Clinical Study Protocol
Amendment 3

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of Femoral Nerve Block with EXPAREL for Postsurgical Analgesia in Subjects Undergoing Total Knee Arthroplasty

Protocol No.:	402-C-326
EudraCT No.:	2015-005179-25
IND No.:	69,198
Study Phase:	Phase 3
Study Drug:	EXPAREL® (bupivacaine liposome injectable suspension)
Date:	07 November 2016 (Amendment 3)
	28 September 2016 (Amendment 2)
	15 February 2016 (Amendment 1)
	16 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 Femoral Nerve Block with EXPAREL for Postsurgical Analgesia in Subjects Undergoing Total Knee Arthroplasty

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 femoral nerve block with EXPAREL in subjects undergoing primary unilateral total knee arthroplasty (TKA).

Secondary Objectives: The secondary objectives of this study are to further 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 TKA.

Methodology: This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study in approximately 231 adult subjects undergoing primary unilateral TKA under general or spinal 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, the study physical therapy assessments (ie, timed walk, timed up and go, and stair climbing tests), 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 1:1:1 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 (Group 1); EXPAREL 266 mg in 20 mL (Group 2); or placebo 20 mL (Group 3). Subjects may receive acetaminophen/ paracetamol up to 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 femoral nerve block at least 1 hour prior to surgery. A confirmatory photo of the ultrasound nerve block needle placement will be obtained. Use of tourniquets and drains, if used, will be recorded. Prior to placement of the prosthesis, 8 mL of bupivacaine HCl (0.5%) diluted with 8 mL of normal saline will be administered by the surgeon as a periarticular infiltration to the posterior capsule (8 mL medially and 8 mL laterally). The use of opioids (other than ultrashort-acting opioids [ie, fentanyl, sufentanil, or remifentanil]), acetaminophen/ paracetamol, ketorolac, or other non-steroidal anti-inflammatory drugs (NSAIDs), and local anesthetics other

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than the study drug will not be permitted intraoperatively, except for emergency use to treat an adverse event (AE). Subjects will be required to remain at the hospital facility through postsurgical Day 4.

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 the following scheduled medications until hospital discharge:

- Acetaminophen/paracetamol up to 1000 mg PO or IV every 8 hours (q8h) unless contraindicated. The total daily dose of acetaminophen/paracetamol should not exceed 3000 mg.
- Cyclobenzaprine (eg, Flexeril®) 10 mg PO x1 dose (PRN at the surgeon's discretion)

No other analgesic agents, including NSAIDs, are permitted through 108 hours (postsurgical Day 4). After 108 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)
- Physical therapy assessments (ie, timed walk, timed up and go, and stair climbing tests; Appendix 9)
- 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 6 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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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 24 hours postdose to postsurgical Day 6. 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 24, 56, 68, 80, and 108 hours. Subjects in Sequence 2 will have samples taken at 48, 60, 76, 96 hours, and Day 6.

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 30 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 60 hours for the 133 mg EXPAREL group and a median T_{max} of 78 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 interim PK data.

Number of Subjects (Planned): Approximately 231 subjects (77 subjects per treatment group) are planned for enrollment in this study in order to have at least 225 evaluable subjects.

Eligibility Criteria:

Inclusion Criteria:

1. Male or female, at least 18 years of age at Screening.
2. Scheduled to undergo primary unilateral TKA under general or spinal anesthesia.
3. American Society of Anesthesiologists (ASA) physical status 1, 2, or 3.
4. 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.
5. Able to demonstrate sensory function by exhibiting sensitivity to cold, pinprick, and light touch.
6. Able to provide informed consent, adhere to the study visit schedule, and complete all study assessments.

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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 (eg, bilateral TKA).
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 knee surgery and which may confound the postsurgical assessments (eg, significant pain from other joints including the non-index knee joint, chronic neuropathic pain, concurrent or prior contralateral TKA, concurrent foot surgery).
4. Previous open knee surgery on the knee being considered for TKA. Prior arthroscopy is permitted.
5. History of hypersensitivity or idiosyncratic reaction to amide-type local anesthetics.
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 medication 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, poorly controlled chronic respiratory disease, rheumatoid arthritis, coagulopathy, or loss of sensation in extremities.
12. Impaired kidney function (eg, 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 (eg, 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.

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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 either 133 mg (10 mL) expanded in volume with 10 mL of normal saline for a total volume of 20 mL (Group 1), or 266 mg in 20 mL (Group 2)

Lot number: To be determined

Mode of administration: Preoperative femoral nerve block

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

Name: Placebo (normal saline)

Active ingredient: Not applicable

Dosage: 20 mL (Group 3)

Lot number: Commercial product to be provided by Pacira.

Mode of administration: Preoperative femoral nerve 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 femoral nerve 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, 72, 84, 96, and 108 hours; and immediately prior to each administration of rescue pain medication through 108 hours (see Appendix 1).
- Date, time of administration, and amount of all opioid rescue medication taken through 108 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 postsurgical Day 10 (see Appendix 3).
- Discharge readiness at 12, 24, 36, 48, 60, 72, 84, and 96 hours or until the subject 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.

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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 femoral nerve block with study drug*.

Primary Endpoint:

The primary endpoint is area under the curve (AUC) of the VAS pain intensity scores through 72 hours.

Secondary Endpoints:

The following secondary endpoints will be analyzed in the following order

1. Total postsurgical opioid consumption (in IV morphine equivalents) through 72 hours.
2. Percentage of opioid-free subjects through 72 hours.
3. Time to first opioid rescue through 72 hours.

Tertiary Endpoints:

- The AUC of the VAS pain intensity scores through 12, 24, 48, and 96 hours.
- The AUC of the VAS pain intensity scores from 24-48, 48-72 hours, and 72-96 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, 72, and 96 hours.
- SPIS from 24-48, 48-72, and 72-96 hours.
- Total opioid consumption in IV morphine equivalents through 24, 48, and 96 hours.
- Total opioid consumption in IV morphine equivalents from 24-48, 48-72, and 72-96 hours.
- Percentage of opioid-free subjects through 24, 48, and 96 hours.
- The OBAS total score at 24 and 72 hours, and postsurgical Day 10.
- Physical therapy assessments (ie, timed walk, timed up and go, and stair climbing tests) will be conducted at Screening; once postsurgically on Day 0; at 8:00 am (±2 hours) and 8:00 pm (±2 hours) from postsurgical Day 1 through hospital discharge; and once on 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, 72, 84, and 96 hours.
- Number of unscheduled phone calls or office visits related to pain after discharge through postsurgical Day 10.

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Pharmacokinetic Assessments:

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Pharmacokinetic Endpoints:

The following PK parameters will be determined:

- Area under the plasma concentration-versus-time curve from time 0 to the last collection time after drug administration ($AUC_{0\text{-}tlast}$).
- Area under the plasma concentration-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 femoral nerve 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; upon arrival at the PACU; at 6, 9, 12, 24, 36, 48, 56, 60, 64, 68, 72, 76, 80, 84, 96, and 108 hours; and on postsurgical Days 6 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, 48, 56, 60, 64, 68, 72, 76, 80, 84, 96, and 108 hours; and on postsurgical Days 6 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, 48, 56, 60, 64, 68, 72, 76, 80, 84, 96, and 108 hours; and on postsurgical Days 6 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 prior to the OR; prior to discharge from the PACU; at 6, 9, 12, 18, 24, 36, 48, 60, 72, 84, 96, and 108 hours; and at hospital discharge (see Appendix 5). If there is a sensory deficit at time of hospital discharge, sensory function will again be assessed on Day 6. If there continues to be a sensory deficit on Day 6, sensory function will again be assessed on Day 10. If there continues to be a sensory deficit on Day 10, the sensory deficit

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will be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent deficit. The subject will return for unscheduled visit(s) at the Investigator's discretion through postsurgical Day 29 or until sensory function has returned to baseline, whichever occurs first.

- Degree of motor nerve block (angle of flexion [active and passive] and angle of extension [active and passive]) 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, 72, 84, 96, and 108 hours; and at hospital discharge (see Appendix 6). If there is a motor function deficit at time of hospital discharge, motor function will again be assessed on Day 6. If there continues to be a motor function deficit on Day 6, motor function will again be assessed on Day 10. If there continues to be a motor function deficit on Day 10, the motor function deficit will be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent deficit. The subject will return for unscheduled visit(s) at the Investigator's discretion through postsurgical Day 29 or until motor function has returned to baseline, whichever occurs first.

  The following criteria (Paauwe 2008) will be used to determine if a subject has achieved a level of clinically meaningful physical rehabilitation or "return to baseline":

  1. Active flexion angle ≥80°.
  2. Active extension angle ≤10°.

  If a subject demonstrates a motor function deficit at Baseline, the subject will be considered to have returned to baseline if, at 108 hours (or before), the following two criteria are met:

  1. The active flexion measurement is no more than 10° less than the Baseline measurement
     AND
  2. The active extension angle is no more than 10° greater than the Baseline measurement
- 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 signs (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 (flexion [active and passive] and extension [active and passive]) at each assessed timepoint.
- Incidence of treatment-emergent AEs (TEAEs) and SAEs through postsurgical Day 29.

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Statistical Methods:

A comprehensive statistical analysis plan 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 as the main effect for the primary efficacy endpoint of AUC of the VAS pain intensity scores through 72 hours. A graphical multiplicity procedure will be used to provide strong control of the type 1 error across the eight key null hypotheses, ie, for the null hypotheses corresponding to the two primary pairwise treatment group comparisons (EXPAREL dosage arms versus placebo) in combination with each of the four (primary and three secondary) endpoints of greatest interest. Other efficacy endpoints will be analyzed using ANOVA, chi-square tests, and Gehan-Wilcoxon tests, as appropriate. Safety endpoints will be summarized descriptively by treatment group. The PK parameters will be calculated using non-compartmental analysis and summarized for each treatment group.

Sample Size

The sample size was estimated based on the results of a Phase-3 study of EXPAREL versus placebo in patients undergoing TKA where the means (standard deviation [SD]) AUC of the NRS-R pain intensity scores through 72 hours were 420 (169) and 514 (160) for the EXPAREL and placebo groups, respectively. Assuming a 2.5% two-sided alpha, common SD of 170 and a 3% drop-out rate, a sample size of 77 subjects per treatment group will have at least 80% power to detect a difference of 100 in at least one of the active treatment groups.Approximately 231 subjects (77 subjects per treatment group) are planned for enrollment in this study in order to have at least 225 evaluable subjects.

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 (Screening) or urine drug screen and alcohol breath test (Day 0 Preop)[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 FNB at least 1 hour prior to surgery; record start and stop times			X							
Take photo of ultrasound NB needle placement			X							
Administer 8 mL of bupivacaine HCl (0.5%) diluted with 8 mL normal saline to posterior capsule prior to placement of prosthesis; record time							X			
Record start and end time of tourniquet use and maximum pressure (mmHg) used							X			
Record date and time of insertion of drain(s), if used							X			
Record intraoperative opioids administered & doses							X			
Record surgery start and stop times							X			
Record date and time of removal of drain(s), if used										
Complete OBAS questionnaire										

Perform physical therapy assessments; record date and time[10]	X									
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[11]	◄----	----	----	----	----	----	----	----	----	---►
Record AEs beginning at the time ICF is signed[2,4, 5,9]	◄----	----	----	----	----	----	----	----	----	---►

Abbreviations: AE = adverse event; D = day; ECG = electrocardiogram; FNB = femoral nerve block; h = hours; 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 femoral nerve 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.

** 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; ie, cardiac AE, neurological AE, or fall), or a serious AE (SAE); see footnote 9.

3 Prior to the FNB 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 AE (ie, cardiac AE, neurological AE, or fall), or an SAE; see footnote 9.

5 Also conduct a 12-lead ECG if a subject experiences an AESI (ie, cardiac AE, neurological AE, or fall), or an SAE; see footnote 9. ECGs must be read within 2 hours.

6 Sensory function will be assessed using cold, pinprick, and light touch testing. If there is a sensory deficit at time of hospital discharge, sensory function will be assessed again on postsurgical Day 6. If there continues to be a sensory deficit on Day 6, sensory function will again be assessed on Day 10. If there continues to be a sensory deficit on Day 10, the sensory deficit will be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent deficit. The subject will return for unscheduled visit(s) at the Investigator's discretion through postsurgical Day 29 or until sensory function has returned to baseline, whichever occurs first.

7 The motor function assessments include flexion (active and passive) and extension (active and passive). If there is a motor function deficit at time of hospital discharge, motor function will be assessed again on postsurgical Day 6. If there continues to be a motor function deficit on Day 6, motor function will again be assessed on Day 10. If there continues to be a motor function deficit on Day 10, the motor function deficit will be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent deficit. The subject will return for unscheduled visit(s) at the Investigator's discretion through postsurgical Day 29 or until motor function has returned to baseline, whichever occurs first.

8 The preoperative pain intensity assessment must be conducted prior to administration of any premedication. Also record VAS pain intensity score immediately prior to each administration of rescue pain medication through 108 hours.

9 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, or 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.

10 Physical therapy assessments (ie, timed walk, timed up and go, and stair climbing tests) will be conducted at Screening; once postsurgically on Day 0; q12h from postsurgical Day 1 through hospital discharge; and on postsurgical Day 10. Preemptive use of opioids or NSAIDs prior to the physical therapy assessment is not permitted.

11 Instruct subject to discontinue prohibited medications. Record date and time of all medications starting at least 30 days prior to study drug administration through 108 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.

12 Assess vital signs every 5 mins during performance of the nerve block

Table 2: Time and Events Schedule of Study Procedures - 6 Hours Through Day 29

	6h	9h	12h	18h	24h	36h	48h	56h	60h	64h	68h	72h	76h	80h	84h	96h	108h	D6 Visit	D10 Visit	D29 Call
Time Window	**±30 min**	**±30 min**	**±30 min**	**±30 min**	**±1h**	**±1h**	**±1h**	**±2h**	**±2h**	**±2h**	**±2h**	**±2h**	**±2h**	**±2h**	**±2h**	**±4h**	**±6h**	**±1d**	**±1d**	**±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	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	X	X	X	X	
Perform 12-lead ECG recordings[5]	X	X	X		X	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	X	X	X[12]	X[12]	
Conduct motor function assessment[7]	X	X	X	X	X	X	X		X			X			X	X	X	X[13]	X[13]	
Record VAS pain intensity scores[8]	X		X		X	X	X		X			X			X	X	X			
Collect PK blood sample; record date and time[9]					S1		S2	S1	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																				
Administer 8 mL of bupivacaine HCl (0.5%) diluted with 8 mL normal saline to posterior capsule prior to placement of prosthesis; record time																				
Record start and end time of tourniquet use and maximum pressure (mmHg) used																				
Record date and time of insertion of drain(s), if used																				
Record intraoperative opioids administered & doses																				
Record surgery start and stop times																				
Record date and time of removal of drain(s), if used					◄	-	-	-	-	-	-	►								
Complete OBAS questionnaire					X							X							X	
Perform physical therapy assessments once postsurgically on Day 0, each day at 8:00 am (±2h) and 8:00 pm (±2h) from Day 1 until hospital discharge, and once on Day 10; record date and time[10]	◄	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	►		X	
Subject satisfaction with postsurgical pain control					X							X							X	

Assess discharge readiness; record date and time			X		X	X	X		X			X			X	X					
Record date and time of actual discharge																	X	X	X		
Document any unscheduled phone calls or office visits related to pain after discharge																		X	X		
Record prior and concomitant medications, including all analgesics[11]	←	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	→
Record AEs beginning at the time ICF is signed[2,7,8,9]	←	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	→

Abbreviations: AE = adverse event; D = day; ECG = electrocardiogram; FNB = femoral nerve block; h = hours; 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 Sequence 1; S2 = PK 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 femoral nerve 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.

** 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; ie, cardiac AE, neurological AE, or fall), or a serious AE (SAE); see footnote 9.

[3] Prior to the FNB 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 AE (ie, cardiac AE, neurological AE, or fall), or an SAE; see footnote 9.

[5] Also conduct a 12-lead ECG if a subject experiences an AESI (ie, cardiac AE, neurological AE, or fall), or an SAE; see footnote 9. ECGs must be read within 2 hours

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

[7] The motor function assessments include flexion (active and passive) and extension (active and passive). If there is a motor function deficit at time of hospital discharge, motor function will be assessed again on postsurgical Day 6. If there continues to be a motor function deficit on Day 6, motor function will again be assessed on Day 10. If there continues to be a motor function deficit on Day 10, the motor function deficit will be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent deficit. The subject will return for unscheduled visit(s) at the Investigator's discretion through postsurgical Day 29 or until motor function has returned to baseline, whichever occurs first. See Section 13.1.6 for the criteria used to determine “return to baseline” for motor function.

[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 108 hours.

[9] 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.

[10] Physical therapy assessments (ie, timed walk, timed up and go, and stair climbing tests) will be conducted once before surgery, once postsurgically on Day 0; q12h from postsurgical Day 1 through hospital discharge; and on postsurgical Day 10. Preemptive use of opioids or NSAIDs prior to the physical therapy assessment is not permitted.

[11] Instruct subject to discontinue prohibited medications. Record date and time of all medications starting at least 30 days prior to study drug administration through 108 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.

[12] Sensory function will be assessed at Day 6 only if there was a sensory deficit noted at hospital discharge. Likewise, sensory function will be assessed at Day 10 only if there was a sensory deficit noted on Day 6. If there continues to be a sensory deficit on Day 10, sensory deficit will be recorded as an AE and the physician will assess the subject for other

etiologies that may explain the persistent deficit. The subject will return for unscheduled visit(s) at the Investigator's discretion through postsurgical Day 29 or until sensory function has returned to baseline, whichever occurs first.

[13] Motor function will be assessed at Day 6 only if there was a motor function deficit noted at hospital discharge. Likewise, motor function will be assessed at Day 10 only if there was a motor function deficit noted on Day 6. If there continues to be a motor function deficit on Day 10, the motor function deficit will be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent deficit. The subject will return for unscheduled visit(s) at the Investigator's discretion through postsurgical Day 29 or until motor function has returned to baseline, whichever occurs first. See Section 13.1.6 for the criteria used to determine "return to baseline" for motor function.

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

	6h	9h	12h	18h	24h	36h	48h	56h	60h	64h	68h	72h	76h	80h	84h	96h	108h	D6 Visit	D10 Visit	D29 Call
Time Window	**±30 min**	**±30 min**	**±30 min**	**±30 min**	**±1h**	**±1h**	**±1h**	**±2h**	**±2h**	**±2h**	**±2h**	**±2h**	**±2h**	**±2h**	**±2h**	**±4h**	**±6h**	**±1d**	**±1d**	**±3d**
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		

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
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
LS	Least squares
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
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- or IEC-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 postsurgical 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, nonsteroidal 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 knee arthroplasty (TKA) is a common surgical procedure that causes postsurgical pain of considerable intensity and duration. While the standard analgesic medications administered prior to the TKA procedure and used to provide analgesic relief immediately after surgery can vary, most experts agree that multimodal pain control has become the standard of care. In TKA, that may include local and regional analgesic techniques (ie, neuraxial blocks, peripheral nerve blocks, and wound infiltration) combined with acetaminophen and an NSAID or a cyclooxygenase-2 selective inhibitor with opioids reserved as rescue analgesics. This approach has been shown to significantly reduce opioid requirements and opioid-related adverse events (AEs). It is clear that opioid-related AEs increase perioperative morbidity, including delay in ambulation and participation in rehabilitation therapy programs. Also, analgesic adjuncts, such as dexamethasone (single intraoperative dose) and gabapentinoids (ie, gabapentin and pregabalin) may provide further benefit (Joshi 2015). Following surgery, additional analgesic treatment often includes opioids. Therefore, TKA was selected as an appropriate pain model 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 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 (eg, 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 (eg, 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 (ie, 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.

7.3.1. Summary of Human Experience with EXPAREL

7.3.1.1. 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 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 adverse events (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.

7.3.1.2. 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.

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 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.

7.4. Postmarketing Exposure

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 femoral nerve block with EXPAREL in subjects undergoing primary unilateral TKA.

8.2. Secondary Objectives

The secondary objectives of this study are to further assess the efficacy, safety, and PK profile of EXPAREL as well as the onset and duration of sensory and motor function blockade following administration for analgesia in subjects undergoing primary unilateral TKA.

9. STUDY DESIGN AND PLAN

9.1. Study Design

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study in approximately 231 adult subjects undergoing primary unilateral TKA under general or spinal 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 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, the study physical therapy assessments (ie, timed walk, timed up and go, and stair climbing tests), 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 1:1:1 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 (Group 1); EXPAREL 266 mg in 20 mL (Group 2); or placebo 20 mL (Group 3). Subjects may receive acetaminophen/paracetamol up to 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 femoral nerve block at least 1 hour prior to surgery. A confirmatory photo of the ultrasound nerve block needle placement will be obtained. Use of tourniquets and drains, if used, will be recorded. Prior to placement of the prosthesis, 8 mL of bupivacaine HCl (0.5%) diluted with 8 mL of normal saline will be administered by the surgeon as a periarticular infiltration to the posterior capsule (8 mL medially and 8 mL laterally). The use of opioids (other than ultrashort-acting opioids [ie, 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 adverse event (AE).

Subjects will be required to remain at the hospital facility through postsurgical Day 4.

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 the following scheduled medications until hospital discharge:

- Acetaminophen/paracetamol up to 1000 mg PO or IV every 8 hours (q8h) unless contraindicated. The total daily dose of acetaminophen is not to exceed 3000 mg.

- Cyclobenzaprine (eg, Flexeril®) 10 mg PO x1 dose (PRN at the surgeon's discretion)

No other analgesic agents, including NSAIDs, are permitted through 108 hours. After 108 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 (see Appendix 6); physical therapy assessments (ie, timed walk, timed up and go, and stair climbing tests; Appendix 9); 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 collected 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 6 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 24 hours postdose to postsurgical Day 6. 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 24, 56, 68, 80, and 108 hours. Subjects in Sequence 2 will have samples taken at 48, 60, 76, and 96 hours, and Day 6.

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 30 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 60 hours for the 133 mg EXPAREL group and a median T_{max} of 78 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 interim PK data.

9.1.1. 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.

9.1.2. 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 will be the trigger for prompting 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 serious AEs 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 further evaluate the efficacy, safety, and pharmacokinetics of femoral nerve block with EXPAREL for postsurgical analgesia in subjects undergoing TKA. 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, the time to first opioid use was similar across the treatment groups likely due to pain in the posterior portion of the knee, which is enervated by the sciatic nerve. Although the femoral nerve block is well-suited for surgery on the anterior thigh and knee, quadriceps tendon repair, and postoperative pain management after femur and knee surgery, it is often combined with a block of the sciatic nerve in order to achieve analgesia of nearly the entire lower extremity. As this study, similar to 402-C-323, involves blockade of only the femoral nerve, prior to the placement of the prosthesis, an additional 8 mL of bupivacaine HCl (0.5%) diluted with 8 mL of normal saline will be administered by the surgeon as a periarticular infiltration to the posterior capsule (8 mL medially and 8 mL laterally). This amount is consistent with the amount of study drug placed into the posterior capsule in prior EXPAREL studies (eg, study 402-C-208).

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 time to maximum plasma concentration (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 30 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.

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. Consistent with analgesia but not anesthesia, significant sensory blockade occurred very infrequently in the nerve block program. In study 402-C-323, the return of motor function was assessed using a validated 20-meter walk test that is commonly used in clinical practice and has been used in numerous clinical trials. The validation of this method was performed with the use of a walker or cane only to ensure subject safety. The percentage of subjects able to complete

the 20-meter walk test was comparable between the EXPAREL and placebo groups at 24 hours, 72 hours, and on Day 30.

As there is no single universally clinically accepted validated outcomes instrument for motor testing, two motor tests of the muscles impacted by the nerve block will be undertaken. The degree of motor nerve block (angle of flexion [active and passive] and angle of extension [active and passive]) will be assessed at baseline (on Day 0 prior to the nerve block); at approximately 15, 30, and 45 minutes; prior to PACU discharge; at 6, 9, 12, 18, 24, 36, 48, 60, 72, 84, 96, and 108 hours; and at hospital discharge.

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 proximal and distal part of innervated dermatomes that express the anterior femoral cutaneous nerve (L2/L3) and saphenous nerve (L4) will be assessed with their eyes closed at baseline (on Day 0 prior to the nerve block); at approximately 15, 30, and 45 minutes; prior to PACU discharge; at 6, 9, 12, 18, 24, 36, 48, 60, 72, 84, 96, and 108 hours; and at hospital discharge.

If there is a sensory and/or motor function deficit at the time of hospital discharge, sensory and/or motor function will again be assessed on Day 6. If there continues to be a sensory and/or motor function deficit on Day 6, sensory and/or motor function will again be assessed on Day 10. If there continues to be a sensory and/or motor function deficit on Day 10, the sensory and/or motor function deficit will be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent deficit(s). The subject will return for unscheduled visit(s) at the Investigator's discretion through postsurgical Day 29 or until sensory and/or motor function has returned to baseline, whichever occurs first. See Section 13.1.6 for the criteria used to determine "return to baseline" for motor function.

All subjects will receive an opioid analgesic(s) to control breakthrough postsurgical pain, as needed.

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. 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.

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 TKA under general or spinal anesthesia.
3. American Society of Anesthesiologists (ASA) physical status 1, 2, or 3.
4. 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.
5. Able to demonstrate sensory function by exhibiting sensitivity to cold, pinprick, and light touch.
6. 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 (eg, bilateral TKA).
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 knee surgery and which may confound the postsurgical assessments (eg, significant pain from other joints including the non-index knee joint, chronic neuropathic pain, concurrent or prior contralateral TKA, concurrent foot surgery).
4. Previous open knee surgery on the knee being considered for TKA. Prior arthroscopy is permitted.
5. History of hypersensitivity or idiosyncratic reaction to amide-type local anesthetics.
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 medication 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 prior to study drug administration.
11. History of impaired kidney function, poorly controlled chronic respiratory disease, rheumatoid arthritis, coagulopathy, or loss of sensation in extremities.
12. Impaired kidney function (eg, 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 (eg, 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, physical therapy assessments, 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 (Group 1), EXPAREL 266 mg in 20 mL (Group 2), or placebo (normal saline, 20 mL) according to the randomization schedule. Study drug administration will be performed in a blinded manner (see Section 11.5.1).

Bupivacaine HCl

In addition to the study drug, prior to the placement of the prosthesis, 8 mL of bupivacaine HCl (0.5%) diluted with 8 mL of normal saline will be administered by the surgeon as a periarticular infiltration to the posterior capsule (8 mL medially and 8 mL laterally).

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 the following scheduled medications until hospital discharge:

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

No other analgesic agents, including NSAIDs, are permitted through 108 hours. After 108 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

Study drug (EXPAREL or placebo) will be administered under ultrasound guidance by the anesthesiologist into the femoral nerve as described below (adopted from Mariano 2009). A confirmatory photo of the ultrasound nerve block needle placement will be obtained.

Subjects will have their femoral nerve located by ultrasound guidance alone. The recommended method is as follows: With a linear array transducer in a sterile sleeve, the femoral nerve will be identified in a transverse (short-axis) view at the inguinal crease. In a transverse view, the internal appearance of the peripheral nerve bundle is a mixture of hypoechoic neural tissue (fascicles) and hyperechoic connective tissue (perineurium and epineurium). Once the optimal image of the femoral nerve is obtained, a local anesthetic skin wheal will be raised lateral to the ultrasound transducer. A needle will be inserted through the skin wheal and directed medially in plane beneath the ultrasound transducer toward the femoral nerve. The study drug (total volume of 20 mL) will be injected posterior to the femoral nerve via the needle.

Bupivacaine HCl

Posterior capsule: bupivacaine HCl should be infiltrated primarily into the peripheral aspects, behind the medial and lateral condyles. Do not inject too deeply into the central portion of the posterior capsule to avoid puncturing the popliteal vessels. Keeping the knee in a flexed position will help the vessels relax and pull away from the capsule.

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 sites 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 placebo.

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 231 subjects (77 per treatment group) are planned for enrollment. Subjects will be randomized in a 1:1:1 ratio to receive a single-dose injection femoral nerve block with EXPAREL 133 mg, EXPAREL 266 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.

Pacira conducted a Phase 2/3, multicenter, randomized, double-blind, parallel-group, placebo-controlled, dose-ranging study in subjects undergoing primary unilateral TKA under general or spinal anesthesia (Study 402-C-323). Three dose levels of EXPAREL versus placebo were evaluated with respect to the magnitude and duration of the analgesic effect achieved following single-dose injection femoral nerve block with EXPAREL.

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. The primary endpoint was the AUC of the NRS-R pain intensity scores through 72 hours. The least squares (LS) mean AUC of the NRS-R pain intensity scores was 533.4 in the EXPAREL 67 mg group, 427.2 in the EXPAREL 133 mg group, 436.2 in the EXPAREL 266 mg group, and 530.5 in the placebo group. The difference between the LS mean for the EXPAREL 67 mg group and the placebo group was not statistically significant (p=0.9494); however, the differences between the other groups (EXPAREL 133 mg and EXPAREL 266 mg) and the placebo group were statistically significant (p=0.0237 and p=0.0386, respectively). The two EXPAREL doses that were significantly superior to placebo for the primary endpoint, 133 mg and 266 mg, were selected for the current study.

The most common volume of local anesthetic administered in the majority of femoral nerve blocks is 10 to 20 mL (Nader 2013), and previous studies with EXPAREL have used a range of concentrations in 20 mL.

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 operating room records to not record information in an unblinded fashion. Pharmacy or any other clinic records providing unblinded information (eg, 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 (ie, through mishaps in the operating room 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 108 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

- 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 or 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 (ie, 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 (eg, 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.
- Intrathecal opioids.
- The use of long-acting opioids (eg, 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.

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

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

Restricted

- No other analgesics, including fentanyl, are permitted within 108 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 108 hours following study drug administration. Therefore, the study staff must adhere closely to the treatment options and requirements noted in the protocol. After 108 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 (eg, pharmacist) in maintaining current and accurate inventory records. At a minimum, the pharmacist 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 an unblinded 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 unblinded 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 femoral nerve 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, 72, 84, 96, and 108 hours; and immediately prior to each administration of rescue pain medication through 108 hours (see Appendix 1).

- Date, time of administration, and amount of all opioid rescue medication taken through 108 hours.
- The OBAS questionnaire at 24 and 72 hours, and on postsurgical Day 10 (see Appendix 2).
- Physical therapy assessments (ie, timed walk, timed up and go, and stair climbing tests) will be conducted once postsurgically on Day 0; at 8:00 am (±2 hrs) and 8:00 pm (±2 hrs) from postsurgical Day 1 through hospital discharge; and on postsurgical Day 10 (Appendix 9). Preemptive use of opioids or NSAIDs prior to the physical therapy assessment is not permitted.
- Subject satisfaction with overall analgesia (using a 5-point Likert scale) at 24 and 72 hours, and postsurgical Day 10 (see Appendix 3).
- Discharge readiness at 12, 24, 36, 48, 60, 72, 84, and 96 hours or until the subject 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.

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 femoral nerve block with study drug*.

Primary Endpoint:

The primary endpoint is AUC of the VAS pain intensity scores through 72 hours.

Secondary Endpoints:

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

1. Total postsurgical opioid consumption (in IV morphine equivalents) through 72 hours.
2. Percentage of opioid-free subjects through 72 hours.
3. Time to first opioid rescue through 72 hours.

Tertiary Endpoints:

- The AUC of the VAS pain intensity scores through 12, 24, 48, and 96 hours.
- The AUC of the VAS pain intensity scores from 24-48, 48-72, and 72-96 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, 72, and 96 hours.
- SPIS from 24-48, 48-72, and 72-96 hours.
- Total opioid consumption in IV morphine equivalents through 24, 48, and 96 hours.

- Total opioid consumption in IV morphine equivalents from 24-48, 48-72, and 72-96 hours.
- Percentage of opioid-free subjects through 24, 48, and 96 hours.
- The OBAS total score at 24 and 72 hours, and postsurgical Day 10.
- Physical therapy assessments (ie, timed walk, timed up and go, and stair climbing tests) will be conducted once postsurgically on Day 0; at 8:00 am (±2 hrs) and 8:00 pm (±2 hrs) from postsurgical Day 1 through hospital discharge; and once on 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, 72, 84, and 96 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 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 24 hours postdose to postsurgical Day 6. 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 24, 56, 68, 80, and 108 hours. Subjects in Sequence 2 will have samples taken at 48, 60, 76, and 96 hours, and Day 6.

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: $AUC_{t\text{-}\infty} = Ct_{last}/\lambda_z$.

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 femoral nerve 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 up to 30 minutes; and every 15 minutes after the block until entering the operating room; upon arrival at the PACU; at 6, 9, 12, 24, 36, 48, 56, 60, 64, 68, 72, 76, 80, 84, 96, and 108 hours; and on postsurgical Days 6 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, 48, 56, 60, 64, 68, 72, 76, 80, 84, 96, and 108 hours; and on postsurgical Days 6 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, 48, 56, 60, 64, 68, 72, 76, 80, 84, 96, and 108 hours; and on postsurgical Days 6 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; and at 6, 9, 12, 18, 24, 36, 48, 60, 72, 84, 96, and 108 hours; and hospital discharge (see Appendix 5). If there is a sensory deficit at time of hospital discharge, sensory function will again be assessed on Day 6. If there continues to be a sensory deficit on Day 6, sensory function will again be assessed on Day 10. If there continues to be a sensory deficit on Day 10, the sensory deficit will be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent deficit. The subject will 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 (angle of flexion [active and passive] and angle of extension [active and passive]) 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; and at 6, 9, 12, 18, 24, 36, 48, 60, 72, 84, 96, and 108 hours; and hospital discharge (see Appendix 6). If there is a motor function deficit at time of hospital discharge, motor function will again be assessed on Day 6. If there continues to be a motor function deficit on Day 6, motor function will again be assessed on Day 10. If there continues to be a motor function deficit on Day 10, the motor function deficit will be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent deficit. The subject will 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. See Section 13.1.6 for the criteria used to determine "return to baseline" for motor function.

- Adverse events from the time the ICF is signed through 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 signs (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 (flexion [active and passive] and extension [active and passive]) 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 femoral nerve 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 collected 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 Assessments

Pain intensity will be assessed using the 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, 72, 84, 96, and 108 hours; and immediately prior to each administration of rescue pain medication through 108 hours (see Appendix 1).

If ice or passive extenders are used, these must be stopped at least 15 minutes prior to the pain intensity assessment. If subjects are in immobilizers, these must be removed at least 15 minutes prior to the pain intensity assessment.

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, 48, 56, 60, 64, 68, 72, 76, 80, 84, 96, and 108 hours; and on postsurgical Days 6 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 must be conducted (see Section 13.1.12).

13.1.5. Sensory Function Assessment

Sensory function (as measured by cold, pinprick, and light touch sensation) will be assessed at Screening; 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; and at 6, 9, 12, 18, 24, 36, 48, 60, 72, 84, 96, and 108 hours; and hospital discharge (see Appendix 5). If there is a sensory deficit at time of hospital discharge, sensory function will again be assessed on Day 6. If there continues to be a sensory deficit on Day 6, sensory function will again be assessed on Day 10. If there continues to be a sensory deficit on Day 10, the sensory deficit will be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent deficit. The

subject will 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 or certified medical professionals (physician, nurse, physical therapist, etc),
2. They have prior experience completing the assessment being conducted or have similar relevant experience,
3. They have participated and completed the 326 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 (angle of flexion [active and passive] and angle of extension [active and passive]) will be assessed at Screening; 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, 72, 84, 96, and 108 hours; and at hospital discharge (see Appendix 6). If there is a motor function deficit at time of hospital discharge, motor function will again be assessed on Day 6. If there continues to be a motor function deficit on Day 6, motor function will again be assessed on Day 10. If there continues to be a motor function deficit on Day 10, the motor function deficit will be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent deficit. The subject will 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.

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

1. They are a licensed or certified medical professionals (physician, nurse, physical therapist, etc),
2. They have prior experience completing the assessment being conducted, or have similar relevant experience,
3. They have participated and completed the 326 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.

The following criteria (Paauwe 2008) will be used to determine if a subject has achieved a level of clinically meaningful physical rehabilitation or "return to baseline":

1. Active flexion angle ≥80°.
2. Active extension angle ≤10°.

If a subject demonstrates a motor function deficit at Baseline, the subject will be considered to have returned to baseline if, at 108 hours (or before), the following two criteria are met:

1. The active flexion measurement is no more than 10° less than the Baseline measurement AND
2. The active extension angle is no more than 10° greater than the Baseline measurement

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 an 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 (see Appendix 8). Clinical laboratory tests, as appropriate, may also be conducted if a subject experiences an AESI (ie, cardiac AE, neurological AE, or fall) or an SAE (see Section 13.1.12).

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 up to 30 minutes; and then every 15 minutes after completion of the block until arrival at the OR; upon arrival at the PACU; at 6, 9, 12, 24, 36, 48, 56, 60, 64, 68, 72, 76, 80, 84, 96, and 108 hours; and on postsurgical Days 6 and 10. Vital signs will also be measured if a subject experiences an AESI (ie, cardiac AE, neurological AE, or fall) or an SAE (see Section 13.1.12). The subject will remain in a supine position during the assessment.

13.1.9. Physical Examination

A full physical examination will be conducted at s 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 lower extremity including the site of the femoral block and the knee itself.

13.1.10. Electrocardiogram

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, 48, 56, 60, 64, 68, 72, 76, 80, 84, 96, and 108 hours; and on postsurgical Days 6 and 10. The 12-lead ECG(s) will also be conducted if a subject experiences an AESI (ie, cardiac AE, neurological AE, or fall) or an SAE (see Section 13.1.12). Note: ECGs must be read within 2 hours.

13.1.11. Physical Therapy Assessments

The physical therapy assessment (ie, timed walk, timed up and go, and stair climbing tests) will be conducted at Screening; once postsurgically on Day 0; each day at 8:00 am (±2h) and 8:00 pm (±2h) from Day 1 through hospital discharge; and once on Day 10.

Preemptive use of opioids or NSAIDs immediately prior to the physical therapy assessment is not permitted.

The physical therapy assessments will be completed in the following order: timed walk test, followed by the timed up and go test, followed by the stair climbing test.

At timepoints when multiple assessments coincide, the physical therapy assessments will be conducted last.

Details regarding the information to be recorded for the physical therapy assessments are provided in Appendix 9.

13.1.12. Adverse Events of Special Interest

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. 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
- Perform sensory function assessment (see Appendix 5)
- Conduct motor function assessment (see Appendix 6)
- Conduct physical therapy assessments (ie, timed walk, timed up and go, and stair climbing tests; see Appendix 9)
- 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 femoral nerve block at least 1 hour prior to surgery
- Measure vital signs (resting heart rate and blood pressure) every 5 minutes during the performance of the block
- Record start and stop times of study drug administration
- Take confirmatory photo of the ultrasound nerve block needle placement
- Record concomitant medications
- Record AEs and any treatment(s) for the events
- Refer to Section 13.1.12 for additional procedures in the event a cardiac AE, neurological AE, fall, or SAE occurs

13.5. Approximately 15, 30, and 45 Minutes After 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 5 minutes upto 30 minutes after the block and then every 15 minutes until entering the OR
- Record concomitant medications
- Record AEs and any treatment(s) for the events
- Refer to Section 13.1.12 for additional procedures in the event a cardiac AE, neurological AE, fall, or SAE occurs

13.6. Intraoperative Procedures

- Prior to placement of the prosthesis, administer 8 mL of bupivacaine HCl (0.5%) (40 mg) diluted with 8 mL of normal saline as a periarticular infiltration to the posterior capsule
- Record time of bupivacaine HCl administration
- Record intraoperative opioids administered and doses

- Record start and stop times of tourniquet use and the maximum pressure (mm Hg)
- Record time of insertion of drain(s), if used
- Record start and stop times of surgery
- Record concomitant medications
- Record AEs and any treatment(s) for the events
- Refer to Section 13.1.12 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 13.1.12 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 degree of motor nerve block (see Appendix 6)
- Record other concomitant medications
- Record AEs and any treatment(s) for the events
- Refer to Section 13.1.12 for additional procedures in the event a cardiac AE, neurological AE, fall, or SAE occurs

13.9. Postsurgical Assessments through Hour 108

- Record VAS pain intensity scores at 6, 12, 24, 36, 48, 60, 72, 84, 96, and 108 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 24 (±1) hrs, 56 (±2) hrs, 68 (±2) hrs, 80 (±2) hrs, and 108 (±6) hrs.
    - *PK Sequence Schedule 2*: Blood collected at 48 (±1) hrs, 60 (±2) hrs, 76 (±2) hrs, 96 (±4) hrs, and Day 6 (±1 day)
- Perform neurological assessment at 6, 9, 12, 24, 36, 48, 56, 60, 64, 68, 72, 76, 80, 84, 96, and 108 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, 48, 56, 60, 64, 68, 72, 76, 80, 84, 96, and 108 hours
- Conduct 12-lead ECG after the subject has rested in a supine position at 6, 9, 12, 24, 36, 48, 56, 60, 64, 68, 72, 76, 80, 84, 96, and 108 hours. ECG must be read within 2 hours
- Assess sensory function at 6, 9, 12, 18, 24, 36, 48, 60, 72, 84, 96, and 108 hours (see Appendix 5)
- Assess degree of motor nerve block at 6, 9, 12, 18, 24, 36, 48, 60, 72, 84, 96, and 108 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)
- Conduct physical therapy assessments (ie, timed walk, timed up and go, and stair climbing tests) once postsurgically on Day 0, and at 8:00 am (±2 hrs) and 8:00 pm (±2 hrs) from postsurgical Day 1 until hospital discharge (see Appendix 9)
- 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
- Record time of removal of drain(s), if used
- Assess discharge readiness at 12, 24, 36, 48, 60, 72, 84, and 96 hours or until the subject is determined to be discharge ready, whichever occurs first (see Appendix 7)
- Record date and time of discharge from hospital
- 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 13.1.12 for additional procedures in the event a cardiac AE, neurological AE, fall, or SAE occurs

13.10. Postsurgical Day 6 Visit

- Collect scheduled blood samples for PK analysis per sequence schedule; 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 the subject has rested in a supine position. ECG must be read within 2 hours
- If there was a sensory deficit at time of hospital discharge, reassess sensory function (see Appendix 5)
- If there was a motor deficit at time of hospital discharge, reassess motor function (see Appendix 6)
- Record date and time of discharge, if applicable
- 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 13.1.12 for additional procedures in the event a cardiac AE, neurological AE, fall, or SAE is reported

13.11. Postsurgical Day 10 Visit

- 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)
- Perform neurological assessment (see Appendix 4)
- If there was a sensory deficit at Day 6, reassess sensory function (see Appendix 5). If a sensory deficit persists, record this as an AE (see Section 13.1.5 for additional details)
- If there was a motor function deficit at Day 6, reassess motor function (see Appendix 6). If a motor function deficit persists, record this as an AE (see Section 13.1.6 for additional details)

- Conduct clinical laboratory tests (hematology, chemistry, and urinalysis; see Appendix 8)
- Conduct physical therapy assessments (ie, timed walk, timed up and go, and stair climbing tests; see Appendix 9)
- Record date and time of discharge, if applicable
- 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 13.1.12 for additional procedures in the event a cardiac AE, neurological AE, fall, or SAE is reported

13.12. Unscheduled Visit(s)

- If a sensory (Appendix 5) or motor function (Appendix 6) deficit persists on postsurgical Day 10, this will be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent deficit(s). 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, whichever occurs first
- Record concomitant medications including all analgesic medication administered
- Record AEs and any treatment(s) for the events

13.13. 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 (eg, 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 (eg, 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 (eg, 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 (ie, 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; ie, lined through and initialed). Whenever possible, abnormal laboratory results must be reported as their clinical corollary (eg, 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 (ie, 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 (eg, 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 an 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); the event itself, however, 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 for determining the AE's causality to the study drug are provided below.

Unrelated:	A causal relationship between the study drug and the AE can be easily ruled out (eg, 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 (eg, 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 (eg, 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 Serious Adverse Event (SAE): An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death[1]
- A life-threatening adverse event[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 Sponsor, 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 (ie, 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 means of the AUC of the VAS pain intensity scores through 72 hours are not different between the EXPAREL and placebo groups.

The alternative hypothesis is:

H_A: The mean AUC of the VAS pain intensity scores through 72 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 estimated based on the results of a Phase-3 study of EXPAREL versus placebo in patients undergoing TKA where the means (standard deviation [SD]) AUC of the NRS-R pain intensity scores through 72 hours were 420 (169) and 514 (160) for the EXPAREL and placebo groups, respectively. Assuming a 2.5% two-sided alpha, common SD of 170 and a 3% drop-out rate, a sample size of 77 subjects per treatment group will have at least 80% power to detect a difference of 100 in at least one of the active treatment groups..

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 72 hours.

For the AUC of the VAS pain intensity scores through 72 hours, each EXPAREL dose will be compared to placebo using analysis of variance (ANOVA) with treatment and site as main effects. Each EXPAREL dose will be compared to placebo at the 0.025 level of significance to control the overall level of significance to not exceed 0.05. Based on the model, the difference between the treatment groups will be estimated along with the 2-sided 97.5% 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 72 hours will be converted to morphine equivalents and analyzed using the same ANOVA model as the primary endpoint. However, the alpha level for the secondary endpoint will be 0.05.

Percentage of opioid-free subjects through 72 hours will be analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by site.

Time to first opioid rescue through 72 hours will be analyzed by the Kaplan-Meier method.

15.6.3.3 Tertiary Efficacy Measures

No statistical comparisons are planned for the tertiary efficacy measures.

Continuous Measures of Efficacy

For the AUC of the 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 preferred terms 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 preferred term.

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

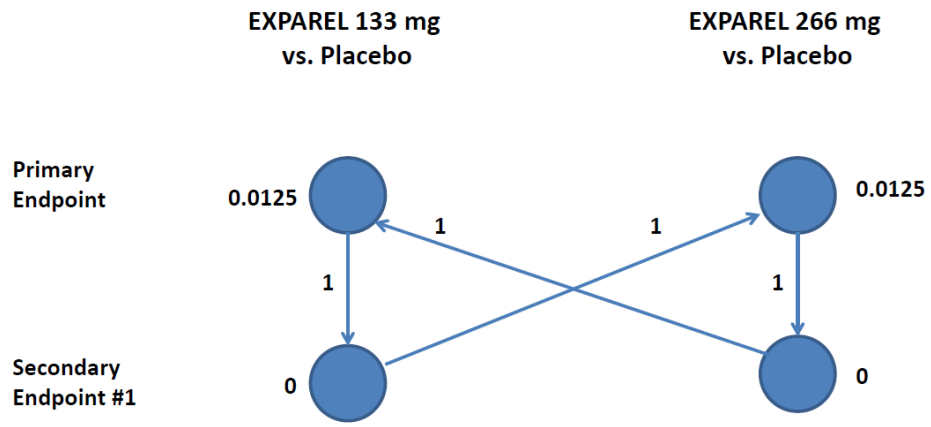
Significance testing will be based on "Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests" (Bretz 2011). The initial alpha will be set to 0.025 for each of the primary efficacy analyses. Subsequent testing will be conducted following the ideas of the paper. The initial testing diagram and other details will be provided in the SAP.

In addition to the primary endpoint (VAS AUC) there are three key secondary endpoints (total opioid consumption, percentage of opioid-free subjects, and time to first rescue medication), and for each of these four endpoints there are two primary pairwise comparisons. The procedure for multiplicity adjustment for these eight comparisons is described below, together with demonstration that it provides strong control of the type 1 error.

Let H_{PrimLD}, H_{Sec1LD}, H_{Sec2LD}, and H_{Sec3LD} represent the null hypotheses for the comparison of EXPAREL 133 mg versus Placebo. Likewise let H_{PrimHD}, H_{Sec1HD}, H_{Sec2HD}, and H_{Sec3HD} represent the null hypotheses for the comparison of EXPAREL 266 mg versus Placebo. Where H_{PrimLD}, H_{Sec1LD}, H_{Sec2LD}, and H_{Sec3LD} are respectively VAS AUC, total opioid consumption, percentage of opioid-free subjects, and time to first rescue medication and similarly for H_{PrimHD}, H_{Sec1HD}, H_{Sec2HD}, and H_{Sec3HD}.

The first stage of the multiplicity adjustment will be carried out using a graphical approach to sequentially rejective multiple test procedures (Bretz et al, 2009). This will be applied to the set of the four null hypotheses $F = \{H_{PrimLD}, H_{PrimHD}, H_{Sec1LD}, H_{Sec1HD}\}$ corresponding to the primary endpoint and the first key secondary endpoint (total post-surgical opioid consumption through 48 hours). Let $F_L = \{H_{PrimLD}, H_{Sec1LD}\}$ and $F_H = \{H_{PrimHD}, H_{Sec1HD}\}$ denote the families of null hypotheses corresponding to comparisons of EXPAREL 133 mg versus Placebo, and EXPAREL 266 mg versus Placebo, respectively. The particular graphical procedure used here initially assigns $\alpha = 0.0125$ one-sided for testing of the first member of each family (corresponding to the primary endpoint) and then within each family the two endpoints are tested in a fixed sequence.

If for either family null hypotheses for both endpoints can be rejected, then the fixed sequence for the other dose level can be conducted using α = 0.025 one-sided. This procedure can be viewed as a Bonferroni-Holm-type approach applied to the families F_L and F_H. This procedure can be depicted graphically as follows:



With F= {H_{PrimLD}, H_{PrimHD}, H_{Sec1LD}, H_{Sec1HD}} as above, then in the notation of Bretz et al (2009) we start with $\boldsymbol{\alpha}$ = (0.0125, 0.0125, 0, 0). A **G** matrix with elements g_{ij} is defined in that paper to denote the fraction of the local level α_i that is allocated to null hypothesis j from set F in the case that null hypothesis i is rejected. This 4x4 matrix **G** takes a simple form in the procedure considered here because $g_{13} = g_{24} = g_{32} = g_{41} = 1$, but all other elements are zero. Bretz et al (2009) provides an updating procedure for the matrix **G** as successive null hypotheses are rejected, and prove that such procedures provide strong control of the type 1 error. The particular procedure used in the current study implements the updating of $\boldsymbol{\alpha}$ and **G** in accordance with Bretz et al's (2009) "Algorithm 1." Further, the regularity conditions $0 \le g_{ij} \le 1$, $g_{ii} = 0$, and $\sum_{k=1}^{4} g_{ik} \le 1$ for all i, j = 1,...4, specified in equation (1) of that paper, are satisfied, and so strong control of type 1 error at α = 0.025 one-sided for testing of the four null hypotheses F = {H_{PrimLD}, H_{PrimHD}, H_{Sec1LD}, H_{Sec1HD}} follows from Bretz et al's proof.

The particular procedure used for the current trial is also given as an example to illustrate the graphical procedure within both Alosh et al (2014) and Bretz et al (2011).

The second stage of the multiplicity adjustment procedure relates to S = {H_{Sec2HD}, H_{Sec2LD}, H_{Sec3HD}, H_{Sec3LD}}, ie, the four null hypotheses related to the second key efficacy parameter (percentage of opioid-free subjects through 48 hours) and the third key efficacy parameter (time to first opioid rescue through 48 hours). These are only tested if all 4 null hypotheses from set F have already been rejected, and in that case H_{Sec2HD}, H_{Sec2LD}, H_{Sec3HD}, and H_{Sec3LD} are then tested sequentially in turn at α = 0.025 one-sided, where statistical significance is required for all preceding tests within set S as well as statistical significance for all tests from set F. If the required preceding null hypotheses have not been rejected then p-values for later tests in this sequence will be viewed only as descriptive.

Given that: (i) strong control of type 1 error at α = 0.025 one-sided has been demonstrated for testing of the four null hypotheses F; (ii) testing only proceeds to set S if all null hypotheses in

set *F* have been rejected; and (iii) the null hypotheses within set *S* are tested in a single step-down procedure, the above procedure has strong control of type 1 error at $\alpha = 0.025$ one-sided for testing of all eight null hypotheses.

Note: While the above procedure is described in terms of one-sided p-values, results will be presented as two-sided p-values.

15.8. Interim Pharmacokinetic Analysis

A blinded interim PK analysis was completed after 30 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 60 hours for the 133 mg EXPAREL group and a median T_{max} of 78 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 interim PK data.

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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 (eg, 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 the Sponsor 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.

_____ _____

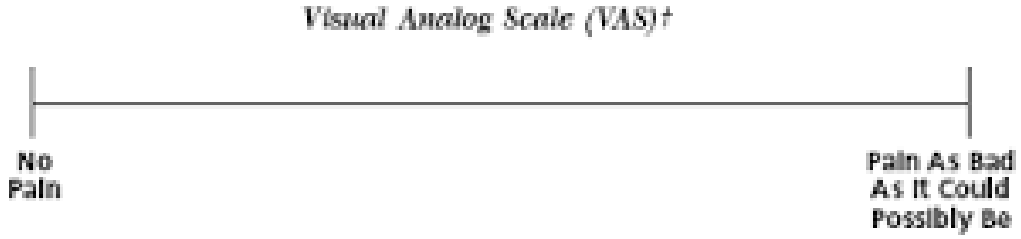
Signature of Investigator Date

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, 72, 84, 96, and 108 hours; and immediately prior to each administration of rescue pain medication through 108 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, 48, 56, 60, 64, 68, 72, 76, 80, 84, 96, and 108 hours; and on postsurgical Days 6 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 must be conducted (see Section 13.1.12).

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 proximal and distal part of innervated dermatomes that express the anterior femoral cutaneous nerve (L2/L3) and saphenous nerve (L4) 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 PACU discharge; at 6, 9, 12, 18, 24, 36, 48, 60, 72, 84, 96, and 108 hours; and at hospital discharge.

If there is a sensory deficit at time of hospital discharge, sensory function will again be assessed on Day 6. If there continues to be a sensory deficit on Day 6, sensory function will again be assessed on Day 10. If there continues to be a sensory deficit on Day 10, the sensory deficit will be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent deficit. The subject will 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" (corresponding to pinprick), "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.

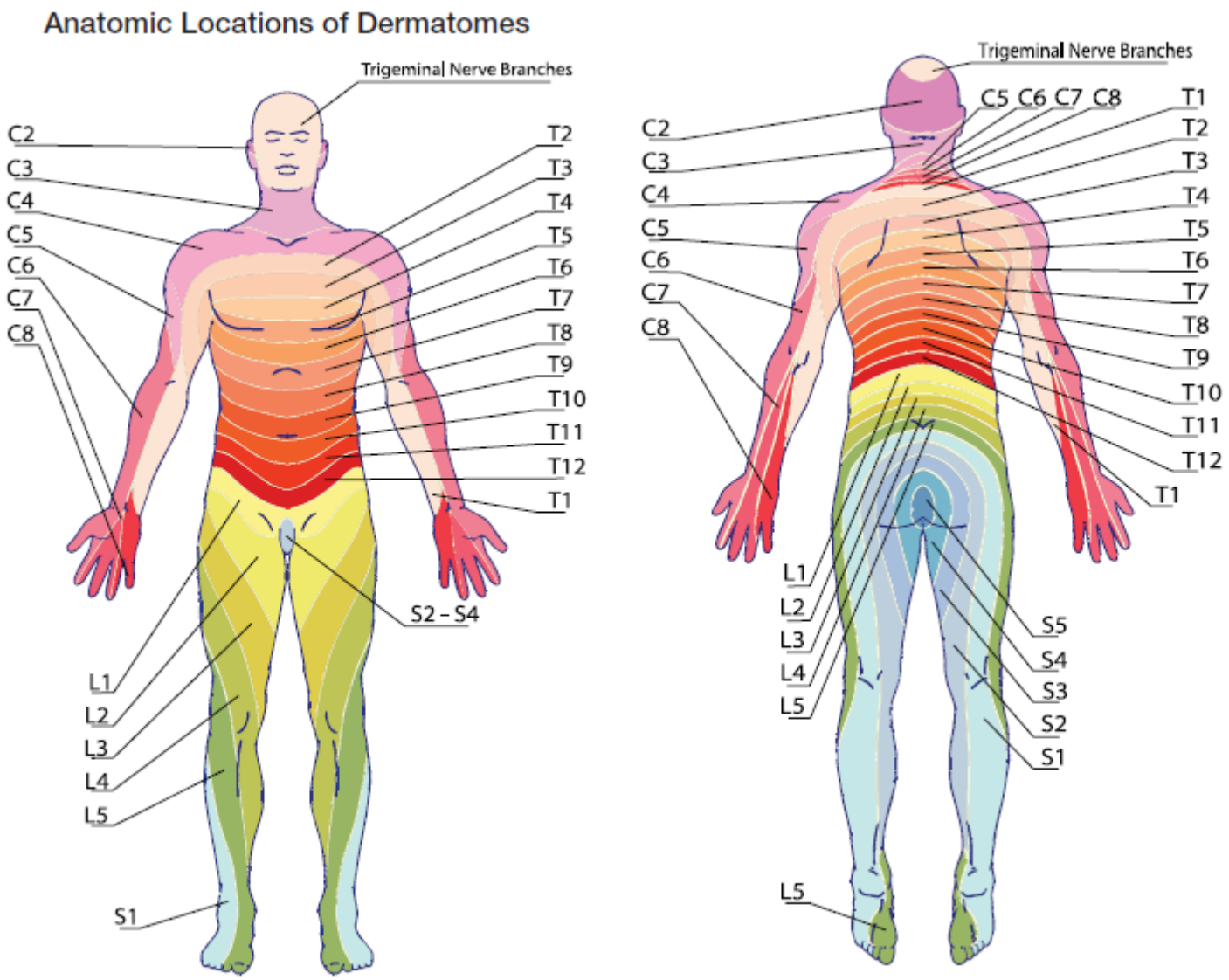
Cold sensitivity will be tested by gently applying ice (Sakura 1998) to contact the skin spot in the proximal and distal part of dermatome for 3 seconds. For the pinprick assessment, a disposable sharp-bevel needle will be used to prick the skin spot in the proximal and distal part of the dermatome. 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 (eg, 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 assessment will be conducted single-blinded (ie, 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. For the proximal sensory cutaneous test, assess the dermatome located roughly 15-20cm on the medial to the midline of the anterior section of the thigh above the knee (patella) that corresponds to the anterior cutaneous nerve of the thigh.

4. For the distal sensory cutaneous test, assess the dermatome located roughly 10 cm above the medial malleolus on the medial aspect of the leg below the knee that corresponds to the the saphenous nerve.
5. 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.
6. 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.


Anatomic Locations of Dermatomes
Trigeminal Nerve Branches
C2
C3
C4
C5
C6
C7
C8
T2
T3
T4
T5
T6
T7
T8
T9
T10
T11
T12
T1
S2 - S4
L1
L2
L3
L4
L5
S1
Trigeminal Nerve Branches
C2
C3
C4
C5
C6
C7
C8
C5 C6 C7 C8
T1
T2
T3
T4
T5
T6
T7
T8
T9
T10
T11
T12
T1
L1
L2
L3
L4
L5
S5
S4
S3
S2
S1
L5

Appendix 6: Motor Function Assessment

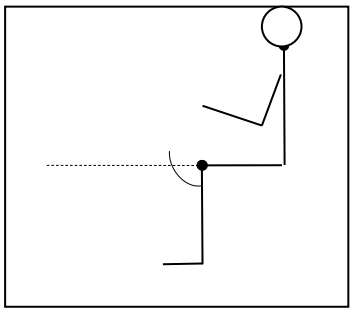
The degree of motor nerve block will be assessed at Screening; baseline (on Day 0 prior to the nerve block); at approximately 15, 30, and 45 minutes prior to the OR; prior to discharge from the PACU; at 6, 9, 12, 18, 24, 36, 48, 60, 72, 84, 96, and 108 hours; and at hospital discharge.

If there is a motor function deficit at time of hospital discharge, motor function will again be assessed on Day 6. If there continues to be a motor function deficit on Day 6, motor function will again be assessed on Day 10. If there continues to be a motor function deficit on Day 10, the motor function deficit will be recorded as an AE and the physician will assess the subject for other etiologies that may explain the persistent deficit. The subject will return for unscheduled visit(s) at the Investigator's discretion through postsurgical Day 29 or until motor function has returned to baseline, whichever occurs first.

The motor nerve block assessment should be conducted after the pain intensity assessment. The motor nerve block assessment will be conducted in accordance with the site's standard of care. Whenever possible, the same physical therapist is to conduct all motor nerve block assessments for a subject to reduce variability.

The following assessments will be conducted at each timepoint:

- Angle of flexion with active (against mild manual resistance, so as not to injure the knee) and passive (with gravitational resistance without assessor intervention);
- Angle of extension with active (against mild manual resistance, so as not to injure the knee) and passive (with gravitational resistance without assessor intervention) (example shown below).



The following criteria (Paauwe 2008), which were previously used in study SKY0402-C-208, will be used to determine if a subject has achieved a level of clinically meaningful physical rehabilitation or "return to Baseline":

1. Active flexion angle ≥80°.
2. Active extension angle ≤10°.

If a subject demonstrates a motor function deficit at Baseline, the subject will be considered to have returned to baseline if, at 108 hours (or before), the following two criteria are met:

1. The active flexion measurement is no more than 10° less than the Baseline measurement AND
2. The active extension angle is no more than 10° greater than the Baseline measurement

Appendix 7: Discharge Readiness

The subject's discharge readiness will be assessed at 12, 24, 36, 48, 60, 72, 84, and 96 hours or until the subject is determined to be discharge ready, whichever occurs first, using the MPADSS 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. Clinical laboratory tests, as appropriate, may also be conducted if a subject experiences an AESI (ie, cardiac AE, neurological AE, or fall) or an SAE (see Section 13.1.12).

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	
	Absolute/percent eosinophil count	
	Absolute/percent basophil count	
Creatinine, serum		
Gamma-glutamyl transpeptidase (GGT)		
Glucose		
Iron		
Iron binding capacity (UIBC/TIBC)		
Lactate dehydrogenase (LDH)		
Lipase		
Magnesium		
Phosphorus		
Potassium		
Sodium		
Total protein		
Transferrin		
Triglycerides		
Uric acid		

Appendix 9: Physical Therapy Assessments

The physical therapy assessments will be conducted at Screening; once postsurgically on Day 0; each day at 8:00 am (±2h) and 8:00 pm (±2h) from Day 1 until hospital discharge; and once on Day 10.

Physical Therapy Assessments List

The following physical therapy assessments will be performed in this study:

- Timed Walk Test
- Timed Up and Go Test
- Stair Climbing Test

General Physical Therapy Assessment Guidelines

- Preemptive use of opioids or NSAIDs immediately prior to the physical therapy assessment is not permitted
- At timepoints when multiple assessments coincide, the physical therapy assessments will be conducted last
- The physical assessments should be completed in the following order:
  1. Timed Walk Test
  2. Timed Up and Go Test
  3. Stair Climbing Test
- For all 3 physical therapy tests, the following will be recorded by the physical therapist:
  - The date of the assessment
  - The time of the assessment
  - Whether the test was performed or not
  - The level of physical assistance required (record for timed walk and timed up and go tests only)
    1. Total assistance (subject contributes < 25% of the effort or is unable to do the task)
    2. Maximal assistance (subject provides less than half of the effort (25–49%))
    3. Moderate assistance (subject still performs 50–75% of the task)
    4. Minimal assistance (requiring incidental hands-on help only (subject performs > 75% of the task))
    5. Supervision (requiring only standby assistance or verbal prompting or help with set-up)
    6. Modified independence (requiring the use of a device but no physical help)
    7. Complete independence (fully independent)
  - If a walking aid used

TIMED WALK TEST

EQUIPMENT REQUIRED

- Timer/stop watch
- Flat walking area (eg, hallway or open space), preferably greater than 20 meters in length. This can be a straight line, oval, or other shape.
- Bright color tape or cones to mark course boundaries, if necessary
- Tape or other marker to provide interval markings at regular intervals (eg, every 3 meters). This may not be necessary if floor is tiled and tile length is consistent and known (eg, 5 foot tiles).
- Chair(s) for resting, if needed, spread out as necessary

INSTRUCTIONS

Therapist instructions

1. Test should be conducted in a flat walking area with a known length
2. Subject is instructed that on the word "GO" they should walk forward at a normal, comfortable pace until they reach the end of the walking area, turn around, and walk back to the starting point (modify instructions as needed based on shape of actual walking area).
3. Physical therapist begins stopwatch and says "GO"
4. Subject is allowed to rest as needed (time is not stopped for resting)
5. The physical therapist walks alongside the subject, for safety purposes, and notes the amount of physical assistance required
6. Physical therapist records how far the subject walks (ie, keeps track of full and partial walking area lengths) during the 6 minute test
    a. If test is not performed, the physical therapist will record the specific reason
7. Physical therapist instructs the subject to stop walking after 6 minutes has passed
    a. If the subject cannot complete the 6 minutes, record distance walked at the time they stopped, but let the clock run out 6 minutes
8. The same walking area should be used for all assessments of study participants

Subject instructions

1. Start with both feet on the start line.
2. On "GO", walk comfortably and safely up and down the hallway (modify instructions as necessary to suit walking area).
3. Do the best you can by going at a normal, comfortable pace, but don't push yourself to a point of overexertion or beyond what you think is safe for you.
4. Keep walking for 6 minutes if possible, but don't be concerned if you need to slow down or stop to rest.
5. Get ready and GO.

Scoring

1. The test starts on the signal to start "GO" and terminates at 6 minutes.
2. The distance walked over the 6 minutes is recorded in meters.
3. A walking aid is allowed and should be recorded, if used.
4. Record the physical assistance required.

TIMED UP AND GO TEST

EQUIPMENT REQUIRED

- Timer/stop watch
- Standard chair (seat height: approximately 17 inches) with two arm rests (arm rest height: approximately 26 inches)
- Ruler to measure seat height and arm rest height
- Measuring tape to measure 3 meters away from the chair (approximately 9 feet 10 inches)
- Tape or other marker to mark the distance so that it is easily seen by the subject

INSTRUCTIONS

Therapist instructions

1. Subject begins seated on a standard chair with arm rests. Ensure the chair cannot slide backwards by placing it against a wall or otherwise bracing it (eg, physical therapist braces with foot).
2. Subject is instructed to sit facing forward, with both feet on the floor, and their buttocks touching the back of the seat
3. A line is placed on the floor 3 meters in front of the chair. Use a measuring tape to measure this distance. Alternatively, place the chair 3 meters away from an existing marker (eg, floor tile).
4. Subject is instructed that "On the word GO you will stand up, walk to the line on the floor, turn around and walk back to the chair and sit down. Walk at your regular pace."
5. The physical therapist then says "GO" and starts the stopwatch and records the time of assessment
6. The physical therapist walks alongside the subject, for safety purposes, and notes the amount of physical assistance required.
7. The goal of the test is to measure the subject's ability to complete the activity without assistance. The therapist should endeavor to not provide assistance unless required for safety reasons.
8. After the subject has completed the activity, the physical therapist stops the stopwatch and records the time lapsed in seconds
    a. If test is not performed, the physical therapist will record the specific reason
    b. Subject should be encouraged to complete the test. Time will continue to run until therapist determines it cannot be completed and the test is stopped.
9. The same chair should be used for all assessments, while on study

Subject instructions

1. Start by sitting in the chair with your back resting on the backrest and your hands on the armrest.
2. On "GO", stand up, walk to the mark, turn around, return and sit back into the chair with your back resting on the back of the chair.

3. Walk as quickly and safely as you can
4. Get ready and GO

Scoring

1. The test starts on the signal to start ("GO") and terminates once the participant sits back down fully with their back resting on the back of the chair.
2. The duration of the test is recorded to nearest 10th of a second.
3. A walking aid is allowed and should be recorded, if used.
4. Record the physical assistance required.

STAIR CLIMBING TEST

EQUIPMENT REQUIRED

- Flight of stairs with handrail on one or both sides

INSTRUCTIONS

Therapist instructions

1. Test should be conducted on a standard flight of stairs, each with a height of approximately 18 cm and a depth of approximately 28 cm, with adequate lighting.
2. Subject is instructed that on the word "GO" they should walk up the steps (facing in the direction they are walking) as quickly and safely as possible to the top, turn around on the landing, and then walk down the steps (facing in the direction they are walking) as quickly as they feel comfortable and return to the starting position
3. Physical therapist should encourage subject to use only their legs if possible, though use of a walking aid or handrail(s) is allowed, as needed
4. The physical therapist walks alongside the subject, for safety purposes
   a. If test is not performed, the physical therapist will record the specific reason
   b. Subject should be encouraged to complete the test
5. The goal of test is to measure the subject's ability to complete the activity without assistance. The therapist should endeavor to not provide assistance unless required for safety reasons.
6. The same stairs should be used for all assessments of study participants

Subject instructions

1. Start with both feet on the bottom landing
2. On "GO", go to the top of the stairs, turn around, and come back to the bottom of the stairs
3. Walk as quickly and safely as you can
4. Stop with both feet back on the bottom landing
5. Use the handrail, if needed
6. Get ready and GO

Scoring

1. The test starts on the signal to start ("GO") and terminates when the participant returns with both feet to the ground level.
2. The participant can stop and rest if needed but the time keeps going.
3. Walking aid is allowed