endpoint of AUC of the VAS pain intensity scores through 48 hours. A hierarchical procedure will be used to provide control of the type 1 error across the four key null hypotheses, i.e., for the null hypotheses corresponding to the primary treatment group comparison (EXPAREL 133 mg treatment group versus placebo) in combination with each of the three secondary endpoints of greatest interest. Efficacy endpoints may be analyzed using ANOVA, chi-square tests, and Gehan-Wilcoxon tests, as

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appropriate. Safety endpoints will be summarized descriptively by treatment group. The PK parameters will be calculated using non-compartmental analysis and summarized for each EXPAREL group.

Sample Size

The sample size was calculated based on efficacy as measured by the AUC of the numeric rating scale at rest (NRS-R) pain intensity scores through 72 hours from a previously conducted nerve block study. Assuming a 2-sided 0.05 alpha and a common standard deviation (SD) of 170 and controlling alpha for the two efficacy comparisons, a sample size of 47 subjects per treatment group should have at least 80% power to detect a 100-unit treatment difference. Approximately 120 subjects (50 subjects randomized to EXPAREL 133 mg, 50 subjects randomized to placebo, and any subjects enrolled under the original protocol and randomized to EXPAREL 266 mg) are planned for enrollment in this study in order to have at least 94 evaluable subjects in the EXPAREL 133 mg and placebo treatment groups.

Table 1: Time and Events Schedule of Study Procedures (Screening Visit through PACU Discharge)

	Screen Visit**	D0 Preop	Dosing	15 min	30 min	45 min	OR	PACU Arrival	Every 15 min Up to PACU Discharge	PACU Discharge
Time Window	**Within 30 days**			**±5 min**	**±5 min**	**±5 min**				
Obtain signed ICF	X									
Assess/confirm eligibility	X	X[3]								
Record medical and surgical history	X	X[3]								
Record demographics and baseline characteristics	X									
Conduct pregnancy test for WOCBP	X	X[3]								
Perform physical examination	X									
Urine drug screen and blood alcohol test[1]	X	X[3]								
Clinical labs (hematology, chemistry, and urinalysis)[2]	X	X[3]								
Perform neurological assessment	X	X[3]						X		
Measure vital signs (heart rate and blood pressure)[4]	X	X[3]	From the beginning of dosing, assess vital signs every 5 mins up to 30 mins after completion of the injection then every 15 mins (±5 mins) until OR					X		
Perform 12-lead ECG recordings[5]	X	X[3]						X		
Perform sensory function assessment[6]	X	X[3]		X	X	X				X
Conduct motor function assessment[7]	X	X[3]		X	X	X				X
Record VAS pain intensity scores[8]		X[3]						X	X	X
Collect PK blood sample; record date and time[9]		X[3]						X		
Randomize subject, prepare study drug		X[3]								
Administer blinded study drug via NB at least 1 hour prior to surgery; record start and stop times			X							
Take photo of ultrasound NB needle placement			X							
Record block type (interscalene or supraventricular)			X							
Record intraoperative opioids administered & doses							X			
Record surgery start and stop times							X			
Complete OBAS questionnaire										
Subject satisfaction with postsurgical pain control										
Assess discharge readiness; record date and time										
Record date and time of actual discharge										
Document any unscheduled phone calls or office visits related to pain after discharge	←	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	→
Record prior and concomitant medications, including all analgesics[10]	←	.....	.....	.....	.....	.....	.....	.....	.....	→
Record AEs beginning at the time ICF is signed[2,4,5,9]										

Abbreviations: AE = adverse event; d = day; D = day; ECG = electrocardiogram; h = hour(s), ICF = informed consent form; min = minutes; NB = nerve block; OBAS = overall benefit of analgesia score; OR = operating room; PACU = post-anesthesia care unit; PK = pharmacokinetic; Preop = preoperative; VAS = visual analog scale; WOCBP = women of childbearing potential.

* Postsurgical safety, efficacy, and PK assessments will be conducted at the timepoints specified *after the beginning of the brachial plexus block with study drug*. At timepoints when multiple assessments coincide, the pain intensity assessment will be conducted first and the blood sample for PK analysis will be conducted second, as applicable.

** The screening visit must take place at least 1 day prior to surgery.

[1] A blood alcohol test will be conducted at screening, and an alcohol breath test will be conducted on Day 0.

[2] Also conduct clinical laboratory tests if a subject experiences an AE of special interest (AESI; i.e., cardiac AE or neurological AE), fall, or a SAE; see footnote 9.

[3] Prior to the nerve block with study drug.

[4] Vital signs will be measured after the subject has rested in a supine position for at least 5 minutes. Also measure vital signs if a subject experiences an AESI (i.e., cardiac AE or neurological AE), fall, or an SAE; see footnote 9.

[5] Also conduct a 12-lead ECG if a subject experiences an AESI (i.e., cardiac AE or neurological AE), or an SAE; see footnote 9.

[6] Sensory function will be assessed using cold, pinprick, and light touch testing. If sensory deficit is present at 72 hours, the subject will be assessed on day 5. If on postsurgical Day 5 there is a sensory deficit, the sensory deficit will be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent sensory deficit. If there was a sensory function deficit on Day 5, the sensory function will be further assessed on postsurgical Day 10. If the sensory deficit persists on postsurgical Day 10, the subject is to return for unscheduled visit(s) at the Investigator's discretion through postsurgical Day 29 or until the sensory function has returned to baseline, whichever occurs first.

[7] The motor function assessment (biceps, wrist, and thumb movement) will be assessed using a 0-10 scale of return to motor function. If motor function deficit (Lovett score below 5) is present at 72 hours, the subject will be assessed again on day 5. If on postsurgical Day 5 there is a motor deficit, ie, the subject's Lovett score has not returned to 5, the motor deficit will be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent motor deficit. If there was a motor function deficit on Day 5, the motor assessment will be further assessed on postsurgical Day 10. If the motor deficit persists on postsurgical Day 10, the subject is to return for unscheduled visit(s) at the Investigator's discretion through postsurgical Day 29 or until the motor function has returned to a Lovett score of 5, whichever occurs first.

[8] The preoperative pain intensity assessment should be conducted prior to administration of any premedication. Also record VAS pain intensity score immediately prior to each administration of rescue pain medication through 72 hours.

[9] If a cardiac or neurological AESI, fall, or SAE occurs during the study, an unscheduled PK blood sample must be collected. In addition, a 12-lead ECG, vital signs, and any appropriate clinical laboratory tests must be conducted. Cardiac AESIs include chest pain (angina, myocardial infarction), abnormal/irregular heart rate (bradycardia, tachycardia, extrasystoles), and shortness of breath requiring intervention. Neurologic AESIs include altered mental status/altered sensorium, rigidity, dysarthria, seizure, tremors, metallic taste, tinnitus, perioral numbness, visual disturbance, severe or worsening dizziness, and dizziness beyond 72 hours postdose. Additionally, the following events are of special interest if they persist or occur beyond 72-hours postdose: hyperesthesia, muscular twitching, and tingling/paresthesia.

[10] Instruct subject to discontinue prohibited medications. Record date/time of all medications starting at least 30 days prior to study drug administration through 72 hours after study drug administration. Record all analgesics taken through postsurgical Day 29. Record medications administered for treatment of an AE through postsurgical Day 29.

Table 2: Time and Events Schedule of Study Procedures (6 hours through Day 29)

Time Window	6h ±30 min	9h ±30 min	12h ±30 min	18h ±30 min	24h ±1h	36h ±1h	40h ±1h	44h ±1h	48h ±1h	52h ±2h	56h ±2h	60h ±2h	72h ±2h	Discharge -2h	D5 Visit ±1d	D10 Visit ±1d	D29 Call ±3d
Obtain signed ICF																	
Assess/confirm eligibility																	
Record medical and surgical history																	
Record demographics and baseline characteristics																	
Conduct pregnancy test for WOCBP																	
Perform physical examination																X	
Urine drug screen and blood alcohol test[1]																	
Clinical labs (hematology, chemistry, and urinalysis)[2]																X	
Perform neurological assessment	X	X	X		X	X	X	X	X	X	X	X	X		X	X	
Measure vital signs (heart rate and blood pressure)[4]	X	X	X		X	X	X	X	X	X	X	X	X		X	X	
Perform 12-lead ECG recordings[5]	X	X	X		X	X	X	X	X	X	X	X	X		X	X	
Perform sensory function assessment[6]	X	X	X	X	X	X			X			X	X		X[6]	X[6]	
Conduct motor function assessment[7]	X	X	X	X	X	X			X			X	X		X[7]	X[7]	
Record VAS pain intensity scores[8]	X		X		X	X			X			X	X				
Collect PK blood sample; record date and time[9]			S1		S1, S2	S2	S1		S2	S1		S2	S1	S2			
Randomize subject, prepare study drug																	
Administer blinded study drug via FNB at least 1 hour prior to surgery; record start and stop times																	
Take photo of ultrasound NB needle placement																	
Record block type (interscalene or supraventricular)																	
Record intraoperative opioids administered & doses																	
Record surgery start and stop times																	
Complete OBAS questionnaire					X								X			X	
Subject satisfaction with postsurgical pain control					X								X			X	
Assess discharge readiness; record date and time			X		X	X			X			X	X				
Record date and time of actual discharge															X	X	
Document any unscheduled phone calls or office visits related to pain after discharge															X	X	X
Record prior and concomitant medications, including all analgesics[10]	←																→
Record AEs beginning at the time ICF is signed[2,7,8,9]	←																→

Abbreviations: AE = adverse event; d = day; D = day; ECG = electrocardiogram; h = hour(s), ICF = informed consent form; min = minutes; NB = nerve block; OBAS = overall benefit of analgesia score; OR = operating room; PACU = post-anesthesia care unit; PK = pharmacokinetic; Preop = preoperative; S1 = PK sampling sequence 1; S2 = PK sampling sequence 2; VAS = visual analog scale; WOCBP = women of childbearing potential.

* Postsurgical safety, efficacy, and PK assessments will be conducted at the timepoints specified *after the beginning of the brachial plexus block with study drug*. At timepoints when multiple assessments coincide, the pain intensity assessment will be conducted first and the blood sample for PK analysis will be conducted second, as applicable.

** The screening visit must take place at least 1 day prior to surgery.

[1] A blood alcohol test will be conducted at screening, and an alcohol breath test will be conducted on Day 0.

[2] Also conduct clinical laboratory tests if a subject experiences an AE of special interest (AESI; i.e., cardiac AE or neurological AE), fall, or a SAE; see footnote 9.

[3] Prior to the nerve block with study drug.

[4] Vital signs will be measured after the subject has rested in a supine position for at least 5 minutes. Also measure vital signs if a subject experiences an AESI (i.e., cardiac AE or neurological AE), fall, or an SAE; see footnote 9.

[5] Also conduct a 12-lead ECG if a subject experiences an AESI (i.e., cardiac AE or neurological AE), fall, or an SAE; see footnote 9.

[6] Sensory function will be assessed using cold, pinprick, and light touch testing. . If sensory deficit is present at 72 hours, the subject will be assessed on day 5. If on postsurgical Day 5 there is a sensory deficit, the sensory deficit will be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent sensory deficit. If there was a sensory function deficit on Day 5, the sensory function will be further assessed on postsurgical Day 10. If the sensory deficit persists on postsurgical Day 10, the subject is to return for unscheduled visit(s) at the Investigator's discretion through postsurgical Day 29 or until the sensory function has returned to baseline, whichever occurs first.

[7] The motor function assessment (biceps, wrist, and thumb movement) will be assessed using a 0-10 scale of return to motor function. If motor function deficit (Lovett score below 5) is present at 72 hours, the subject will be assessed again on day 5. If on postsurgical Day 5 there is a motor deficit, ie, the subject's Lovett score has not returned to 5, the motor deficit will be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent motor deficit. If there was a motor function deficit on Day 5, the motor assessment will be further assessed on postsurgical Day 10. If the motor deficit persists on postsurgical Day 10, the subject is to return for unscheduled visit(s) at the Investigator's discretion through postsurgical Day 29 or until the motor function has returned to a Lovett score of 5, whichever occurs first

[8] The preoperative pain intensity assessment should be conducted prior to administration of any premedication. Also record VAS pain intensity score immediately prior to each administration of rescue pain medication through 72 hours.

[9] If a cardiac or neurological AESI, fall, or SAE occurs during the study, an unscheduled PK blood sample must be collected. In addition, a 12-lead ECG, vital signs, and any appropriate clinical laboratory tests must be conducted. Cardiac AESIs include chest pain (angina, myocardial infarction), abnormal/irregular heart rate (bradycardia, tachycardia, extrasystoles), and shortness of breath requiring intervention. Neurologic AESIs include altered mental status/altered sensorium, rigidity, dysarthria, seizure, tremors, metallic taste, tinnitus, perioral numbness, visual disturbance, severe or worsening dizziness, and dizziness beyond 72 hours postdose. Additionally, the following events are of special interest if they persist or occur beyond 72-hours postdose: hyperesthesia, muscular twitching, and tingling/paresthesia.

[10] Instruct subject to discontinue prohibited medications. Record date/time of all medications starting at least 30 days prior to study drug administration through 72 hours after study drug administration. Record all analgesics taken through postsurgical Day 29. Record medications administered for treatment of an AE through postsurgical Day 29.

Table 3: Time and Events Schedule of Study Procedures – Scheduled Pharmacokinetic Samples Blood Draws

Time Window	6h ±30 min	9h ±30 min	12h ±30 min	18h ±30 min	24h ±1h	36h ±1h	40h ±1h	44h ±1h	48h ±1h	52h ±2h	56h ±2h	60h ±2h	72h ±2h	Dis.* -2hr
Sequence 1 (S1): Collect PK blood sample; record date and time			**S1**		**S1**		**S1**			**S1**			**S1**	
Sequence 2 (S2): Collect PK blood sample; record date and time					**S2**	**S2**			**S2**			**S2**		**S2**

*Dis. = hospital discharge, regardless of day.

Note: If a cardiac AE or neurological AESI, fall, or SAE occurs during the study, an unscheduled PK blood sample must be collected. In addition, a 12-lead ECG, vital signs, and any appropriate clinical laboratory tests must be conducted. If conducted, the ECG must be read within 2 hours. Cardiac AESIs include chest pain (angina, myocardial infarction), abnormal/irregular heart rate (bradycardia, tachycardia, extrasystoles), and shortness of breath requiring intervention. Neurologic AESIs include altered mental status/altered sensorium, rigidity, dysarthria, seizure, tremors, metallic taste, tinnitus, perioral numbness, visual disturbance, severe or worsening dizziness, and dizziness beyond 72 hours postdose. Additionally, the following events are of special interest if they persist or occur beyond 72-hours postdose: hyperesthesia, muscular twitching, and tingling/paresthesia.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

4.1. List of Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ANOVA	Analysis of variance
AUC	Area under the curve
$AUC_{0\text{-tlast}}$	Area under the plasma concentration-versus-time curve from the time of administration to the time of the last quantifiable concentration
$AUC_{0\text{-}\infty}$	Area under the plasma concentration-versus-time curve from the time of administration extrapolated to infinity
BDR	Blinded Data Review
CFR	Code of Federal Regulations
CI	Confidence interval
C_{max}	The maximum observed plasma concentration obtained directly from the experimental data without interpolation
CRF	Case Report Form
C_{tlast}	Time of the last quantifiable concentration
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
MPADSS	Modified Postanesthesia Discharge Scoring System
NDA	New Drug Application
NRS	Numeric rating scale
NRS-R	Numeric rating scale at rest
NSAIDs	Non-steroidal anti-inflammatory drugs
OBAS	Overall benefit of analgesia score
OR	Operating room
PACU	Post-anesthesia care unit

PCA	Patient-controlled analgesia
PK	Pharmacokinetic
PO	Oral
PRN	As needed
PT	Preferred term
PTAE	Pretreatment adverse event
q4h	Every 4 hours
q8h	Every 8 hours
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SNRI	Selective norepinephrine reuptake inhibitor
SPIS	Sum of the pain intensity scores
SSRI	Selective serotonin reuptake inhibitor
λ_z	The apparent terminal elimination rate constant
$t_{1/2el}$	The apparent terminal elimination half-life
TEAE	Treatment-emergent adverse event
TKA	Total knee arthroplasty
T_{max}	The time to maximum plasma concentration
ULN	Upper limit of normal
US	United States (of America)
VAS	Visual analog scale

4.2. Definition of Terms

Pharmacokinetic (PK) terms are defined in Section 12.4.

5. ETHICS

5.1. Institutional Review Board/Independent Ethics Committee

Prior to screening subjects into this study, each study site will obtain the approval of an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) that complies with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and/or the United States (US) Food and Drug Administration (FDA) Title 21 Code of Federal Regulations (CFR) Part 56. For study sites with IECs that comply with ICH GCP, but not US FDA 21 CFR Part 56, a waiver request will be submitted to FDA. If granted, then FDA's letter documenting the waiver will be provided to the Investigator to be maintained with the signed Investigator statement (Form FDA 1572) in the Investigator's study binder. Attention is directed to the basic elements that are required to be incorporated into the informed consent form (ICF) under 21 CFR Part 50.25 and ICH GCP.

5.2. Ethical Conduct of the Study

This study will be conducted in accordance with the clinical research guidelines established by the FDA Title 21 CFR, Parts 50, 54, 56, and 312, the Directive 2001/20/EC of the European Parliament and of the Council of 04 April 2001 and amendments, the Commission Directive 2005/28/EC of 08 April 2005 and amendments, and the ICH GCP. Study documents will be maintained in accordance with applicable regulations.

5.3. Subject Information and Consent

Before a subject undergoes any study-specific screening procedures, the Investigator or designee will thoroughly explain to the subject the purpose of the study, the associated procedures, and any expected effects and potential adverse reactions. A copy of the IRB-approved ICF will be provided to the subject, who will be given sufficient time and opportunity to inquire about the details of the study and decide whether or not to participate. The subject, and the study staff with whom he or she discusses the ICF, will sign and date the ICF. A photocopy of the signed ICF will be given to the subject.

The Investigator will explain to the subject that he or she is completely free to decline entry into the study and may withdraw from the study at any time, for any reason, without risking his or her medical care. Similarly, the Investigator and/or Pacira Pharmaceuticals, Inc. (Pacira) is free to withdraw the subject at any time for safety or administrative reasons. Any other requirements necessary for the protection of the human rights of the subject will also be explained, according to the current ICH GCP (E6) and the Declaration of Helsinki (1964, and as amended through 2013).

6. INVESTIGATORS AND STUDY ADMINISTRATION STRUCTURE

Information regarding the Investigators, sites, laboratories, and other service providers is available upon request to the IRB/IECs and regulatory agencies.

7. INTRODUCTION

7.1. Indication

EXPAREL® was developed to provide a prolonged period of decreased pain and decreased opioid use with a single dose administration without the use of indwelling catheters. It is indicated for use as an analgesic injected into the surgical site for postsurgical pain relief.

Effective postsurgical pain control is a critical element in patient recovery following surgery, as the majority of patients may experience significant pain, particularly in the first few days. Improved postsurgical 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 1995).

7.2. Current Therapies/Treatments

Current modalities of postoperative analgesic treatment include wound infiltration and nerve block with local anesthetic agents usually combined with the systemic administration of analgesics (multimodal therapy). Multimodal therapy usually includes opioid medications, non-steroidal anti-inflammatory drugs (NSAIDs), and/or acetaminophen provided through a variety of routes including intravenous (IV), transdermal patch, and oral (PO) administration. Opioids are widely used and considered some of the most powerful analgesics; however, they also have considerable drawbacks including time and resources required for monitoring opioid-related side effects. A reduction in the use of postoperative opioids is desirable to decrease the incidence and severity of opioid-induced adverse effects, such as respiratory depression, nausea, vomiting, constipation, somnolence, pruritus, and urinary retention.

Total shoulder arthroplasty and rotator cuff repair are frequently performed surgical procedures that cause postsurgical pain of considerable intensity and duration. Standard analgesic medications used to provide analgesic relief after surgery include a multimodal approach, often with conventional PO and parenteral analgesia (including NSAIDs, acetaminophen, and narcotics); interscalene analgesia or intra-articular analgesia with or without continuous infusion; or suprascapular nerve block combined with local anesthetic wound infiltration (Beecroft 2008). Therefore, total shoulder arthroplasty and rotator cuff repair were selected as an appropriate pain model(s) for investigating a sustained-release formulation of bupivacaine, which has the potential to overcome the limitation reported in previous studies with regard to the duration of the analgesic effect obtained with commercially-available products.

With over 70 million surgeries performed annually in the US, postoperative pain is a ubiquitous condition among our population. While it 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 (inability to ambulate early, etc.), diminish quality of life, and extend length of stay, thereby increasing hospital expenditures (Oderda 2007) and reducing patient satisfaction. Effective relief of acute pain with minimal opioid complications, on the other hand, may improve clinical outcomes, avoid complications (like delay in regaining bowel function or an inability to tolerate liquid and solid oral intake, etc.), and conserve healthcare resources. As such, the Joint Commission on Accreditation of Healthcare Organizations requires

that all healthcare facilities practice adequate pain management and monitor opioid-related adverse events (AEs) (Apfelbaum 2003).

Opioid analgesics have long been established to be the most effective agents used for the management of moderate to severe postoperative pain, and are currently considered the mainstay of treatment. Adverse events related to opioid administration (e.g., nausea, vomiting, ileus, confusion), however, represent one important reason that there is a need to develop opioid-sparing strategies. Indeed, fear of gastrointestinal side effects such as nausea and vomiting, as well as respiratory depression, present major limitations for the widespread use of opioid analgesics (Chernin 2001 and Viscusi 2009). Furthermore, management of opioid-related events often requires medical attention (e.g., opioid antagonists, antiemetic agents) and increased pharmacy/nursing time, which may raise healthcare expenses (Carroll 1994).

7.3. EXPAREL (bupivacaine liposome injectable suspension)

Bupivacaine is one of the longer-acting local anesthetics, but even so it has a limited duration of action after local administration, usually reported as less than 8 hours. EXPAREL (Pacira Pharmaceuticals, Inc., Parsippany, NJ) is a bupivacaine liposome injectable suspension. It consists of microscopic spherical, multivesicular liposomes (DepoFoam® drug delivery system), organized in a honeycomb-like structure comprising numerous non-concentric internal aqueous chambers containing a bupivacaine base at a concentration of 13.3 mg/mL. Each chamber is separated from adjacent chambers by lipid membranes. The lipids (phospholipids, cholesterol, and triglycerides) are naturally occurring or close analogs of endogenous lipids. 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. A small amount of extra-liposomal bupivacaine (i.e., not bound within the DepoFoam particles) enables EXPAREL to have a similar onset of action to standard bupivacaine HCl. Because of this, EXPAREL has been noted in wound infiltration studies to have a bimodal curve (Apseloff 2013), with an initial peak at approximately 0-2 hours and a second peak at approximately 24-48 hours (Hu 2013).

EXPAREL was approved by the US FDA in 2011 for administration into the surgical site to produce postsurgical analgesia. The active ingredient (bupivacaine) and inactive ingredient (DepoFoam) of EXPAREL are each contained, though separately, in FDA-approved products:

- Bupivacaine HCl solution, a well-characterized anesthetic/analgesic, with more than 35 years of its use in the US.
- DepoFoam, a liposomal extended-release formulation contained in the marketed product DepoCyt® (1999). The form of DepoFoam used in each of the products – DepoCyt and EXPAREL – has a slightly different mixture of lipid components.

7.4. Summary of Human Experience with EXPAREL

7.4.1. Wound Infiltration New Drug Application (NDA)

During the original clinical development program (wound infiltration), Pacira conducted 21 clinical studies and one observational follow-up study (SKY0402-C-318) to investigate EXPAREL (formerly known as SKY0402™). Across these studies, a total of 1307 human

subjects received EXPAREL at doses ranging from 10-750 mg (or 9-665 mg free base) and by various routes: local administration into the surgical wound, subcutaneous, perineural, and epidural. The investigational drug product has been well tolerated and the reported AEs occurred at a similar rate as the corresponding bupivacaine HCl controls in the active comparator studies.

In doses up to 665 mg of EXPAREL, no signal of any of the central nervous system or cardiovascular system AEs observed with high doses of bupivacaine HCl solution have been observed. Two thorough QTc studies have been conducted; EXPAREL did not cause significant QTc prolongation even at the highest dose evaluated.

Across all studies, the types of treatment-emergent AEs (TEAEs) reported and the incidence rates generally were similar between the EXPAREL All Doses group (all doses combined) and the bupivacaine HCl group. The incidence rate for each of the three most common TEAEs (nausea, constipation, and vomiting) was lower in the EXPAREL All Doses group than in the bupivacaine HCl group.

EXPAREL was demonstrated to produce statistically significant and clinically meaningful analgesia in two pivotal placebo-controlled Phase 3 studies (SKY0402-C-317 and SKY0402-C-316) involving both orthopedic and soft tissue procedures over 36 and 72 hours, respectively. In addition to meeting their primary endpoints (area under the curve [AUC] of the numeric rating scale [NRS] at rest [NRS-R] pain intensity scores through 72 hours [Study SKY0402-C-316] and through 24 hours [Study SKY0402-C-317]), key secondary endpoints also were met, demonstrating prolonged analgesia and reduction of opioid use by various measures (percentage of subjects who received no supplementary opioid medication; total amount of postoperative consumption of opioid medication; and time to first use of opioid medication). The robust nature of the efficacy results in both pivotal studies SKY0402-C-316 and SKY0402-C-317 was demonstrated across subgroups of subjects with various prognostic features and across demographic subgroups.

An analysis was performed to compare the incidence of opioid-related AEs between the EXPAREL and bupivacaine HCl groups in all bupivacaine-controlled, parallel-group wound infiltration studies (SIMPLE TKA 311, SKY0402-C-208, SIMPLE Hemorrhoidectomy 312, SKY0402-C-209, SKY0402-C-207, SKY0402-C-201, and SIMPLE Breast Augmentation 315). There was a statistically significantly lower incidence of opioid-related AEs in the EXPAREL ≤300 mg group compared to the bupivacaine HCl group through 72 hours postdose. This was consistent with the statistically significantly lower total postoperative consumption of opioids in the EXPAREL ≤300 mg group through 72 hours postdose. Fewer subjects in the EXPAREL ≤300 mg group had at least one opioid-related AE compared to the bupivacaine HCl group (25.6% versus 45.6%; $p<0.0001$). The total opioid medication administered (adjusted geometric mean) through 72 hours postdose was statistically significantly lower in the EXPAREL ≤300 mg group (7.94 mg) compared to the bupivacaine HCl group (15.84 mg); $p<0.0001$. The EXPAREL >300 mg group did not show a statistically significant advantage favoring EXPAREL; the mean (standard deviation [SD]) of the average number of opioid-related AEs per subject was 0.58 (0.522), and the total opioid medication administered (adjusted geometric mean) through 72 hours postdose was 22.82 mg in the EXPAREL >300 mg group.

Please see the EXPAREL Full Prescribing Information for safety information regarding the use of EXPAREL for the treatment of postsurgical pain in the setting of wound infiltration.

7.4.2. Nerve Block Supplemental NDA

A total of 335 human subjects received EXPAREL as a nerve block over six clinical studies (SKY0402-002, SKY0402-C-111, SKY0402-C-203, SKY0402-C-211, 402-C-322, and 402-C-323) utilizing three different surgical models (femoral nerve block, intercostal nerve block, and ankle nerve block). Doses administered ranged from 2 mg to 310 mg. The data from three of these studies (SKY0402-002, SKY0402-C-203, and SKY0402-C-211) were included in the wound infiltration NDA as well as the nerve block supplemental NDA. As of May 2015, these are the only six studies Pacira has conducted in the setting of nerve block in human subjects.

Phase 3 Nerve Block Studies

Study 402-C-322 was a Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled study to investigate the efficacy and safety of EXPAREL (total of 266 mg in 20 mL) divided into three equal doses in three syringes of approximately 88 mg in 6.6 mL volume per nerve and administered to each of three nerve segments (index nerve, nerve above, and nerve below) compared with saline placebo nerve block. The primary objective was to evaluate the efficacy of intercostal nerve block using EXPAREL compared with placebo in subjects undergoing posterolateral thoracotomy.

Intercostal nerve block with EXPAREL was well tolerated in subjects undergoing posterolateral thoracotomy. However, the study did not meet its primary efficacy endpoint: there was no statistically significant difference in the mean AUC of the NRS-R pain intensity scores through 72 hours between subjects in the EXPAREL group and in the placebo group although a treatment effect was evident through 12 to 24 hours based upon a post hoc analysis.

Fifty-six subjects (59.6%) in the EXPAREL group and 46 subjects (50.5%) in the placebo group experienced one or more TEAEs. Most of the TEAEs were mild or moderate in severity. Three subjects (3.2%) in the EXPAREL group and no subjects in the placebo group experienced a TEAE that were assessed by the Investigator as related to study drug. Twelve subjects (12.8%) in the EXPAREL group and 9 subjects (9.9%) in the placebo group experienced one or more treatment-emergent serious AEs (SAEs). Two of these subjects in the EXPAREL group and four of these subjects in the placebo group died. None of the SAEs or deaths was assessed by the Investigator as related to study drug. Two subjects (2.1%) in the EXPAREL group and seven subjects (7.4%) in the placebo group were withdrawn from the study due to an AE.

Study 402-C-323 was a Phase 2/3, multicenter, randomized, double-blind, parallel-group, placebo-controlled, dose-ranging study in subjects undergoing primary unilateral total knee arthroplasty (TKA) under general or spinal anesthesia. The primary objectives of Part 1 were to (1) evaluate three dose levels of EXPAREL versus placebo with respect to the magnitude and duration of the analgesic effect achieved following single dose injection femoral nerve block with EXPAREL, and (2) select a single therapeutic dose of EXPAREL from the three dose levels to be tested in Part 2.

The primary objective of Part 2 was to compare the magnitude and duration of the analgesic effect of single injection femoral nerve block of a single dose level of EXPAREL (selected from Part 1) with placebo (preservative-free normal saline for injection).

Femoral nerve block with EXPAREL at 67 mg, 133 mg, and 266 mg was well tolerated in subjects undergoing TKA. There were no discernible safety differences across the treatment

groups. There was a dose response in EXPAREL-treated subjects. A dose of 266 mg was selected for Part 2.

Part 2 of the study met its primary efficacy endpoint: the difference in the AUC of the NRS-R pain intensity scores through 72 hours between the EXPAREL group and the placebo group was statistically significant. Additionally, the difference in the total postsurgical opioid consumption (mg) through 72 hours between the EXPAREL 266 mg group and the placebo group was statistically significant indicating lower opioid consumption in the EXPAREL group.

In Part 1, there were no discernible safety differences across the treatment groups. In Part 2, the incidences of TEAEs and treatment-emergent SAEs were similar between the EXPAREL 266 mg group and the placebo group. There were no deaths or withdrawals due to an AE during the study.

During Part 2 of the study, three subjects experienced a fall; each subject was in the EXPAREL 266 mg group. Each of the three subjects was able to complete the 20-meter walk test at 24 hours, 72 hours, and on Day 30. The rate of inpatient falls in study 402-C-323, 1.8%, was very similar to the overall incidence of inpatient falls in TKA patients (between 1% and 2%).

The 20-meter walk test was used to determine whether there was any significant degree of motor blockade with use of EXPAREL. The percentage of subjects who were able to complete the walk test at 24 hours and 72 hours did not differ significantly across the EXPAREL and placebo groups in Part 1. In Part 2, the percentage of subjects who were able to complete the walk test was comparable between EXPAREL 266 mg and placebo groups at 24 hours (53.0% vs. 58.5%, respectively) and 72 hours (83.1 vs. 92.6%, respectively). This suggested a lack of significant motor blockade with EXPAREL. This is confirmed by physician satisfaction with return of sensory/motor function.

Pooled Nerve Block Safety Data

In the All Studies pool, 335 subjects received EXPAREL (All Doses), 33 subjects received bupivacaine HCl, and 207 subjects received placebo.

Overall, 184/335 subjects (54.9%) in the EXPAREL All Doses group, 15/35 subjects (45.5%) in the bupivacaine HCl group, and 99/207 subjects (47.8%) in the placebo group experienced at least one TEAE in a preferred term (PT) that had an incidence of ≥2%. The incidence and types of TEAEs (PTs) were similar between the EXPAREL All Doses group and the placebo group.

In the EXPAREL All Doses group, the TEAEs reported with an incidence ≥2% were anemia (5.1%), bradycardia (2.1%), sinus tachycardia (2.1%), constipation (13.4%), feeling cold (3.3%), local swelling (2.1%), pyrexia (20.3%), procedural hypotension (5.1%), body temperature increased (2.4%), headache (4.5%), hypoesthesia (7.8%), paresthesia (2.1%), urinary retention (4.2%), and pruritus (12.2%).

In the EXPAREL 266 mg group, the TEAEs reported with an incidence ≥2% were anemia (5.7%), sinus tachycardia (2.4%), constipation (18.1%), feeling cold (4.8%), local swelling (2.9%), pyrexia (24.3%), procedural hypotension (6.2%), body temperature increased (3.8%), mobility decreased (2.9%), headache (3.3%), hypoesthesia (2.4%), urinary retention (5.7%), and pruritus (16.7%).

In the bupivacaine HCl group (N=33 subjects), the TEAEs reported with an incidence ≥2% were abdominal pain (3.0%), diarrhea (6.1%), flatulence (3.0%), chills (3.0%), injection site

discomfort (3.0%), injection site erythema (9.1%), pyrexia (6.1%), drug hypersensitivity (3.0%), procedural hypotension (3.0%), back pain (6.1%), joint swelling (3.0%), headache (6.1%), hypoesthesia (24.2%), paresthesia (12.1%), nasal congestion (3.0%), and oropharyngeal pain (3.0%).

In the placebo group, the TEAEs reported with an incidence ≥2% were anemia (3.9%), constipation (16.9%), feeling cold (3.9%), local swelling (2.4%), pyrexia (18.8%), procedural hypotension (2.9%), mobility decreased (2.4%), headache (3.4%), urinary retention (2.9%), and pruritus (15.9%).

There were 17 TEAEs (anemia, bradycardia, sinus tachycardia, constipation, diarrhea, feeling cold, injection site erythema, pyrexia, postoperative wound infection, procedural hypotension, back pain, cluster headache, hypoesthesia, paresthesia, urinary retention, and pruritus) that occurred at an incidence of ≥5% in the EXPAREL 266 mg group where the incidence was greater in the EXPAREL group than in the placebo group.

Please refer to the Investigator's Brochure for additional information regarding the completed studies.

7.5. Postmarketing

As of June 2016, more than 2 million patients have received EXPAREL in the postmarketing setting.

8. OBJECTIVES

8.1. Primary Objectives

The primary objective of this study is to evaluate the magnitude and duration of the analgesic effect achieved following single-dose injection brachial plexus block with EXPAREL in subjects undergoing primary unilateral total shoulder arthroplasty or rotator cuff repair.

8.2. Secondary Objectives

The secondary objectives of this study are to assess the efficacy, safety, and PK profiles of EXPAREL, as well as the onset and duration of sensory and motor function blockade, following administration for analgesia in subjects undergoing primary unilateral total shoulder arthroplasty or rotator cuff repair.

9. STUDY DESIGN AND PLAN

9.1. Study Design

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study in approximately 120 adult subjects undergoing primary unilateral total shoulder arthroplasty or rotator cuff repair with general anesthesia.

Subjects will be screened within 30 days prior to study drug administration. During the screening visit, which must take place at least 1 day prior to surgery, subjects will be assessed for past or present neurologic, cardiac, and general medical conditions that in the opinion of the Investigator would preclude them from study participation. After the ICF is signed, the patient's eligibility for participating in the study will be confirmed and demographic and baseline characteristics will be recorded. A medical history, surgical history, neurological assessment, sensory and motor function assessments, physical examination, 12-lead electrocardiogram (ECG), vital sign measurements, urine drug screen, blood alcohol test, clinical laboratory tests (hematology, chemistry, and urinalysis), and urine pregnancy test for women of childbearing potential will be conducted.

On Day 0, eligible subjects will be randomized in a 1:1 ratio to receive a single dose of EXPAREL 133 mg in 10 mL expanded in volume with 10 mL of normal saline for a total volume of 20 mL or placebo 20 mL. Subjects may receive acetaminophen/paracetamol 1000 mg PO or IV every 8 hours (q8h) (maximum total daily dose of 3000 mg) prior to surgery.

Study drug (EXPAREL or placebo) will be administered in a blinded manner via an ultrasound guided single-dose brachial plexus block at least 1 hour prior to surgery. A confirmatory photo of the ultrasound nerve block needle placement will be taken. The type of brachial plexus block (i.e., interscalene or supraclavicular) will be documented. The use of opioids (other than ultrashort-acting opioids [i.e., fentanyl, sufentanil, or remifentanil]), acetaminophen/paracetamol, ketorolac, or other NSAIDs, and local anesthetics other than the study drug will not be permitted intraoperatively, except for emergency use to treat an AE.

Subjects will be required to remain at the hospital facility through 72 hours.

Postsurgical Rescue Medication

Subjects should only receive rescue medication upon request for pain control, as needed. Postsurgical rescue medication will consist of PO immediate-release oxycodone (initiating at 5-10 mg every 4 hours [q4h] or as needed [PRN]). If a subject cannot tolerate PO medication, IV morphine (2.5-5 mg) or hydromorphone (0.5-1 mg) may be administered q4h or PRN. **Patient-controlled analgesia (PCA) is not permitted**. Postsurgically, all subjects will receive acetaminophen/paracetamol up to 1000 mg PO or IV q8h unless contraindicated. The total daily dose of acetaminophen/paracetamol should not exceed 3000 mg.

No other analgesic agents, including NSAIDs, are permitted through 72 hours. After 72 hours, the analgesic regimen may be adjusted for each subject individually as deemed appropriate by the physician responsible for the postsurgical care.

Postsurgical Assessments

Postsurgical assessments will include pain intensity scores using a 10-cm visual analog scale (VAS; see Appendix 1); total postsurgical opioid consumption; overall benefit of analgesia score (OBAS) questionnaire (see Appendix 2); subject satisfaction with overall analgesia using a 5-point Likert scale (see Appendix 3); neurological assessment (see Appendix 4); sensory function assessment (as measured by cold, pinprick, and light touch testing; see Appendix 5); degree of motor nerve block (biceps, wrist, and thumb movement; see Appendix 6); discharge readiness (see Appendix 7); unscheduled phone calls or office visits related to pain; 12-lead ECGs; vital sign measurements; and clinical laboratory tests (hematology, chemistry, and urinalysis; see Appendix 8). At timepoints when multiple assessments coincide, the pain intensity assessment will be conducted first and the blood draw for PK analysis will be conducted second, as applicable.

Adverse events will be recorded from the time the ICF is signed through postsurgical Day 29. If a cardiac or neurological AE of special interest (AESI), fall or SAE occurs during the study, an unscheduled PK blood sample must be collected. In addition, a 12-lead ECG, vital signs, and any appropriate clinical laboratory tests must be conducted. If conducted, the ECG must be read within 2 hours. Cardiac AESIs include chest pain (angina, myocardial infarction), abnormal/ irregular heart rate (bradycardia, tachycardia, extrasystoles), and shortness of breath requiring intervention. Neurologic AESIs include altered mental status/altered sensorium, rigidity, dysarthria, seizure, tremors, metallic taste, tinnitus, perioral numbness, visual disturbance, severe or worsening dizziness, and any dizziness beyond 72 hours postdose. Additionally, the following events are of special interest if they persist or occur beyond 72-hours postdose: hyperesthesia, muscular twitching, and tingling/paresthesia.

Follow-up visits will be scheduled for all subjects on postsurgical Days 5 and 10. A follow-up phone call will be made on postsurgical Day 29 to all subjects who received study drug to assess for AEs.

Pharmacokinetic Assessment

A population PK analysis will be utilized to limit the number of blood draws. A total of 7 PK samples will be collected from each subject for this study. All subjects will have PK samples taken at baseline and upon arrival at the PACU. An additional 5 blood samples will be collected at the assigned time windows, spanning from 12 hours postdose to hospital discharge. There are two PK collection sequences for this study and a subject can only be randomized to one sequence. The PK schedule sequence will be indicated for each subject at the time of randomization and will also be noted on the randomization confirmation. Subjects in Sequence 1 will have samples taken at 12, 24, 40, 52, and 72 hours. Subjects in Sequence 2 will have samples taken at 24, 36, 48, and 60 hours, and at hospital discharge.

Blood samples for PK analysis may be drawn using a properly maintained indwelling cannula (PICC line) at the discretion of the Investigator. Blood samples will be collected from all subjects to maintain the treatment double-blind. Blood samples from the subjects randomized to placebo will be analyzed through the 24-hour timepoint.

Interim PK Analysis

A blinded interim PK analysis was completed after 13 subjects completed the assessments through postsurgical Day 10. All of the plasma samples from the subjects who received EXPAREL were analyzed and the plasma samples from the subjects randomized to placebo were analyzed through the 24-hour timepoint. Enrollment continued while the interim PK data were analyzed. The goal of this blinded analysis was to determine the appropriateness of the PK timepoints selected and make recommendations to keep, remove, or revise them in order to fully characterize the PK profile.

The results of this analysis showed a median T_{max} of 48 hours for the 133 mg EXPAREL group and a median T_{max} of 60 hours for the 266 mg EXPAREL group. These data informed the changes to the PK collection schedule contained in this protocol amendment.

In addition, the safety assessment timepoints, including the neurological exam, vital signs, and ECG were adjusted based on the initial interim PK data; a confirmatory blinded PK interim analysis will be conducted once 30 subjects have completed the assessments through postsurgical Day 10.

Duration of the Study and Subject Participation

Participation will begin at the signing of the ICF. No more than 30 days should pass between signing of the ICF and the administration of EXPAREL. The time from study drug administration through the end of participation is 30 ± 3 days. Therefore, subjects may participate in the study for up to 63 days.

Study Stopping Rules

If Pacira, the investigator, or officials from regulatory authorities discover conditions during the study that indicate that the study or study site should be terminated, this action may be taken after Pacira has consulted with appropriate regulatory authorities and notified the Investigator(s).

Blinded Data Review (BDR) of the subject data will be conducted by an independent Safety Monitor Committee after the first 30 subjects have completed Day 29 and subsequently after every 30 subjects have completed Day 29. The independent Safety Monitors will communicate their review findings to the Pacira Medical Management and Biostatistics team and records will be maintained.

The outcome of the BDR process may trigger the Safety Stopping Rules based on the incidence rate of serious or severe AE based on the following rules:

- Incidence rate of severe or serious AESIs as defined by the protocol including cardiac AESIs and neurologic AESIs exceeding 5% and in at least 5 subjects
- Incidence rate of severe dizziness exceeding 10% and in at least 5 subjects
- Incidence rate of severe or SAEs regardless of relationship to study drug exceeding 20% and in at least 10 subjects

The study will be halted and an unblinded review of the data and a relative risk data analysis will occur if the study stopping rule is triggered. If the relative risk is greater than 2, the next step will be one of the following actions:

- Permanently stop the study

- Revise eligibility criteria to exclude subjects who appear to be at higher risk for a particular AE.

In addition to the study stopping rules described above, any death will be thoroughly reviewed and appropriate action taken

9.2. Discussion of Study Design

EXPAREL is approved for infiltration into a surgical site. This Phase 3, multicenter, randomized, double-blind, placebo-controlled study is designed to evaluate the efficacy, safety, and PK of brachial plexus block with EXPAREL for postsurgical analgesia in subjects undergoing total shoulder arthroplasty or rotator cuff repair. The double-blind study design is intended to avoid potential bias resulting from subject or Investigator knowledge of the assigned treatment.

In the femoral nerve block study 402-C-323, following a blinded review of the initial plasma samples from 13 subjects who received the 266 mg dose of EXPAREL, it was apparent that in some subjects the last plasma sample collected contained the highest bupivacaine concentration, and that it could not be definitively determined whether their T_{max} occurred prior to 72 hours, at 72 hours, or later. Therefore, in the current study, the PK sampling period was extended through postsurgical Day 10 with more frequent PK blood draws scheduled between 60-84 hours for the first 13 subjects. An interim assessment of the PK data from these subjects was then conducted and the protocol amended to revise the PK and safety assessment timepoints. A confirmatory blinded PK interim analysis will be conducted once 30 subjects have completed the assessments through postsurgical Day 10.

EXPAREL was developed in nerve block as an analgesic and not an anesthetic. It does not produce a dense, consistent sensory blockade as would be required for anesthesia; this is reflected in the current package insert. There is no expectation of a complete or sustained block.

As there is no single universally clinically accepted validated outcomes instrument for motor testing, several motor tests of the muscles impacted by the nerve block will be undertaken. All subjects are required to have a Lovett score of 5 (normal) to be enrolled in the study. Onset of loss of motor function is the first timepoint after baseline at which the Lovett scale decreases to below a 3 in at least one of the motor function assessments (biceps, wrist, and thumb movement). Onset of return of motor function is the first timepoint after study drug administration where any of the motor function assessments increases to return to a 3 or above on the Lovett scale. The motor function assessment will be conducted at baseline (on Day 0 prior to the nerve block); approximately every 15 minutes before the subject goes to the operating room (OR); prior to discharge from the PACU; and at 6, 9, 12, 18, 24, 36, 48, 60, and 72 hours.

Similarly, there is no universally clinically accepted validated outcomes instrument for sensory testing. Prior experience with EXPAREL (study 402-C-203) utilized warm threshold, cool threshold, and vibratory sensation as well as pinprick testing. In the current study, the subject's sensitivity to cold, pinprick, and light touch in the distal part of innervated dermatomes (musculocutaneous, median, ulnar, radial, and axillary) will be assessed with their eyes closed at baseline (on Day 0 prior to the nerve block); approximately every 15 minutes before the subject goes to the OR; prior to discharge from the PACU; and at 6, 9, 12, 18, 24, 36, 48, 60, and 72 hours.

If a subject has a motor or sensory deficit at 72 hours, they will be further evaluated on postsurgical Day 5. If on postsurgical Day 5 there continues to be a motor or sensory deficit, the deficit will be recorded as an AE. The motor or sensory function will be further assessed on postsurgical Day 10. If the a sensory deficit persists, or the Lovett Score is less than 5 on postsurgical Day 5, a physician must evaluate the subject to rule out other etiologies for persistent sensory and motor deficits, and the subject is to return for unscheduled visit(s) at the Investigator's discretion through postsurgical Day 29 or until the motor or sensory function has returned to baseline, whichever occurs first.

All subjects will receive an opioid analgesic(s) as needed to control breakthrough postsurgical pain. In addition, all subjects will receive acetaminophen/paracetamol up to 1000 mg PO or IV q8h unless contraindicated. The total daily dose of acetaminophen/paracetamol should not exceed 3000 mg.

If a cardiac or neurological AESI, fall, or SAE occurs during the study, an unscheduled PK blood sample should be collected. In addition, a 12-lead ECG, vital signs, and any appropriate clinical laboratory tests should be conducted. Cardiac AESIs include chest pain (angina, myocardial infarction), abnormal/irregular heart rate (bradycardia, tachycardia, extrasystoles), and shortness of breath requiring intervention. Neurologic AESIs include altered mental status/altered sensorium, rigidity, dysarthria, seizure, tremors, metallic taste, tinnitus, perioral numbness, visual disturbance, severe or worsening dizziness, and dizziness beyond 72 hours postdose. Additionally, the following events are of special interest if they persist or occur beyond 72-hours postdose: hyperesthesia, muscular twitching, and tingling/paresthesia.

10. STUDY POPULATION

10.1. Inclusion Criteria

Subjects eligible for study entry must meet all of the following criteria:

1. Male or female, at least 18 years of age at screening.
2. Scheduled to undergo primary unilateral total shoulder arthroplasty or rotator cuff repair.
3. Subjects scheduled for rotator cuff repair must have a magnetic resonance imaging (MRI) with a reading confirming a tear of at least 1 cm.
4. American Society of Anesthesiologists (ASA) physical status 1, 2, or 3.
5. Female subject must be surgically sterile; or at least 2 years postmenopausal; or have a monogamous partner who is surgically sterile; or practicing double-barrier contraception; or practicing abstinence (must agree to use double-barrier contraception in the event of sexual activity); or using an insertable, injectable, transdermal, or combination oral contraceptive approved by the FDA for greater than 2 months prior to screening and commit to the use of an acceptable form of birth control for the duration of the study and for 30 days after completion of the study.
6. Able to demonstrate normal motor function (by obtaining a 5 on the Lovett Scale when exhibiting biceps, wrist, and thumb movement) and sensory function (by exhibiting sensitivity to cold, pinprick, and light touch) in the location where sensory function will be measured throughout the study: 2 cm superior to the coracoid process on the skin overlying the acromioclavicular joint.
7. Able to provide informed consent, adhere to the study visit schedule, and complete all study assessments.

10.2. Exclusion Criteria

A subject will not be eligible for the study if he or she meets any of the following criteria:

1. Currently pregnant, nursing, or planning to become pregnant during the study or within 1 month after study drug administration.
2. Planned concurrent surgical procedure.
3. Concurrent painful physical condition that may require analgesic treatment (such as an NSAID or opioid) in the postsurgical period for pain that is not strictly related to the shoulder surgery and which may confound the postsurgical assessments (e.g., significant pain from other joints, chronic neuropathic pain).
4. History of hypersensitivity or idiosyncratic reaction to amide-type local anesthetics.
5. Smoking history of greater than 25 pack-years.
6. Contraindication to any of the following: bupivacaine, oxycodone, morphine, or hydromorphine.

7. Use of any of the following medications within the times specified before surgery: long-acting opioid medications or NSAIDs (except for low-dose aspirin used for cardioprotection) within 3 days, or any opioid medication within 24 hours.
8. Initiation of treatment with any of the following medications within 1 month of study drug administration or if the medication(s) are being given to control pain: selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin (Lyrica®), or duloxetine (Cymbalta®). If a subject is taking one of these medications for a reason other than pain control, he or she must be on a stable dose for at least 1 month prior to study drug administration.
9. Current use of systemic glucocorticosteroids within 1 month of enrollment in this study.
10. Use of dexmedetomidine HCl (Precedex®) within 3 days of study drug administration.
11. History of impaired kidney function, emphysema or other chronic respiratory disease, rheumatoid arthritis, coagulopathy, or loss of sensation in extremities.
12. Impaired kidney function (e.g., serum creatinine level >2 mg/dL [176.8 µmol/L] or blood urea nitrogen level >50 mg/dL [17.9 mmol/L]) or impaired liver function (e.g., serum aspartate aminotransferase [AST] level >3 times the upper limit of normal (ULN) or serum alanine aminotransferase [ALT] level >3 times the ULN.
13. Uncontrolled anxiety, psychiatric, or neurological disorder that might interfere with study assessments.
14. Any chronic neuromuscular deficit effecting the peripheral nerves or muscles of the surgical extremity.
15. Any chronic condition or disease that would compromise neurological or vascular assessments.
16. Malignancy in the last 2 years, with the exception of non-metastatic basal cell or squamous cell carcinoma of the skin or localized carcinoma in situ of the cervix.
17. Suspected or known history of drug or alcohol abuse within the previous year.
18. Body weight <50 kg (110 pounds) or a body mass index >44 kg/m^2.
19. Previous participation in an EXPAREL study.
20. Administration of an investigational drug within 30 days or 5 elimination half-lives of such investigational drug, whichever is longer, prior to study drug administration, or planned administration of another investigational product or procedure during the subject's participation in this study.

10.3. Removal of Subjects from Therapy or Assessment

Every reasonable effort should be made to maintain subject compliance and participation in the study. Reasons for discontinuation of any subject from the study will be recorded.

If a subject who withdraws from the study has an ongoing AE, every effort must be made to follow such events until satisfactory resolution is obtained, or further follow-up is otherwise no longer warranted.

10.3.1. Withdrawal Secondary to Adverse Events

If a subject experiences an AE that renders him or her incapable of continuing with the remaining study assessments, then he or she will be discontinued from further participation in the study. A final evaluation should be performed so that the subject's study participation can be terminated in a safe and orderly manner.

10.3.2. Voluntary or Study Investigator Withdrawal

Subjects are free to discontinue from the study at any time, without prejudice to future treatment. Nevertheless, subjects will be encouraged to complete at least the study safety assessments. In addition, a subject may be discontinued from the study if he or she refuses to comply with study procedures. Reasons for discontinuation from the study will be recorded.

If a subject is discontinued by the Investigator or voluntarily withdraws from the study after receiving study drug, the subject will be asked to complete a final evaluation so that he or she can be withdrawn in a safe and orderly manner. In the final evaluation, vital signs (heart rate and blood pressure), sensory function, motor function, and any changes in the subject's health status will be recorded.

After termination from the study, the subject may be followed for safety including monitoring of AEs through postsurgical Day 29.

11. TREATMENTS

11.1. Treatment to be Administered

Study Drug

Subjects will receive a single dose of either EXPAREL 133 mg expanded in volume with 10 mL of normal saline to achieve a total volume of 20 mL, or placebo 20 mL according to the randomization schedule. Study drug administration will be performed in a blinded manner (see Section 11.5.1).

Postsurgical Rescue Medication

Subjects should only receive rescue medication upon request for pain control, as needed. Postsurgical rescue medication will consist of PO immediate-release oxycodone (initiating at 5-10 mg q4h or PRN). If a subject cannot tolerate PO medication, IV morphine (2.5-5 mg) or hydromorphone (0.5-1 mg) may be administered q4h or PRN. **PCA is not permitted**. Postsurgically, all subjects will receive acetaminophen/paracetamol up to 1000 mg PO or IV q8h unless contraindicated. The total daily dose of acetaminophen/paracetamol should not exceed 3000 mg. No other analgesic agents, including NSAIDs, are permitted through 72 hours. After 72 hours, the analgesic regimen may be adjusted for each subject individually as deemed appropriate by the physician responsible for the postsurgical care. All analgesic use must be recorded through postsurgical Day 29.

11.1.1. Administration Technique

Study drug (EXPAREL or placebo) will be administered under ultrasound guidance by the anesthesiologist into the brachial plexus as described below. A confirmatory photo of the ultrasound nerve block needle placement will be taken.

The 10-13 MHz transducer is initially placed over the external jugular vein to visualize the brachial plexus, approximately 3 cm above the clavicle. Alternatively, the anesthesiologist may start at the supraclavicular fossa and scan cephalad. Once the brachial plexus roots/trunks are clearly visualized with an ultrasound probe (an ideal view would include C5, C6, and C7 between the anterior scalene muscle and the middle scalene muscle), a blunt tip block needle will be advanced in an "in plane" approach from posterior to anterior towards the superior portion of the brachial plexus at the level of a standard interscalene block (ideally within the interscalene space, inside the sheath – i.e., within the interscalene groove, and adjacent to the brachial plexus via in plane ultrasound guidance in order to visualize the entire needle). Once the needle is clearly seen approximated by the neural bundle, an injection of study drug will be deposited so as to surround the middle to superior portion of the plexus. If the study drug does not immediately spread as desired, the needle will be repositioned during the procedure to ensure proper administration of study drug around the middle to superior portion of the plexus. Final probe, needle path, endpoints for needle target, and type of block needle are all at the discretion of the anesthesia team.

11.1.2. Study Drug Administration Considerations

Since there is a potential risk of severe adverse effects associated with the administration of bupivacaine, the study site must be equipped to manage subjects with any evidence of cardiac toxicity.

EXPAREL may not be administered to a subject if it has been held in a syringe for more than 4 hours after preparation. In order to prevent the study drug from settling, gently inverting and re-inverting the syringe several times prior to administration is recommended. No agents are to be admixed with EXPAREL.

11.2. Identity of Investigational Product(s)

11.2.1. Description of EXPAREL

EXPAREL is formulated as a sterile, non-pyrogenic, white to off-white, preservative-free, homogeneous suspension of bupivacaine encapsulated into multivesicular lipid-based particles (the DepoFoam drug delivery system). Bupivacaine is present at a nominal concentration of 13.3 mg/mL. EXPAREL will be provided in 20 mL, 1.3% (13.3 mg/mL) single-use, clear glass vials. EXPAREL vials should be stored refrigerated between 2°C to 8°C (36°F to 46°F).

11.2.2. Description of Reference Product

Placebo will consist of normal saline for injection. Subjects in the placebo group will receive 20 mL of normal saline.

11.2.3. Description of Diluents

Normal saline for injection will be added to the 133 mg (10 mL) dose of EXPAREL to achieve a total volume of 20 mL.

11.3. Method of Assigning Subjects to Treatment

11.3.1. Randomization Scheme

Approximately 120 subjects (50 subjects randomized to EXPAREL 133 mg, 50 subjects randomized to placebo, and any subjects enrolled under the original protocol and randomized to EXPAREL 266 mg) are planned for enrollment. Subjects will be randomized in a 1:1 ratio to receive a single-dose injection brachial plexus block with EXPAREL 133 mg or placebo.

The randomization code will be generated by a centralized randomization system, which will also be used to communicate subject randomizations to study sites. All randomized subjects will have both a unique subject identifier and a unique random code identifier. No subject or random code identifiers are to be reused once assigned.

11.3.2. Randomization Procedures

Once a subject is identified as being qualified for the study per the eligibility criteria (see Section 10.1 and Section 10.2), and is at the study site for surgery, the unblinded research pharmacist or designee will obtain a randomization assignment. The subject will be considered randomized into the study once the study treatment assignment is received.

11.3.3. Replacement of Subjects

Subjects who are randomized but are withdrawn from the study before receiving study drug or do not undergo the surgical procedure may be replaced. Once assigned, subject numbers will not be reused; subjects enrolled to replace those who withdraw will be assigned a unique subject number and randomized to treatment according to the procedures outlined above.

11.4. Selection of Doses in the Study

During the clinical development of EXPAREL, single doses ranging from 2 mg to 665 mg have been safely administered via various routes. Pharmacokinetic studies have shown that because EXPAREL releases bupivacaine gradually as the lipid structure breaks down, administration of EXPAREL 266 mg results in a maximum plasma concentration (C_{max}) equivalent to that seen with standard bupivacaine HCl 100 mg. EXPAREL 266 mg, the FDA-approved marketed dose, was chosen for the nerve block. In an effort to ensure that the minimal effective dose is chosen, the study initially examined two doses levels of EXPAREL (133 mg and 266 mg), each compared to placebo. After completion of the first PK interim analysis conducted after 13 subjects completed Day 10, a single dose of 133 mg was selected for the remainder of the study.

11.5. Blinding

11.5.1. Blinding Procedures

EXPAREL and placebo are visually distinguishable; therefore, to maintain the double-blind study design, only unblinded study personnel who are NOT involved with protocol-specific, postsurgical assessments may prepare and administer the study drug. Staff members conducting study-specific, postsurgical assessments and the subjects will remain blinded to the assigned treatment throughout the study. If a subject experiences an SAE, Pacira will not automatically unblind the subject's treatment, unless it is necessary to manage treatment of the SAE. Expedited SAEs will be unblinded by Pacira for regulatory reporting purposes.

At each site, only the designated unblinded pharmacist will receive unblinded randomization assignments and be responsible for preparing study drug.

Assignment of blinded and unblinded responsibilities regarding the preparation of study drug should take into account that **EXPAREL must be administered within 4 hours of opening the vial**.

The individuals preparing and administering study drug will not be allowed to perform any of the study assessments or reveal the assigned study treatment to any other members of the study team at any time. Syringes containing study drug will need to be gently inverted several times to re-suspend any settling of the study drug that may have occurred prior to administration. The administration of study drug will be recorded using the minimal amount of information necessary to avoid unblinding staff who will be participating in blinded procedures (see Pharmacy Manual for additional details).

No crossover will be permitted between the blinded and unblinded study site personnel during the study period. The assignment of site monitors will also be segregated. Blinded monitors will review case report forms (CRFs), clinic charts, and all other study-related documents that do not disclose the allocation of study treatment. Care should be taken in recording and review of OR

records to not record information in an unblinded fashion. Pharmacy or any other clinic records providing unblinded information (e.g., randomization, study drug preparation, study drug accountability, study drug administration) will be reviewed by specialized unblinded monitors who will notify Pacira of treatment noncompliance.

11.5.2. Unblinding Procedures

Subject treatment assignments should not be unblinded during the study by blinded study personnel. The Investigator will have the ability to unblind a subject through the randomization system if he or she feels that subject safety warrants such unblinding. However, the Investigator should discuss the safety issues with the Medical Monitor before attempting such unblinding, if possible. Any unblinding will be documented through immediate notification of the Pacira study team and the Investigator within the interactive response technology (IRT) system used for randomization. The reason for unblinding will be documented. Any accidental unblinding events (i.e., through mishaps in the OR or miscommunication among study staff) must be reported to Pacira immediately.

Any unblinding performed through the randomization system will be recorded as a transaction and the appropriate study personnel will be notified that such a transaction occurred.

Any incidence(s) of unblinding will be noted in the clinical study report with a full discussion of the events leading to the decision to unblind.

11.6. Prior and Concomitant Therapy and Medications

All medications taken within 30 days prior to study drug administration through 72 hours after study drug administration or until the subject is withdrawn from the study, whichever is sooner, will be recorded on the CRF. All analgesic use must be recorded through postsurgical Day 29. Additionally, any medications administered in association with an AE will be recorded through postsurgical Day 29.

11.6.1. Before Study Drug Administration

Permitted Prior Medications and Therapy

- Low-dose aspirin for cardioprotection.
- Acetaminophen/paracetamol up to 1000 mg PO or IV q8h (maximum total daily dose of 3000 mg) is permitted.
- 1-2 mg of midazolam (Versed) pre-op

Restricted Prior Medications and Therapy

- Systemic glucocorticosteroids are prohibited within 1 month of enrollment in this study.
- Initiation of treatment with any of the following medications is prohibited within 1 month of study drug administration or if the medication(s) are being given to control pain: SSRIs, SNRIs, gabapentin, pregabalin (Lyrica), or duloxetine (Cymbalta). If a subject is taking one of these medications for a reason other than pain control, he or she must be on a stable dose for at least 1 month prior to study drug administration.

- Long-acting opioid medications and NSAIDs (except for low-dose aspirin used for cardioprotection) are not permitted within 3 days of study drug administration.
- Dexmedetomidine HCl (Precedex) use is not permitted within 3 days of study drug administration.
- No opioid medications are permitted within 24 hours of study drug administration.
- Use of an investigational product within 30 days or 5 elimination half-lives of such investigational drug, whichever is longer, prior to study drug administration, or planned administration of another investigational product or procedure during the subject's participation in this study is not permitted.

11.6.2. During Surgery

Permitted

- Ultra-short acting opioids (i.e., fentanyl, sufentanil, or remifentanil) will be permitted during surgery.
- Single-dose administration of ondansetron or metoclopramide may be used intra-operatively for nausea/vomiting prevention. If not available or contraindicated, a single dose of dexamethasone 10 mg IV may be administered.

Restricted

- No drugs are to be admixed with study drug (e.g., epinephrine, dexamethasone, clonidine).
- Lidocaine and other local anesthetics will not be permitted to be locally administered during surgery because they are known to interact with EXPAREL resulting in the displacement of bupivacaine and elevated plasma levels.
- The use of long-acting opioids (e.g., morphine, hydromorphone HCl), acetaminophen/ paracetamol, ketorolac, or other NSAIDs will not be permitted intraoperatively except for emergency use to treat an AE.

11.6.3. After Surgery

Permitted

- The permitted rescue medication is oxycodone (initiating at 5-10 mg q4h or PRN). If a subject cannot tolerate PO medication, IV morphine (2.5-5 mg) or hydromorphone (0.5-1 mg) may be administered q4h or PRN.

Post surgically, all subjects will receive the following scheduled medications until hospital discharge:

- Cyclobenzaprine (eg, Flexeril®) 10 mg PO x1 dose (PRN at surgeon discretion)
- Acetaminophen/paracetamol up to 1000 mg PO or IV q8h unless contraindicated. The total daily dose of acetaminophen/paracetamol should not exceed 3000 mg.

Restricted

- No other analgesics, including fentanyl, are permitted within 72 hours after study drug administration.
- PCA is not permitted.
- Dexmedetomidine HCl (Precedex) use is prohibited.
- Anesthetics in the "caine" family, which may interfere with the bupivacaine PK profile, are prohibited through postsurgical Day 10.

For study purposes, it is important to standardize pain management modalities during the first 72 hours following study drug administration. Therefore, the study staff must adhere closely to the treatment options and requirements noted in the protocol. After 72 hours, the analgesic regimen may be adjusted for each subject individually, as deemed appropriate by the physician responsible for the postsurgical care.

All postsurgical analgesics administered must be documented through postsurgical Day 29.

11.7. Treatment Compliance

Not applicable, since study drug (EXPAREL or placebo) will be administered preoperatively by the study staff.

11.8. Accountability of Study Drug

Any shipment of EXPAREL for the study will contain an investigational drug transmittal and receipt form to assist the Investigator or designee (e.g., pharmacist) in maintaining current and accurate inventory records. At a minimum, the Investigator or designee will maintain accurate records demonstrating dates and units of drug received, lot numbers, subjects to whom drug was administered, and accounts of any drug destroyed accidentally or deliberately. The Investigator must retain vials containing used, unused, or expired EXPAREL for return or destruction, as instructed by Pacira, following confirmation of drug accountability data by a study monitor. A record of drug return or destruction will be maintained and provided to Pacira. Inventory records must be readily available for inspection by the study monitor and appropriate regulatory authorities at any time. A copy of the inventory records, drug accountability information, and notice of return or destruction will be returned to Pacira at the end of the study. Only authorized personnel identified by the Investigator will have the ability to access and administer the drug.

12. STUDY ENDPOINTS AND MEASUREMENTS

12.1. Efficacy Assessments

The following efficacy measurements will be assessed at the times specified *after the beginning of the brachial plexus block with study drug*:

- Pain intensity scores using the VAS at predose (on Day 0 prior to the nerve block and prior to any premedication); upon arrival at the PACU, every 15 minutes while in the PACU, and prior to PACU discharge; at 6, 12, 24, 36, 48, 60, and 72 hours; and immediately prior to each administration of rescue pain medication through 72 hours (see Appendix 1).
- Date, time of administration, and amount of all opioid rescue medication taken through 72 hours.
- The OBAS questionnaire at 24 and 72 hours, and on postsurgical Day 10 (see Appendix 2).
- Subject satisfaction with overall analgesia (using a 5-point Likert scale) at 24 and 72 hours, and on postsurgical Day 10 (see Appendix 3).
- Discharge readiness at 12, 24, 36, 48, 60, and 72 hours or when the subject is considered to be discharge ready, whichever occurs first (see Appendix 7).
- Unscheduled phone calls or office visits related to pain after discharge through postsurgical Day 10.

12.2. Efficacy Endpoints

The efficacy endpoints listed below will be assessed based on the efficacy measurements conducted at the times specified *after the beginning of the brachial plexus block with study drug*.

Primary Endpoint:

The primary endpoint is the AUC of the VAS pain intensity scores through 48 hours.

Secondary Endpoints:

The following secondary endpoints will be analyzed in the following order:

1. Total postsurgical opioid consumption (in IV morphine equivalents) through 48 hours.
2. Percentage of opioid-free subjects through 48 hours.
3. Time to first opioid rescue through 48 hours.

Tertiary Endpoints:

- The AUC of the VAS pain intensity scores through 12, 24, and 72 hours.
- The AUC of the VAS pain intensity scores from 24-48 hours and 48-72 hours.
- VAS pain intensity scores at each assessed timepoint.

- Proportion of subjects who are pain free (defined as a VAS pain intensity score of ≤1.5 without prior rescue medication use) at each assessed timepoint.
- Sum of the pain intensity scores (SPIS) through 24, 48, and 72 hours.
- SPIS from 24-48 and 48-72 hours.
- Total opioid consumption in IV morphine equivalents through 24 and 72 hours.
- Total opioid consumption in IV morphine equivalents from 24-48 hours and 48-72 hours.
- Percentage of opioid-free subjects through 24 and 72 hours.
- The OBAS total score at 24 and 72 hours, and postsurgical Day 10.
- Subject satisfaction with overall analgesia (using a 5-point Likert scale) at 24 and 72 hours, and on postsurgical Day 10.
- Proportion of subjects meeting MPADSS criteria for discharge readiness at 12, 24, 36, 48, 60, and 72 hours.
- Number of unscheduled phone calls or office visits related to pain after discharge through postsurgical Day 10.

12.3. Pharmacokinetic Analysis

A population PK analysis will be utilized to limit the number of blood draws. A total of 7 PK samples will be collected from each subject for this study. All subjects will have PK samples taken at baseline and upon arrival at the PACU. An additional 5 blood samples will be collected at the assigned time windows, spanning from 12 hours postdose to just prior to discharge. There are two PK collection sequences for this study and a subject can only be randomized to one sequence. The PK schedule sequence will be indicated for each subject at the time of randomization and will also be noted on the randomization confirmation. Subjects in Sequence 1 will have samples taken at 12, 24, 40, 52, and 72 hours. Subjects in Sequence 2 will have samples taken at 24, 36, 48, and 60 hours, and at hospital discharge.

Blood samples for PK analysis may be drawn using a properly maintained indwelling cannula (PICC line) at the discretion of the Investigator. Blood samples will be collected from all subjects to maintain the treatment double-blind. Blood samples from the subjects randomized to placebo will be analyzed through the 24-hour timepoint.

12.4. Pharmacokinetic Endpoints

Pharmacokinetic parameters will be estimated from the plasma bupivacaine measurements using non-compartmental analysis. The following parameters will be determined:

$AUC_{0\text{-}tlast}$ The area under the plasma concentration-versus-time curve from the time of administration to the time of the last quantifiable concentration calculated using the log-linear trapezoidal rule.

$AUC_{0\text{-}\infty}$ The area under the plasma concentration-versus-time curve from the time of administration extrapolated to infinity. The residual area from the time of the last quantifiable concentration (C_{tlast}) to infinity is to be calculated using the approximation: $AUC_{0\text{-}\infty} = C_{tlast}/ \lambda_z$.

C_{max}	The maximum observed plasma concentration obtained directly from the experimental data without interpolation.
T_{max}	The time to maximum plasma concentration (C_{max}).
λ_z	The apparent terminal elimination rate constant determined by log-linear regression of the terminal log-linear segment of the plasma concentration-versus-time curve.
$t_{1/2el}$	The apparent terminal elimination half-life calculated as $0.693/\lambda_z$.

12.5. Safety Assessments

The following safety assessments will be conducted at the times specified *after the beginning of the brachial plexus block with study drug*:

- Clinical laboratory tests (hematology, chemistry, and urinalysis) at baseline (on Day 0 prior to the nerve block) and on postsurgical Day 10.
- Vital signs (resting heart rate and blood pressure) at baseline (on Day 0 prior to the nerve block); every 5 minutes during performance of the block up to 30 minutes; and every 15 minutes until entering the OR; at PACU arrival; at 6, 9, 12, 24, 36, 40, 44, 48, 52, 56, 60, and 72 hours; and on postsurgical Days 5 and 10.
- 12-lead ECG recordings at baseline (on Day 0 prior to the nerve block); upon arrival at the PACU; at 6, 9, 12, 24, 36, 40, 44, 48, 52, 56, 60, and 72 hours; and on postsurgical Days 5 and 10. Note: ECGs must be read within 2 hours.
- Neurological assessment at baseline (on Day 0 prior to the nerve block); upon arrival at the PACU; at 6, 9, 12, 24, 36, 40, 44, 48, 52, 56, 60, and 72 hours; and on postsurgical Days 5 and 10 (see Appendix 4).
- Sensory function assessment (as measured by cold, pinprick, and light touch testing) at baseline (on Day 0 prior to the nerve block); at approximately 15, 30, and 45 minutes after the nerve block; prior to discharge from the PACU; at 6, 9, 12, 18, 24, 36, 48, 60, and 72 hours (see Appendix 5). If sensory deficit is present at 72 hours, the subject will be assessed on postsurgical Day 5. If on postsurgical Day 5 there is a sensory deficit, the sensory deficit will be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent sensory deficit. If there continues to be a sensory function deficit on Day 5, the sensory function will be further assessed on postsurgical Day 10. If the sensory deficit persists on postsurgical Day 10, the subject is to return for unscheduled visit(s) at the Investigator's discretion through postsurgical Day 29 or until the sensory function has returned to baseline, whichever occurs first.
- Motor nerve function assessment (biceps, wrist, and thumb movement) at baseline (on Day 0 prior to the nerve block); at approximately 15, 30, and 45 minutes after the nerve block; prior to discharge from the PACU; at 6, 9, 12, 18, 24, 36, 48, 60, and 72 hours (see Appendix 6). If motor function deficit (Lovett score below 5) is present at 72 hours, the subject will be assessed again on postsurgical Day 5. If on postsurgical Day 5 there is a motor deficit, ie, the subject's Lovett score has not returned to 5, the motor deficit will be recorded as an AE and the physician will assess the subject for other

etiologies that may explain the persistent motor deficit. If there continues to be a motor function deficit on Day 5, the motor assessment will be further assessed on postsurgical Day 10. If the motor deficit persists on postsurgical Day 10, the subject is to return for unscheduled visit(s) at the Investigator's discretion through postsurgical Day 29 or until the motor function has returned to a Lovett score of 5, whichever occurs first.

- Adverse events from the time the ICF is signed through postsurgical Day 29.

12.6. Safety Endpoints

The following safety endpoints will be assessed based on the safety measurements conducted at the specified timepoints:

- Change from baseline in clinical laboratory data at each assessed timepoint.
- Change from baseline in vital sign data (resting heart rate and blood pressure) at each assessed timepoint.
- Change from baseline in ECG data at each assessed timepoint.
- Summary of neurological assessments (proportion of subjects who are oriented, and proportion of subjects who have any of the neurologic events).
- Cold sensation at each assessed timepoint.
- Pinprick sensation at each assessed timepoint.
- Light touch sensation at each assessed timepoint.
- Change from baseline in motor function (biceps, wrist, and thumb movement) at each assessed timepoint.
- Incidence of TEAEs and SAEs through postsurgical Day 29.

12.7. Appropriateness of Measures

Endpoints selected for this study were based on validated methodologies and other well established clinical measurements used in peer-reviewed studies in both the peer reviewed literature and at regulatory authorities. Measurements were further refined in this study based on previous nerve block experience with EXPAREL including the Phase 2/3 femoral nerve block study 402-C-323 in TKA and feedback from the FDA.

13. STUDY PROCEDURES

A time and events schedule for all study procedures is provided in Table 1, Table 2, and Table 3.

13.1. Instructions for Conducting Procedures and Measures

All safety, efficacy, and PK assessments conducted after baseline will be timed from the *beginning of the brachial plexus block with study drug*.

At timepoints when multiple assessments coincide, the pain intensity assessment will be conducted first and the blood draw for PK analysis will be conducted second, as applicable.

Day 0 is defined as the day on which study drug is administered. The beginning of surgery is defined as the time of the first incision. The end of surgery is defined as the time of the last suture. Postsurgical is defined as after the end of surgery.

Postsurgical analgesia and collection of study data through the primary endpoint will take place under the supervision of study staff.

13.1.1. Pain Intensity Assessment

Pain intensity will be assessed using a 10-cm VAS (Carlsson 1983, McCormack 1988, and Scott 1976) at baseline (on Day 0 prior to the nerve block and prior to any premedication); upon arrival at the PACU; every 15 minutes while in the PACU, and prior to PACU discharge; at 6, 12, 24, 36, 48, 60, and 72 hours; and immediately prior to each administration of rescue pain medication through 72 hours (see Appendix 1).

13.1.2. Overall Benefit of Analgesia Score Questionnaire

The OBAS questionnaire will be completed at 24 and 72 hours, and on postsurgical Day 10 (see Appendix 2).

13.1.3. Subject Satisfaction with Postsurgical Pain Control

The subject's satisfaction with postsurgical pain control will be assessed using the Likert Scale at 24 and 72 hours, and on postsurgical Day 10 (see Appendix 3).

13.1.4. Neurological Assessment

A neurological assessment will be conducted at screening; baseline (on Day 0 prior to the nerve block); upon arrival at the PACU; at 6, 9, 12, 24, 36, 40, 44. 48, 52, 56, 60, and 72 hours; and on postsurgical Days 5 and 10. The examination will include the subject's orientation. Additionally, the subject will be asked whether he or she is experiencing any numbness of the lips, the tongue, or around the mouth; a metallic taste in the mouth; vision problems; hearing problems; or muscle twitching (see Appendix 4). If the subject answers "yes" to any of these questions, the event should be recorded as an AE and additional safety procedures should be conducted (see Section 13.1.11).

13.1.5. Sensory Function Assessment

Sensory function (as measured by cold, pinprick, and light touch testing) will be assessed at screening; baseline (on Day 0 prior to the nerve block); approximately every 15 minutes before the subject goes to the OR; prior to discharge from the PACU; at 6, 9, 12, 18, 24, 36, 48, 60, and 72 hours (see Appendix 5). If sensory deficit is present at 72 hours, the subject will be assessed on day 5. If on postsurgical Day 5 there is a sensory deficit, the sensory deficit will be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent sensory deficit. If there continues to be a sensory function deficit on Day 5, the sensory function will be further assessed on postsurgical Day 10. If the sensory deficit persists on postsurgical Day 10, the subject is to return for unscheduled visit(s) at the Investigator's discretion through postsurgical Day 29 or until the sensory function has returned to baseline, whichever occurs first.

The assessors will be deemed to be qualified if the following three conditions are met:

1. They are a licensed medical professionals (physician, nurse, physical therapist, etc),
2. They have prior experience completing the assessment being conducted or have similar and applicable experience,
3. They have participated and completed the 327 protocol specific training on the study assessment through either one of the following:
    a. Participation at the Investigator Meeting

       OR
    b. Completed the Pacira Pharmaceuticals ComplianceWire Training (the study specific Learning Management System) including review of the slide deck and training videos.

13.1.6. Motor Nerve Block Assessment

The motor nerve block assessment (i.e., biceps, wrist, and thumb movement) (Marashi 2015) will be assessed at screening; baseline (on Day 0 prior to the nerve block); approximately every 15 minutes before the subject goes to the OR; prior to discharge from the PACU; at 6, 9, 12, 18, 24, 36, 48, 60, and 72 hours (see Appendix 6). If motor function deficit (Lovett score below 5) is present at 72 hours, the subject will be assessed again on day 5. If on postsurgical Day 5 there is a motor deficit, ie, the subject's Lovett score has not returned to 5, the motor deficit will be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent motor deficit. If there continues to be a motor function deficit on Day 5, the motor assessment will be further assessed on postsurgical Day 10. If the motor deficit persists on postsurgical Day 10, the subject is to return for unscheduled visit(s) at the Investigator's discretion through postsurgical Day 29 or until the motor function has returned to a Lovett score of 5, whichever occurs first.

The assessors will be deemed to be qualified if the following three conditions are met:

1. They are licensed medical professionals (physician, nurse, physical therapist, etc.),

2. They have prior experience completing the assessment being conducted or have similar and applicable experience,
3. They have participated and completed the 327 protocol specific training on the study assessment through either one of the following:
    a. Participation at the Investigator Meeting

       OR

    b. Completed the Pacira Pharmaceuticals ComplianceWire Training (the study specific Learning Management System) including review of the slide deck and training videos.

13.1.7. Clinical Laboratory Tests

A urine drug screen and blood alcohol test will be conducted at screening, and a urine drug screen and alcohol breath test will be conducted at baseline (on Day 0 prior to the nerve block).

The scheduled clinical laboratory tests (hematology, chemistry, and urinalysis) will be conducted at screening; baseline (on Day 0 prior to the nerve block); and on postsurgical Day 10. Clinical laboratory tests, as appropriate, may also be conducted if a subject experiences an AESI (i.e., cardiac AE or neurological AE), fall, or an SAE (see Section 13.1.11).

13.1.8. Vital Signs

The scheduled vital signs (heart rate and blood pressure) will be measured after the subject has rested in a supine position for at least 5 minutes at screening; baseline (on Day 0 prior to the nerve block); every 5 minutes during the performance of the nerve block and up to 30 minutes after completion of the block and then every 15 minutes until entering the OR; upon arrival at the PACU; at 6, 9, 12, 24, 36, 40, 44, 48, 52, 56, 60, and 72 hours; and on postsurgical Days 5 and 10. Vital signs will also be measured if a subject experiences a cardiac or neurological AESI, fall, or an SAE (see Section 13.1.11). The subject will remain in a supine position during the assessment.

13.1.9. Physical Examination

A full physical examination will be conducted at screening. Superficial abnormalities that may interfere with participation in the study will be noted. A targeted physical examination will be conducted on postsurgical Day 10 and will include examination of the upper extremity including the site of the brachial plexus block and the shoulder itself.

13.1.10. Electrocardiograms

The scheduled 12-lead ECGs will be conducted after the subject has rested in a supine position for at least 5 minutes at screening; baseline (on Day 0 prior to the nerve block); upon arrival at the PACU; at 6, 9, 12, 24, 36, 40, 44, 48, 52, 56, 60, and 72 hours; and on postsurgical Days 5 and 10. A 12-lead ECG will also be conducted if a subject experiences an AESI (i.e., cardiac AE or neurological AE), fall, or an SAE (see Section 13.1.11). If conducted, the ECG must be read within 2 hours.

13.1.11. Adverse Events of Special Interest

If a cardiac AE or neurological AESI, fall, or SAE occurs during the study, an unscheduled PK blood sample should be collected. In addition, a 12-lead ECG, vital signs, and any appropriate clinical laboratory tests should be conducted. If conducted, the ECG must be read within 2 hours.

Cardiac AESIs include:

- Chest pain (angina, myocardial infarction)
- Abnormal/irregular heart rate (bradycardia, tachycardia, extrasystoles)
- Shortness of breath requiring intervention.

Neurologic AESIs include:

- Altered mental status/altered sensorium
- Rigidity
- Dysarthria
- Seizure
- Tremors
- Metallic taste
- Tinnitus
- Perioral numbness
- Visual disturbance
- Severe or worsening dizziness
- Dizziness beyond 72 hours postdose

Additionally, the following events are of special interest if they persist or occur beyond 72-hours postdose:

- Hyperesthesia
- Muscular twitching
- Tingling/paresthesia

13.2. Screening Procedures

- Explain study purpose and procedures.
- Obtain signed ICF.
- Assess eligibility.
- Record relevant medical/surgical history, demographics, and baseline characteristics.
- Conduct urine pregnancy test for women of childbearing potential.
- Perform physical examination.

- Conduct urine drug screen and blood alcohol test.
- Conduct clinical laboratory tests (hematology, chemistry, and urinalysis) (see Appendix 8).
- Perform neurological assessment (see Appendix 4).
- Measure vital signs (heart rate and blood pressure) after subject has rested in a supine position.
- Conduct 12-lead ECG after subject has rested in a supine position. ECG must be read within 2 hours.
- Perform sensory function assessment (see Appendix 5).
- Conduct motor function assessment (see Appendix 6).
- Record concomitant medications.
- Record AEs starting at signing of the ICF.

13.3. Baseline Procedures (Day 0 - Prior to Study Drug Administration)

- Confirm eligibility.
- Update relevant medical and surgical history.
- Conduct urine pregnancy test for women of childbearing potential.
- Conduct urine drug screen and alcohol breath test.
- Record baseline VAS pain intensity score prior to any premedication (see Appendix 1).
- Collect baseline blood sample for PK analysis.
- Perform neurological assessment (see Appendix 4).
- Measure vital signs (heart rate and blood pressure) after subject has rested in a supine position.
- Conduct 12-lead ECG after subject has rested in a supine position. ECG must be read within 2 hours.
- Perform sensory function assessment (see Appendix 5).
- Conduct motor function assessment (see Appendix 6).
- Conduct clinical laboratory tests (hematology, chemistry, and urinalysis; see Appendix 8).
- Randomize subject and prepare study drug.
- Record changes to concomitant medications since screening.
- Record AEs and any treatment(s) for the events.

13.4. Baseline Procedures (Time 0)

- Administer blinded study drug via brachial plexus block at least 1 hour prior to surgery.
- Measure vital signs (resting heart rate and blood pressure) every 5 minutes during performance of the block
- Record start and stop times of study drug administration.
- Take confirmatory photo of the ultrasound nerve block needle placement.
- Record type of brachial plexus block (i.e., interscalene or supraclavicular).
- Record concomitant medications.
- Record AEs and any treatment(s) for the events.
- Refer to Section 13.1.11 for additional procedures in the event a cardiac AE, neurological AE, fall, or SAE occurs.

13.5. Approximately 15, 30, and 45 Minutes After Beginning of Study Drug Administration

- Perform sensory function assessment (see Appendix 5).
- Conduct motor function assessment (see Appendix 6).
- Measure vital signs (resting heart rate and blood pressure) every 15 minutes until entering the OR
- Record concomitant medications.
- Record AEs and any treatment(s) for the events.
- Refer to Section 13.1.11 for additional procedures in the event a cardiac AE, neurological AE, fall, or SAE occurs.

13.6. Intraoperative Procedures

- Record intraoperative opioids administered and doses.
- Record start and stop times of surgery.
- Record concomitant medications.
- Record AEs and any treatment(s) for the events.
- Refer to Section 13.1.11 for additional procedures in the event a cardiac AE, neurological AE, fall, or SAE occurs.

13.7. Upon Arrival at the Post-Anesthesia Care Unit

- Record VAS pain intensity score (see Appendix 1) upon arrival at the PACU, and then every 15 minutes until PACU discharge.
- Collect scheduled PK blood sample; record date and time.
- Perform neurological assessment (see Appendix 4).

- Measure vital signs (heart rate and blood pressure) after subject has rested in a supine position.
- Conduct 12-lead ECG after subject has rested in a supine position. ECG must be read within 2 hours
- Administer rescue medication upon request, as needed (see Section 11.1).
- Record times and doses of all opioid and non-opioid rescue medication administered.
- Record other concomitant medications.
- Record AEs and any treatment(s) for the events.
- Refer to Section 13.1.11 for additional procedures in the event a cardiac AE, neurological AE, fall, or SAE occurs.

13.8. Prior to PACU Discharge

- Record VAS pain intensity score (see Appendix 1)
- Assess sensory function (see Appendix 5).
- Assess motor function (see Appendix 6).
- Record other concomitant medications.
- Record AEs and any treatment(s) for the events.
- Refer to Section 13.1.11 for additional procedures in the event a cardiac AE, neurological AE, fall, or SAE occurs.

13.9. Postsurgical Assessments through Hour 72

- Record VAS pain intensity score at 6, 12, 24, 36, 48, 60, and 72 hours; and immediately prior to each administration of rescue pain medication (see Appendix 1).
- Collect scheduled blood samples for PK analysis per sequence schedule; record the date and time each sample is collected.
    - *PK Sequence Schedule 1*: Blood collected at 12 (±30 min) hrs, 24 (±1) hrs, 40 (±1) hrs, 52 (±2) hrs, and 72 (±2) hrs.
    - *PK Sequence Schedule 2*: Blood collected at 24 (±1) hrs, 36 (±1) hrs, 48 (±1) hrs, and 60 (±2) hrs.
- Perform neurological assessment at 6, 9, 12, 24, 36, 40, 44, 48, 52, 56, 60, and 72 hours (see Appendix 4).
- Measure vital signs (heart rate and blood pressure) after subject has rested in a supine position at 6, 9, 12, 24, 36, 40, 44, 48, 52, 56, 60, and 72 hours.
- Conduct 12-lead ECG after subject has rested in a supine position at 6, 9, 12, 24, 36, 40, 44, 48, 52, 56, 60, and 72 hours.
- Perform sensory function assessment at 6, 9, 12, 18, 24, 36, 48, 60, and 72 hours (see Appendix 5).

- Conduct motor function assessment at 6, 9, 12, 18, 24, 36, 48, 60, and 72 hours (see Appendix 6).
- Complete OBAS questionnaire at 24 and 72 hours (see Appendix 2).
- Obtain overall rating of subject satisfaction with postsurgical pain control using the Likert scale at 24 and 72 hours (see Appendix 3).
- Administer rescue medication upon request, as needed (see Section 11.1).
- Record date, time, and amount of all opioid and non-opioid rescue medication administered.
- Record other concomitant medications.
- Assess discharge readiness at 12, 24, 36, 48, 60, and 72 hours, or when subject is determined to be discharge ready, whichever occurs first (see Appendix 7).
- Record date and time of discharge.
- Document any unscheduled phone calls or office visits related to pain after discharge.
- Record AEs and any treatment(s) for the events.
- Refer to Section 13.1.11 for additional procedures in the event a cardiac AE, neurological AE, fall, or SAE occurs.

13.10. Hospital Discharge

- Collect blood samples for PK analysis for subjects in Sequence Schedule 2.
- Record date and time of discharge.

13.11. Postsurgical Day 5 Visit

- Perform neurological assessment (see Appendix 4).
- Measure vital signs (heart rate and blood pressure) after subject has rested in a supine position.
- Conduct 12-lead ECG after the subject has rested in a supine position. ECG must be read within 2 hours.
- If sensory deficit was present at 72 hours, perform sensory function assessment (see Appendix 5). If deficit persists, it should be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent deficit.
- If motor function deficit was present at 72 hours, perform motor function assessment (see Appendix 6). If deficit persists, it should be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent deficit.
- Document any unscheduled phone calls or office visits related to pain after discharge.
- Record concomitant medications including all analgesic medication administered.
- Record AEs and any treatment(s) for the events.

- Refer to Section 13.1.11 for additional procedures in the event a cardiac AE, neurological AE, fall, or SAE occurs.

13.12. Postsurgical Day 10 Visit

- Perform neurological assessment (see Appendix 4).
- Measure vital signs (heart rate and blood pressure) after subject has rested in a supine position.
- Conduct 12-lead ECG after the subject has rested in a supine position. ECG must be read within 2 hours.
- Conduct targeted physical examination.
- Complete OBAS questionnaire (see Appendix 2).
- Obtain overall rating of subject satisfaction with postsurgical pain control using the Likert scale (see Appendix 3).
- If on postsurgical Day 5 there was a sensory deficit, reassess sensory function (see Appendix 5).
- If on postsurgical Day 5 there was a motor deficit, reassess motor function (see Appendix 6).
- Conduct clinical laboratory tests (hematology, chemistry, and urinalysis; see Appendix 8).
- Document any unscheduled phone calls or office visits related to pain after discharge.
- Record concomitant medications including all analgesic medication administered.
- Record AEs and any treatment(s) for the events.
- Refer to Section 13.1.11 for additional procedures in the event a cardiac AE, neurological AE, fall, or SAE occurs.

13.13. Unscheduled Visit(s)

- If a sensory or motor function deficit persists on postsurgical Day 10, the subject is to return for unscheduled visit(s) at the Investigator's discretion through postsurgical Day 29 or until the sensory or motor function has returned to baseline, (see Appendix 5 and Appendix 6, respectively) whichever occurs first.
- Record concomitant medications including all analgesic medication administered.
- Record AEs and any treatment(s) for the events.

13.14. Postsurgical Day 29 Phone Call

- Record concomitant medications including all analgesic medication administered.
- Record AEs and any treatment(s) for the events.

14. ADVERSE EVENT REPORTING

Consistent with the current regulatory guidance provided by the US FDA CFR Part 312 and the ICH GCP, AEs and SAEs are defined in Section 14.1.1 and Section 14.2.1, respectively.

The concepts of AEs and SAEs represent regulatory instruments used to evaluate and monitor the safety of clinical study subjects. Therefore, these terms only apply in light of their regulatory definition. The term serious, in a regulatory sense, does not necessarily mean severe. The SAE concept is used primarily to identify, during the conduct of the study, those SAEs that may require expedited reporting to regulatory authorities.

14.1. Adverse Events

14.1.1. Definitions

Definition of Adverse Event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (e.g., off-label use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

An AE can be any unfavorable and unintended change in a body structure or body function. Adverse events include any clinically significant deterioration of a subject's medical status. The AE may involve any organ or system and can be represented by the new onset or deterioration of a disease, a syndrome, a symptom, a physical sign, as well as by findings and results of instrumental examinations and laboratory tests. Any medically relevant and untoward change after the subject signs the ICF, including frequency or pattern changes for a fluctuating condition (e.g., migraine) is considered an AE.

An AE that occurs after the ICF is signed and before the start of the study drug administration is identified as a pretreatment AE (PTAE). An AE that occurs after the administration of the study treatment is considered a TEAE.

Definition of Adverse Reaction: Any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

Definition of Suspected Adverse Reaction: Any AE for which there is a reasonable possibility that the drug caused the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug. Suspected adverse reactions are a subset of all AEs for which there is a reasonable possibility that the drug caused the event.

14.1.2. Recording Adverse Events

It is the responsibility of the Investigator to document all AEs (i.e., PTAEs and TEAEs) with an onset after the subject signs the ICF. For the purpose of this study, all AEs that occur through postsurgical Day 29 must be recorded regardless of whether or not they are considered related to study drug. Whenever feasible, AE terms must be documented as medical diagnoses (highest

possible level of integration); otherwise, the AEs must be reported separately as individual signs or symptoms. Only one AE per line should be recorded in the AE CRF; for example, an AE of nausea and vomiting would be listed as two separate events: the event of nausea and the event of vomiting. If a diagnosis is established after symptoms are recorded on the AE CRF, the diagnosis must be recorded and the symptoms collapsed (removed; i.e., lined through and initialed). Whenever possible, abnormal laboratory results must be reported as their clinical corollary (e.g., low potassium should be recorded as hypokalemia).

A continuous AE with varying grades of severity must be recorded as one AE. The highest grade of severity experienced by that subject during the course of the continuous AE must be recorded.

Any condition noted before the subject signs the ICF will be listed as Medical History and is considered a pre-existing condition. If a pre-existing condition changes (i.e., becomes more severe or more frequent) at any time after the ICF is signed, or after study drug administration, it is considered an AE. Note: A change in treatment for a pre-existing condition (e.g., new high blood pressure medication), does not necessarily indicate an AE.

Information recorded on the AE CRF will include the AE term, the date and time of onset, severity, seriousness, relationship to study drug, action taken with subject due to AE, and the outcome of the AE, including the date and time of resolution, if applicable.

14.1.3. Severity of Adverse Events

The severity of an AE must be categorized using the following guidelines:

Mild:	An AE that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
Moderate:	An AE that is discomforting and interferes with normal everyday activities.
Severe:	An AE that prevents normal everyday activities.

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); however, the event itself, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

14.1.4. Relationship of Adverse Events to Study Drug

The Investigator must assess the relationship of the AE to study drug after careful medical consideration on a case-by-case basis. General guidelines are provided below.

Unrelated:	A causal relationship between the study drug and the AE can be easily ruled out (e.g., based on the temporal sequence, absence of a reasonable pathophysiological mechanism, or direct evidence of actual cause).

Unlikely:	A clinical event with a temporal relationship to study drug administration which makes a causal relationship improbable and in which other drugs, chemicals, or underlying disease provide a plausible explanation;
Possible:	A clinical event with a reasonable time sequence to administration of the study drug but which could also be explained by a concurrent disease or other drugs or chemicals;
Probable:	A clinical event with a reasonable time sequence to administration of the study drug unlikely to be attributed to a concurrent disease or other drugs or chemicals and which follows a clinically reasonable response on withdrawal (dechallenge); or
Definite:	The pharmacological properties of the study drug(s) or of the substance class, and the course of the AE after dechallenge and, if applicable, after rechallenge, and/or specific test indicate involvement of the study drug(s) in the occurrence/worsening of the AE, and no indication of other causes exists.

14.1.5. Outcome of Adverse Events

The Investigator will assess the outcome of the AE after careful medical consideration, on a case-by-case basis. General guidelines are provided below:

Recovered/Resolved:	The event resolved and the subject recovered from the AE.
Recovered/Resolved with Sequelae:	The initial event resolved, but has a continuing abnormal condition as a result of the AE.
Not Recovered/ Not Resolved:	At the time of last assessment, the event was ongoing, with an undetermined outcome. Note: ongoing AEs are not to be considered resolved as a result of death.
Recovering/Resolving:	At the time of last assessment, the event was decreasing in frequency, severity, etc., and a resolution was expected.
Fatal:	The AE directly caused death.
Unknown:	There was an inability to access the subject or the subject's records to determine the outcome (e.g., subject withdrew consent or was lost to follow-up).

14.1.6. Action Taken with Subject due to an Adverse Event

The Investigator will provide any actions taken regarding the subject (e.g., treatment, diagnostic tests, laboratory tests, or therapy) for each reported AE.

- None.
- Medication.

- Non-pharmaceutical therapy. (The specific therapy used must be recorded in the CRF.)
- Discontinued from study.
- Other. (The specific action taken must be recorded.)

14.2. Serious Adverse Events

14.2.1. Definition of a Serious Adverse Event

Definition of a SAE: An AE is considered "serious" if, in the view of either the Investigator or Pacira, it results in any of the following outcomes:

- Death[1].
- A life-threatening AE[2].
- Inpatient hospitalization or prolongation of existing hospitalization[3].
- A persistent or significant incapacity[4].
- Congenital anomaly/birth defect.
- Medically significant[5].

[1]**Death:** Any event resulting in a subject's death must be reported as an SAE. However, death, in and of itself, is not an AE; it is an outcome. The cause of death is the AE. Therefore, the Investigator must make every effort to obtain and document the cause of death for all subjects who die during the study. If, despite all efforts, the cause of death remains unknown, the AE must be documented as an "unspecified fatal event."

[2]**Life-threatening**: An AE is considered life-threatening if, in the view of either the Investigator or Pacira, its occurrence places the subject at immediate risk of death. It does not include an AE that had it occurred in a more severe form might have caused death.

[3]**Hospitalization**: It should be noted that hospitalization, in and of itself, does not represent an SAE. It is the AE leading to the subject's hospitalization that becomes "serious" when it requires inpatient care. Consequently, an SAE must not be reported in case of preplanned hospitalizations for a pre-existing condition that did not worsen during the study. However, any medical condition that delays a subject's discharge from the hospital (i.e., prolonged hospitalization) or requires the subject to be readmitted must be reported as an SAE.

[4]**Persistent or significant incapacity**: A substantial disruption of a person's ability to conduct normal life functions.

[5]**Medically Significant**: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medically significant events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

14.2.2. Reporting Serious Adverse Events

Any SAE or death that occurs at any time after the subject signs the ICF through postsurgical Day 29, whether or not related to EXPAREL, must be reported by the Investigator or designee to Pacira Drug Safety within 24 hours of discovery by either email (drugsafety@pacira.com) or fax (973-201-0649). In addition, the Investigator or designee is encouraged to contact the Medical Monitor to discuss the case, as needed.

Investigators should not wait to receive additional information to fully document the event before notifying Pacira Drug Safety or designee of the SAE. The fax or email report must be followed by a full written summary using the SAE Form detailing relevant aspects of the SAE in question. Where applicable, information from relevant hospital records and autopsy reports must be obtained and all patient-identifying information redacted prior to forwarding to Pacira. In the event of a fatal or life-threatening SAE, any required follow-up must be provided to Pacira Drug Safety or designee immediately. The Investigator will follow all SAEs until resolved or the condition stabilizes and further follow-up is not warranted.

If the Investigator is made aware of any SAEs after postsurgical Day 29, these must also be reported to Pacira Drug Safety or designee provided the SAE is considered related to EXPAREL. The site would then provide a completed SAE form within 1 business day and the event would be followed until resolution, or until adequate stabilization is met.

15. STATISTICAL METHODS

A comprehensive statistical analysis plan (SAP) will be developed for this study.

15.1. Study Hypothesis

The primary null hypothesis is:

H_0: The mean of the AUC of the VAS pain intensity scores through 48 hours is not different between the EXPAREL and placebo groups.

The alternative hypothesis is:

H_A: The mean AUC of the VAS pain intensity scores through 48 hours for the EXPAREL group is less than that of the placebo group.

15.2. Study Endpoints

The endpoints to be assessed in this study are listed in Section 12.2 (Efficacy Endpoints), Section 12.4 (PK Endpoints), and Section 12.6 (Safety Endpoints).

15.3. Determination of Sample Size

The sample size was calculated based on efficacy as measured by the AUC of the NRS-R pain intensity scores through 72 hours from a previously conducted nerve block study. Assuming a 2-sided 0.05 alpha and a common SD of 170 and controlling alpha for the two efficacy comparisons, a sample size of 50 subjects per treatment group should have at least 80% power to detect a 100-unit treatment difference.

15.4. Analysis Populations

The following analysis sets are planned:

Safety: The safety analysis set will include all subjects who receive study drug and will be based on actual treatment received.

Efficacy: The efficacy analysis set will include all subjects in the safety analysis set who undergo the planned surgery and will be based on randomized treatment, regardless of actual treatment received.

15.5. Handling Subject Dropouts and Discontinuations

For the calculation of the AUC of VAS pain intensity scores through any of the time periods, the following methods will be used for imputing missing data:

Missing scores before the first non-missing score will be replaced by the median score at the missing timepoint from other subjects in the same treatment group. Missing scores after the last non-missing score will be replaced by the last non-missing score (last observation carried forward). Missing scores between two non-missing scores will use linear interpolation to replace the missing score.

Additional methods for dealing with missing data will be described in the SAP.

15.6. Statistical Analyses

15.6.1. Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group.

15.6.2. Study Compliance

The percentage of subjects in each analysis set and the percentage who fail to complete the study (as well as the reasons for discontinuation) will be displayed by treatment group.

15.6.3. Efficacy Analyses

All efficacy analyses will be based on randomized treatment, regardless of actual treatment received.

15.6.3.1 Primary Efficacy Measures

The primary efficacy measure in this study is the AUC of the VAS pain intensity scores through 48 hours.

For the AUC of the VAS pain intensity scores through 48 hours, EXPAREL will be compared to placebo using analysis of variance (ANOVA) with treatment and site as main effects. A two-sided test will be performed comparing EXPAREL to placebo, at the two-sided 5% significance level. Based on the model, the difference between treatment groups will be estimated along with the 2-sided 95% confidence intervals (CIs).

Handling of Subjects Requiring Rescue Medication

For AUC of the VAS pain intensity scores, prior to analysis the windowed Worst-Observation-Carried-Forward (wWOCF) imputation method will be applied. For subjects who take rescue pain medication, their pain intensity scores recorded within the window of controlled type of rescue medication will be replaced by the 'worst' observation. All pain scores within that window will be replaced by the 'worst' observation. The worst observation will be the highest score in the time interval from the end of surgery up to the time prior to taking their first rescue pain medication. Note that pain intensity scores in the window that are higher than the worst value prior to rescue pain medication will not be overwritten. If no pain intensity score is available prior to the first rescue pain medication, the worst observation from all available measurements will be used instead.

15.6.3.2 Secondary Efficacy Measures

See significance testing in Section 15.7 for an explanation of the statistical approach for secondary efficacy measures.

Total postsurgical opioid consumption through 48 hours will be converted to IV morphine equivalents and analyzed using the same ANOVA model as the primary endpoint.

Percentage of opioid-free subjects through 48 hours will be analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by site.

Time to first opioid rescue through 48 hours will be analyzed by the Kaplan-Meier method and the Gehan-Wilcoxon test.

15.6.3.2 Tertiary Efficacy Measures

Statistical testing will not be performed on any of the tertiary endpoints.

Continuous Measures of Efficacy

For the AUC of pain intensity scores, missing data will be imputed as described in Section 15.5 and fully described in the SAP.

Summary statistics for each measure will be shown at each timepoint by treatment group.

Categorical Measures of Efficacy

For categorizing subjects as pain-free, the VAS pain intensity score must be ≤1.5 without prior rescue medication use at the assessed timepoint.

The proportion of subjects in each category will be calculated and summarized at each timepoint by treatment group.

Time to Event Measures

The time from start of study drug administration to event will be summarized with Kaplan-Meier estimates.

15.6.4. Pharmacokinetic Analyses

Pharmacokinetic parameters will be estimated using a population PK approach.

15.6.5. Safety Analyses

All safety analyses will be based on actual treatment received.

15.6.5.1. Adverse Events

Adverse event verbatim terms will be mapped to PTs and related system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). Events that start prior to the start of study drug administration will be identified in listings only. Incidence rates of TEAEs and the proportion of subject prematurely withdrawn from the study due to a TEAE will be shown for each treatment group. Incidence rates will also be displayed for each treatment group for study drug-related TEAEs and by severity. Incidence rates of SAEs will also be shown for each treatment group. All incidence rates will be categorized and displayed by system organ class and PT.

15.6.5.2. Vital Signs

Descriptive statistics for each vital sign for baseline, each timepoint, and change from baseline at each timepoint will be summarized for each treatment group.

15.6.5.3. Clinical Laboratory Data

Descriptive statistics for each laboratory test for baseline, each timepoint, and change from baseline at each timepoint will be summarized for each treatment group.

15.6.5.4. Electrocardiograms

Descriptive statistics for each ECG parameter for baseline, each timepoint, and change from baseline at each timepoint will be summarized for each treatment group.

15.6.5.5. Neurological Assessment

The proportion of subjects who are oriented at each timepoint will be summarized for each treatment group. The proportion of subjects who have at least one of the neurological events will be summarized for each treatment group.

15.7. Significance Testing

EXPAREL will be compared with placebo using ANOVA with treatment and site as the main effects for the primary efficacy endpoint of AUC of the VAS pain intensity scores through 48 hours. A hierarchical procedure will be used to provide control of the type 1 error across the four key null hypotheses, i.e., for the null hypotheses corresponding to the primary treatment group comparison (EXPAREL 133 mg treatment group versus placebo) in combination with each of the three secondary endpoints of greatest interest. Efficacy endpoints may be analyzed using ANOVA, chi-square tests, and Gehan-Wilcoxon tests, as appropriate.

15.8. Interim Pharmacokinetic Analysis

A blinded interim PK analysis was completed after 13 subjects completed the assessments through postsurgical Day 10. All of the plasma samples from the subjects who received EXPAREL were analyzed, including the samples from subjects who had discontinued from the study or who had missing samples. Enrollment continued while the interim PK data were analyzed. The goal of this unblinded analysis was to determine the appropriateness of the PK timepoints selected and make recommendations to keep, remove, or revise them in order to fully characterize the PK profile.

The results of this analysis showed a median T_{max} of 48 hours for the 133 mg EXPAREL group and a median T_{max} of 60 hours for the 266 mg EXPAREL group. These data informed the changes to the PK collection schedule contained in this protocol amendment.

In addition, the safety assessment timepoints, including the neurological exam, vital signs, and ECG were adjusted based on the initial interim PK data; a confirmatory blinded PK interim analysis will be conducted once 30 subjects have completed the assessments through postsurgical Day 10.

15.8.1. Sample Size Reestimation Interim Analysis

An interim analysis will be performed after 66 subjects have completed the assessments through Day 5. The objective of the interim analysis is to verify the assumptions for the study sample size. The verification of sample size assumptions will be based on the "quick and simple" procedure described by Kieser (2000) to estimate the pooled sample variance; all other assumptions used for the original sample size estimate will remain constant. No adjustment to the study significance level will be made to complete this interim analysis (Keiser 2000). The interim analysis and verification of the sample size will be performed by a blinded biostatistician not involved in the conduct of the study. The statistician performing the interim analysis will communicate any change in sample size resulting from the interim analysis; all

other interim analyses and results will be embargoed until after database lock. Results from the interim assessment of sample size will be included as an appendix in the clinical study report.

Pacira will be informed after completion of the assessment of the study sample size that either (a) the sample size will remain the same, no adjustments are to be made, or (b) the sample size will be increased to the determined study sample size up to a maximum of 200. Note that the only adjustment to the sample size allowed by this interim assessment is an increase. The study sample size will not be reduced, and no comparative evaluation of efficacy to evaluate either superiority or futility will be completed as part of this interim assessment.

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17. INVESTIGATOR AGREEMENT

Printed Name of Investigator: _____

Printed Title/Position: _____

Printed Institution Address: _____

_____

_____

_____

_____

I have reviewed this protocol (including Appendices) and agree:

- To assume responsibility for the proper conduct of the study at this site;
- To conduct the study in compliance with this protocol, with any future amendments, and with any other study conduct procedures provided by Pacira Pharmaceuticals, Inc. (Pacira) or designee. I also agree to comply with Good Clinical Practice and all regulatory requirements;
- Not to implement any changes to the protocol without agreement from Pacira or designee and prior review and written approval from the Independent Ethics Committee, except where it is necessary to eliminate an immediate hazard to the subjects or for administrative aspects of the study (where permitted by applicable regulatory requirements);
- That I am thoroughly familiar with the appropriate use of the investigational product(s), as described in this protocol, and with other relevant information (e.g., the Investigator's Brochure);
- To ensure that all persons assisting me with the conduct of this study are adequately informed about the investigational product(s) and about their study-related duties and functions as described in this protocol;
- That I am aware that regulatory authorities may require Investigators to disclose all information about significant ownership interests and/or financial ties related to Pacira and/or the investigational product(s). Consequently, I agree to disclose all such significant financial information to Pacira and to update this information promptly if any relevant changes occur during the course of the study through 1 year following completion of the study. I also agree that any information regarding my significant financial interest related to Pacira and/or the investigational product(s) will be disclosed to the regulatory authorities by Pacira.

_____ _____

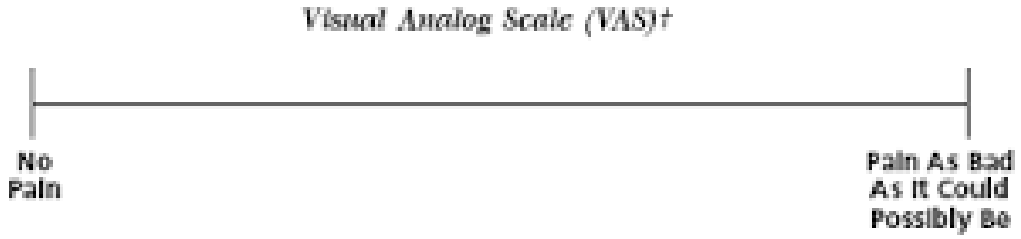
Signature of Investigator Date

18. APPENDICES

Appendix 1: Subject's Reported Pain Intensity

Subjects will be evaluated for pain using a 10-cm VAS at baseline (on Day 0 prior to the nerve block and prior to any premedication); upon arrival at the PACU, every 15 minutes while in the PACU, and prior to PACU discharge; at 6, 12, 24, 36, 48, 60, and 72 hours; and immediately prior to each administration of rescue pain medication through 72 hours.

Subjects will be asked, "How much pain are you experiencing right now? Please place a vertical mark on the line below to indicate the level of pain you are experiencing right now."



(For reference only; not for clinical use.)

Appendix 2: Overall Benefit of Analgesia Score (OBAS) Questionnaire

The OBAS questionnaire will be completed at 24 and 72 hours, and on postsurgical Day 10 (Lehmann 2010).

1. Please rate your current pain at rest on a scale between 0 = minimal pain and 4 = maximum imaginable pain
2. Please grade any distress and bother from vomiting in the past 24 h (0 = not at all to 4 = very much)
3. Please grade any distress and bother from itching in the past 24 h (0 = not at all to 4 = very much)
4. Please grade any distress and bother from sweating in the past 24 h (0 = not at all to 4 = very much)
5. Please grade any distress and bother from freezing in the past 24 h (0 = not at all to 4 = very much)
6. Please grade any distress and bother from dizziness in the past 24 h (0 = not at all to 4 = very much)
7. How satisfied are you with your pain treatment during the past 24 h (0 = not at all to 4 = very much)

Appendix 3: Subject Satisfaction with Postsurgical Pain Control (Likert Scale)

The subject's satisfaction with postsurgical pain control will be assessed at 24 and 72 hours, and on postsurgical Day 10.

Please circle the number below that best describes your overall satisfaction with the pain medication you received after surgery. (Circle one number only.)

1. Extremely dissatisfied
2. Dissatisfied
3. Neither satisfied nor dissatisfied
4. Satisfied
5. Extremely satisfied

Appendix 4: Neurological Assessment

The neurological assessment will be conducted at screening; baseline (on Day 0 prior to the nerve block); upon arrival at the PACU; at 6, 9, 12, 24, 36, 40, 44, 48, 52, 56, 60, and 72 hours; and on postsurgical Days 5 and 10.

The examination will include the subject's orientation.

- Is the subject oriented?
  Yes △ No △ Not Assessable

If the subject is not oriented, the event should be recorded as an AE.

Additionally, the subject will be asked the following questions:

- Since your last assessment have you had numbness of the lips, the tongue, or around the mouth?
  Yes △ No
- Since your last assessment have you had a metallic taste in your mouth?
  Yes △ No
- Since your last assessment, have you had problems with your hearing not related to the use of a hearing aid? △ Yes △ No
- Since your last assessment, have you had problems with your vision not related to the use of eye glasses? △ Yes △ No
- Since your last assessment, have your muscles been twitching?
  Yes △ No

If the subject answers “yes” to any of these questions, the event should be recorded as an AE and additional safety procedures should be conducted (see Section 13.1.11).

Appendix 5: Sensory Function Assessment (Cold, Pinprick, and Light Touch Tests)

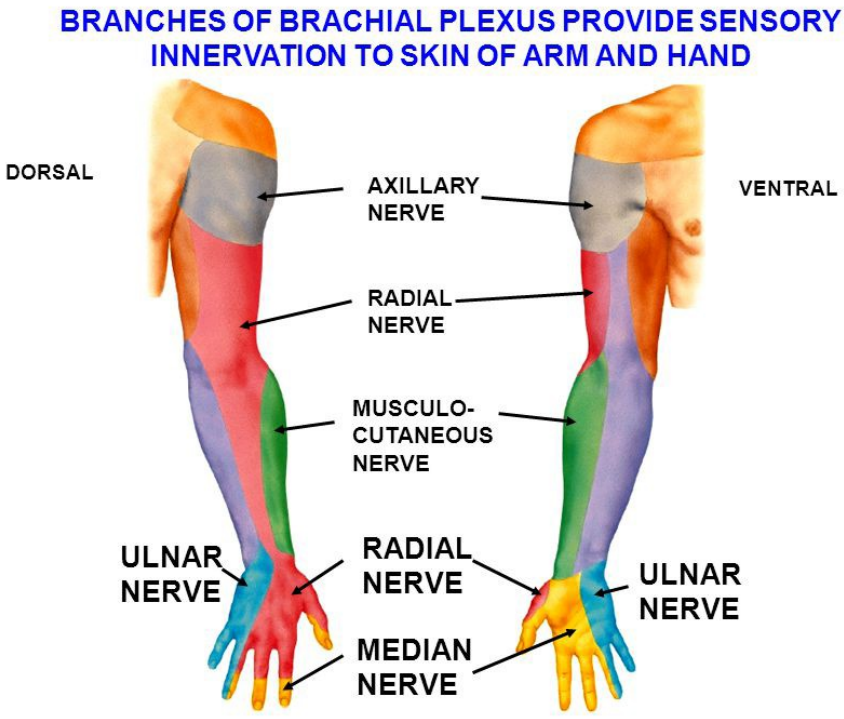
For the sensory function assessment, the subject's sensitivity to cold, pinprick, and light touch in the distal part of innervated dermatomes (musculocutaneous, median, ulnar, radial, and axillary; see diagrams below) will be assessed with their eyes closed at screening, baseline (on Day 0 prior to the nerve block); at approximately 15, 30, and 45 minutes prior to the OR; prior to discharge from the PACU; at 6, 9, 12, 18, 24, 36, 48, 60, and 72 hours. If sensory deficit is present at 72 hours, the subject will be assessed on day 5. If on postsurgical Day 5 there is a sensory deficit, the sensory deficit will be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent sensory deficit. If there continues to be a sensory function deficit on Day 5, the sensory function will be further assessed on postsurgical Day 10. If the sensory deficit persists on postsurgical Day 10, the subject is to return for unscheduled visit(s) at the Investigator's discretion through postsurgical Day 29 or until the sensory function has returned to baseline, whichever occurs first.

The cold, pinprick, and light touch tests will be conducted, starting with the cold test, followed randomly by the pinprick and light touch tests interspaced with blunt touch. Subjects will be given four choices for reporting their perception of the stimulus: "sharp," "blunt," "cold, "or "light touch." The test may be repeated in case of ambiguous or inconsistent responses until the examiner is satisfied with the accuracy of the assessment. Only cold, pinprick, and light touch sensitivity will be assessed and recorded for study purposes. Blunt touch stimulation serves as a way to gauge the subject response and reduce the chance that the subject may guess the correct answer.

Cold sensitivity will be tested by gently applying ice (Sakura 1998) to contact the skin spot in the distal part of dermatome for 3 seconds. For the pinprick assessment, a disposable sharp-bevel needle will be used to prick the skin spot in the distal part of the dermatome using the point and guard in a random fashion. The subject should reply "sharp" or "dull" with eyes closed. Care is to be taken to prevent penetration of the dermis, and the sharp object used should be discarded after the test. Blunt touch with a cotton swab (e.g., Q-tip) will be conducted the same way. Testing for light touch will be done using a wisp of cotton pulled from a cotton ball. The assessments will be conducted single-blinded (i.e., the nature of the stimulus will be concealed from the subject) and the result will be defined as presence/absence of cold, pinprick, and light touch sensation.

Instructions

1. To prepare subjects for the cold, pinprick, and light touch tests, they should be placed in a comfortable position with their eyes closed.
2. Before starting the assessments, all subjects should be well trained in all aspects of the testing. It is critical that each subject knows precisely what to expect during the testing.
3. Interactions between study subjects and Investigators should be limited to those necessary for collecting data. Joking and small talk should be discouraged because they may compromise data consistency.
4. Keep the instructions clear, simple, and consistent. Emphasize that pain is subjective, and there are no right or wrong answers. It is most important to be consistent.


BRANCHES OF BRACHIAL PLEXUS PROVIDE SENSORY INNERVATION TO SKIN OF ARM AND HAND
DORSAL
VENTRAL
AXILLARY NERVE
RADIAL NERVE
MUSCULO-CUTANEOUS NERVE
ULNAR NERVE
RADIAL NERVE
MEDIAN NERVE
ULNAR NERVE

Appendix 6: Motor Function Assessment

The degree of motor nerve block will be assessed at screening; baseline (on Day 0 prior to the nerve block); at approximately 15, 30, and 45 minutes prior to the OR; prior to discharge from the PACU; at 6, 9, 12, 18, 24, 36, 48, 60, and 72 hours . If motor function deficit (Lovett score below 5) is present at 72 hours, the subject will be assessed again on Day 5. If on postsurgical Day 5 there is a motor deficit, ie, the subject's Lovett score has not returned to 5, the motor deficit will be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent motor deficit. If there continues to be a motor function deficit on Day 5, the motor assessment will be further assessed on postsurgical Day 10. If the motor deficit persists on postsurgical Day 10, the subject is to return for unscheduled visit(s) at the Investigator's discretion through postsurgical Day 29 or until the motor function has returned to a Lovett score of 5, whichever occurs first.

The motor block will be evaluated by performing thumb abduction (radial nerve), thumb adduction (ulnar nerve), thumb opposition (median nerve), and elbow flexion in seated position (musculocutaneous nerve).

Onset of loss of motor function is the first timepoint after baseline at which the Lovett scale (Florence 1992, Paternostro-Sluga 2008) decreases to below a 3 in at least one of the motor function assessments (biceps, wrist, and thumb movement). Return of motor function is the first timepoint after loss of motor function where any of the motor function assessments return to a 3 or above on the Lovett scale (Liu 2013).

Lovett Scale for grading muscle strength and function level

Functional Level	Lovett Scale	Grade	Percentage of Normal
No evidence of contractility	Zero (Z)	0	0
Evidence of slight contractility	Trace (T)	1	10
Complete range of motion without gravity	Poor (P)	2	25
Complete range of motion with gravity	Fair (F)	3	50
Complete range of motion against gravity with some resistance	Good (G)	4	75
Complete range of motion against gravity with full resistance	Normal (N)	5	100

Appendix 7: Discharge Readiness

The subject's discharge readiness will be assessed at 12, 24, 36, 48, 60, and 72 hours until the subject is determined to be discharge ready, whichever occurs first, using the MPADSS shown below (Chung 1995a; Chung 1995b). This discharge readiness assessment will be used for data collection only and is not intended to interfere with the surgical center's policy for determining when the subject should be discharged from the site. Only subjects who achieve a score of 9 or higher are considered ready for discharge. Discontinue assessing discharge readiness once a score of 9 or higher is reached.

Modified Postanesthesia Discharge Scoring System (MPADSS)

Parameter	Score
Vital Signs	
≤20% of preoperative value	2
20%-40% of preoperative value	1
>40% of preoperative value	0
Ambulation	
Steady gait/no dizziness	2
With assistance	1
None/dizziness	0
Nausea and Vomiting	
Minimal	2
Moderate	1
Severe	0
Pain	
Minimal	2
Moderate	1
Severe	0
Surgical Bleeding	
Minimal	2
Moderate	1
Severe	0

Appendix 8: Clinical Laboratory Tests

The scheduled clinical laboratory tests (hematology, chemistry, and urinalysis) will be conducted at screening; baseline (on Day 0 prior to the nerve block); and on postsurgical Day 10.

Additionally, appropriate clinical laboratory tests should be conducted if a subject experiences an AESI (i.e., cardiac AE or neurological AE), fall, or an SAE (see Section 13.1.11).

General Chemistry Analysis	General Hematology (CBC with Differential) Components	Urinalysis
Albumin	White blood cells	Color
Alkaline phosphatase	Red blood cells	Appearance
Alanine transaminase (ALT)	Hemoglobin	Specific gravity
Amylase	Hematocrit	pH
Aspartate transaminase (AST)	Mean corpuscular volume	Protein
Bilirubin, direct	Mean corpuscular hemoglobin	Glucose
Bilirubin, total	Mean corpuscular hemoglobin concentration	Ketones
Blood urea nitrogen	Red cell distribution width	Bilirubin
Calcium	Platelets	Blood
Carbon dioxide (bicarbonate)	Mean platelet volume	Urobilinogen
Chloride	Absolute/percent neutrophil count	Nitrite
Cholesterol	Absolute/percent lymphocyte count	Leukocyte esterase
Creatine kinase (CK), total (or creatine phosphokinase [CPK])	Absolute/percent monocyte count	
Creatinine, serum	Absolute/percent eosinophil count	
Gamma-glutamyl transpeptidase (GGT)	Absolute/percent basophil count	
Glucose		
Iron		
Iron binding capacity (UIBC/TIBC)		
Lactate dehydrogenase (LDH)		
Lipase		
Magnesium		
Phosphorus		
Potassium		
Sodium		
Total protein		
Transferrin		
Triglycerides		
Uric acid		