CLINICAL STUDY PROTOCOL
AMENDMENT 2

A Multicenter, Randomized, Double-Blind, Controlled Study of EXPAREL for Postsurgical Pain Management in Subjects Undergoing Open Lumbar Spinal Fusion Surgery

Protocol No.:	402-C-409
EudraCT No.:	Not applicable
IND No.:	69,198
Study Phase:	Phase 4
Study Drug:	EXPAREL® (bupivacaine liposome injectable suspension)
Date:	02 August 2017 (Amendment 2) 21 December 2016 (Version 2.0) 17 October 2016 (Version 1.1) 31 August 2016 (Version 1.0)
Study Sites:	Multicenter study in the US
Sponsor:	Pacira Pharmaceuticals, Inc. 5 Sylvan Way Parsippany, NJ 07054 Telephone: (973) 254-3560

1. SIGNATURE PAGE

James B Jones, MD, PharmD, FACEP
Sr Vice President and Chief Medical Officer
8/3/2017
Date

Michael Rozycki, PhD
Vice President, Regulatory Affairs
08/3/2017
Date

Vincent Yu
Sr Director, Biometrics
08/03/2017
Date

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, Controlled Study of EXPAREL for Postsurgical Pain Management in Subjects Undergoing Open Lumbar Spinal Fusion Surgery

Principal Investigator(s): To be determined

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

Publications (Reference): None

Objectives:

Primary Objective: The primary objective of this study is to compare postsurgical pain control following local infiltration analgesia (LIA) with EXPAREL admixed with bupivacaine HCl versus LIA with bupivacaine HCl in adult subjects undergoing open lumbar posterior spinal fusion surgery.

Secondary Objectives: The secondary objectives of this study are to compare additional efficacy, safety, and health economic outcomes following LIA with EXPAREL admixed with bupivacaine HCl versus LIA with bupivacaine HCl in adult subjects undergoing open lumbar posterior spinal fusion surgery.

Methodology:

This is a Phase 4, multicenter, randomized, double-blind, controlled study in approximately 194 adult subjects undergoing primary, 1-2 level, open lumbar spinal fusion surgery under general anesthesia.

Subjects will be screened within 30 days prior to study drug administration and at least one day prior to surgery.

If a subject can only be screened on the day of surgery, the consent process must have started prior to the day of surgery to give ample time for the subject to review the consent. Screening procedures that are standard of care (SOC) at the institution may be completed prior to written informed consent, however any screening procedures that are not SOC, must be completed after written informed consent, and prior to surgery.

During the screening visit, 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, a medical history, surgical history, physical examination, 12-lead electrocardiogram (ECG), vital sign measurements, select clinical laboratory evaluations, urine drug screen, alcohol breath test, and urine pregnancy test for women of childbearing potential will be conducted.

On Day 1, all eligible subjects will receive the following medications within 4 hours prior to surgery:

- Acetaminophen 975-1000 mg, orally (PO)
- Celecoxib 200 mg, PO
    - If a subject has an allergy to celecoxib, naproxen 500 mg PO twice a day or meloxicam 7.5 mg PO once a day may be used.
- Gabapentin (eg, Neurontin®) up to 900 mg PO
- Tranexamic Acid (TXA) 1 gm (PO or IV) may be used at the start of surgery at the physician's discretion.
- Versed 1-2 mg IV for anxiety may be used pre-operatively per physician discretion

Subjects will be randomized 1:1 to two treatment groups and stratified by surgery type (1-Level or 2-Level). Screw type (pedicle or cortical screws) will be recorded in the CRF. Subjects in Group 1 will receive LIA with EXPAREL admixed with bupivacaine HCl and subjects in Group 2 will receive LIA with bupivacaine HCl. For

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		

subjects in Group 1 undergoing 1-Level procedures, EXPAREL 266 mg in 20 mL will be admixed with bupivacaine HCl 0.5% in 20 mL and expanded in volume with 20 mL normal saline for a total volume of 60 mL, while for subjects undergoing 2-Level procedures EXPAREL 266 mg in 20 mL will be admixed with bupivacaine HCl 0.5% in 20 mL and expanded in volume with 50 mL normal saline for a total volume of 90 mL. Subjects in Group 2 undergoing 1-Level procedures will receive LIA with bupivacaine HCl 0.5% in 20 mL expanded in volume with 40 mL normal saline for a total volume of 60 mL, while subjects undergoing 2-Level procedures will receive LIA with bupivacaine HCl 0.5% in 20 mL expanded in volume with 70 mL normal saline for a total volume of 90 mL.

Trained and qualified Investigators will use their usual surgical technique to perform the surgery. The following medications are permitted during surgery

- Propofol for induction and/or intraoperatively.
- Lidocaine without epinephrine (0.5% or 1%) pre-incision to anaesthetize the incisional area
    - Must precede the use of EXPAREL or bupivacaine HCl by at least 20 minutes.
- Fentanyl or short-acting analogues
- Medication for nausea/vomiting prevention per physician's discretion

Intraoperative administration of other opioids or any other analgesic, local anesthetics, or anti-inflammatory agents will be prohibited in both groups, unless needed to treat an AE.

Study drug, approximately 1-2 mL every 1.0-1.5 cm, will be administered using 20- or 22-gauge needles prior to wound closure. The tissue should visibly expand with minimal leakage. Study drug should be injected in the prescribed locations based on the areas of highest nerve density to include the muscular (above and below the fascia) and subdermal layers. Approximately 2/3 of study drug will be placed subfascial circumferentially above and below the paraspinous muscles, the remainder subdermal and subcutaneously. Drains may be used at the surgeon's discretion.

If the surgery extends beyond 3 hours and the patient received TXA at the beginning of surgery, an additional 1 gm TXA may be dosed at the end of surgery.

In addition to LIA, all study participants will receive a standardized approach for managing postsurgical pain that includes a scheduled multimodal pain regimen including adjunctive analgesics, non-steroidal anti-inflammatory drugs (NSAIDs). Rescue analgesics will be available as needed.

Postsurgically, all subjects are required to receive the following scheduled medications until hospital discharge:

- Acetaminophen 975-1000 mg PO every 8 hours (q8h). The total daily dose of acetaminophen is not to exceed 3000 mg. Acetaminophen IV can be used if the patient unable to tolerate oral acetaminophen.
- Celecoxib 200 mg PO every 12 hours (q12h) up to 48 hours post surgery.
    - If a subject has an allergy to celecoxib, naproxen 500 mg PO twice a day or meloxicam 7.5 mg PO once a day may be used.
- Gabapentin up to 900 mg PO q8h
- Cyclobenzaprine (eg, Flexeril®) 10 mg PO x1 dose (PRN at surgeon discretion)

Patients can be discharged based on current clinical practice but, at a minimum, should:

- No longer require parenteral pain management
- Be able to tolerate a liquid diet
- Demonstrate safe mobility as determined with occupational therapy/physical therapy input per hospital

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		

standards

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 up to 10 mg. The subject may re-dose, per physician judgment, as needed (PRN), if the initial rescue medication fails. If a subject cannot tolerate PO medication or has repeated failure of the rescue medication with oxycodone (PO), 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**. No other rescue analgesic agents, including NSAIDs, are permitted until hospital discharge. After discharge, the analgesic regimen may be adjusted for each subject individually as deemed appropriate by the physician responsible for the postsurgical care.

Postsurgical Assessments

Postsurgical clinical assessments will include pain intensity scores using a 10-cm visual analog scale (VAS) (see Appendix 1); overall benefit of analgesia score (OBAS) questionnaire (see Appendix 2); total postsurgical opioid consumption; predefined opioid-related AEs; and nurse's satisfaction with overall analgesia (see Appendix 3).

Adverse events will be recorded from the time the ICF is signed through Day 30. If a cardiac AE (eg, chest pain [angina, myocardial infarction], abnormal/irregular heart rate [bradycardia, tachycardia, extrasystoles], or shortness of breath), neurological AE (eg, altered mental status/altered sensorium, dizziness, dysarthria, hyperesthesia, metallic taste, peroral numbness, seizure, tinnitus, tremors, visual disturbance, muscular twitching or rigidity beyond 72 hours postdose, or tingling/paresthesia beyond 72 hours postdose), or serious AE (SAE) occurs during the study a 12-lead ECG, vital signs, and any appropriate clinical laboratory tests should be conducted.

Postsurgical health economic outcome assessments will include hospital length of stay (LOS), use of skilled nursing facility, hospital readmissions, and use of other health services following discharge (phone calls related to postsurgical pain, unscheduled visits related to postsurgical pain, and visits to emergency department) through Day 30.

A follow-up visit will be scheduled for all subjects on postsurgical Day 14. A follow-up phone call will be made on Day 30 to all subjects who received study drug to assess for adverse events (AEs).

Number of Subjects (Planned):

Approximately 194 subjects are planned for enrollment in this study in order to have at least 184 evaluable subjects.

Eligibility Criteria:

Inclusion Criteria:

1. Male or female, at least 18 years of age at screening.
2. Primary surgical indication is lumbar pain, radiculopathy, disc degeneration, disc herniation, foraminal stenosis, or 1-2 level spondylolisthesis or deformity.
3. Scheduled to undergo primary, 1-2 level, open lumbar spinal fusion surgery under general anesthesia.
4. American Society of Anesthesiologists (ASA) physical status 1, 2, or 3.

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		

5. Female subjects 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, or transdermal, contraceptive approved by the FDA for greater than 2 months prior to screening. All women of childbearing potential (ie, premenopausal without permanent sterilization) must commit to the use of an acceptable form of birth control for the duration of the study and for 30 days after completion of the study.
6. Able to provide informed consent, adhere to the study visit schedule, and complete all study assessments.

Exclusion Criteria:

1. Currently pregnant, nursing, or planning to become pregnant during the study or within 1 month after study drug administration.
2. Serious spinal conditions (to include cauda equina syndrome, infection, tumor, fracture, or severe osteoporosis [ie, if taking Bisphosphonate or TNF-α blockers]).
3. Planned anterior or laterial incisions
4. Previous spinal surgery at the same level other than microdiscectomy or hemilaminectomy (eg, bi-lateral laminectomy, fusion).
5. Planned concurrent surgical procedure.
6. Identification of a dural tear during surgery will be an intra-operative exclusion unless it is well repaired (no evidence of cerebrospinal fluid [CSF] leak with Valsalva and no plan to restrict activity post-operatively). Any injury to the nerve root occurring during surgery will also be considered an intra-operative exclusion.
7. 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 spinal surgery and which may confound the postsurgical assessments.
8. Comorbidity impacting current physical function or Investigator opinion that it may impact postsurgical rehabilitation.
9. Allergy, hypersensitivity, or contraindication to any of the study medications (ie, bupivacaine, oxycodone, morphine, hydromorphone, gabapentin, acetaminophen, or cyclobenzaprine) for which an alternative medication is not provided in the protocol.
10. Use of any of the following medications within the times specified before surgery: long-acting opioid medication (eg, morphine including MS Contin®, hydromorphone [Dilaudid®], oxycodone [Oxycontin®], methadone) daily for more than 3 months duration or within 3 days of surgery. Patients receiving short-acting opioids or NSAIDs should be at a steady or plateau dose. Such patients should require or receive no more than 40 mg morphine (oral) equivalents (eg, approximately 5 mg oxycodone) within 24 hours of surgery.
11. 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), 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.
12. Current use of systemic glucocorticosteroids within 1 month of enrollment in this study.
13. Use of dexmedetomidine HCl (Precedex®) within 3 days of study drug administration.
14. History of coronary or vascular stent placed within the past 3 months (may be extended to 1 year if medically indicated per physician discretion).

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		

15. Have been treated for a deep vein thrombosis, pulmonary embolism, myocardial infarction, or ischemic stroke within the past 6 months (may be extended to 1 year if medically indicated per physician discretion).
16. Severely impaired renal (eg, serum creatinine clearance ≤ 30) or hepatic function (eg, serum aspartate aminotransferase [AST] level >3 times the upper limit of normal [ULN] or serum alanine aminotransferase [ALT] level >3 x ULN).
17. Any neurologic or psychiatric disorder that might impact postsurgical pain or interfere with study assessments.
18. Malignancy in the last 2 years, per physician discretion.
19. History of misuse, abuse, or dependence on opioid analgesics, other prescription drugs, illicit drugs, or alcohol as defined in DSM-IV. Dependence or chronic opioid use will be defined as use of more than 30 morphine equivalents per day during the prior 90 days.
20. Failure to pass the alcohol breath test or urine drug screen positive for illicit drugs.
21. Body weight <50 kg (110 pounds) or a body mass index >44 kg/m^2.
22. Subjects receiving Worker's compensation for a disability or who are involved in litigation.
23. Previous participation in an EXPAREL study.
24. Administration of an investigational drug within 30 days or 5 elimination half-lives of such investigational drug, whichever is longer, prior to study drug administration, or planned administration of another investigational product or procedure during the subject's participation in this study.

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

Name: EXPAREL (bupivacaine liposome injectable suspension) and bupivacaine HCl 0.5% (Group 1)

Active ingredients: Bupivacaine

Dosage:

- For subjects undergoing 1-Level procedures: EXPAREL 266 mg in 20 mL admixed with bupivacaine HCl 0.5% in 20 mL and expanded in volume with 20 mL normal saline for a total volume of 60 mL
- For subjects undergoing 2-Level procedures: EXPAREL 266 mg in 20 mL admixed with bupivacaine HCl 0.5% in 20 mL and expanded in volume with 50 mL normal saline for a total volume of 90 mL.

Lot number: To be determined

Mode of administration: Intraoperative local infiltration

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

Name: Bupivacaine HCl 0.5% (Group 2)

Active ingredient: Bupivacaine

Dosage:

- For subjects undergoing 1-Level procedures: bupivacaine HCl 0.5% in 20 mL expanded in volume with 40 mL normal saline for a total volume of 60 mL
- For subjects undergoing 2-Level procedures: bupivacaine HCl 0.5% in 20 mL expanded in volume with 70 mL normal saline for a total volume of 90 mL.

Lot number: To be determined. Commercial product will be provided by Pacira.

Mode of administration: Intraoperative local infiltration

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		

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 end of surgery:

- Pain intensity scores using the VAS on Day 1, pre-operative; upon arrival at the post-anesthesia care unit (PACU); at 4, 6, 8, 10, 12, 24, 28, 32, 36, 48, 52, 56, 60, and 72 hours; immediately prior to each administration of rescue pain medication; and just prior to hospital discharge (see Appendix 1). Note: if the subject is sleeping, do not wake him or her for an assessment of pain at 24 or 48 hours after surgery. If he or she awakens within the assessment window (ie, 1 hour for the 24-hour assessment and 2 hours for the 48-hour assessment), a pain score may be collected then.

  †: If discharge occurs prior to any of the scheduled VAS assessments collected at 4 to 72 hours postsurgery or scheduled OBAS assessments collected at 24 to 72 hours, the study coordinator must stress to the subject the importance of completing the scheduled VAS and OBAS Assessments. These assessments should be recorded by the subject in the patient log provided upon discharge.
- Amount of all opioid rescue analgesics taken through postsurgical Day 30.
- Predefined treatment-emergent opioid-related AEs.
- The OBAS questionnaire at 24, 48, and 72 hours (see Appendix 2). Note: if discharge occurs before 72 hours, the study coordinator must stress to the patient the importance of completing the scheduled OBAS questionnaire up to 72 hours. Completion of the questionnaire should be recorded by the patient in the patient log provided upon discharge.
- Nurse's satisfaction with overall analgesia will be assessed at 24, 48, and 72 hours or upon hospital discharge (see Appendix 3).
- The Pain Interference Scale (short form 6b) pre-op and Day 14 (see Appendix 4)

Efficacy Endpoints:

The efficacy endpoints listed below will be assessed based on the efficacy measurements conducted at the times specified after the end of surgery.

Primary Efficacy Endpoint:

The primary efficacy endpoint is the area under the curve (AUC) of the VAS pain intensity scores from 0-72 hours.

Secondary Endpoints:

- Total opioid consumption (in IV morphine equivalents) from 0–48 hours
- Proportion of subjects who are pain free (defined as a VAS pain intensity score of ≤1.5 and no prior rescue medication) at each assessed timepoint.
- The VAS pain intensity scores at each assessed timepoint.
- The AUC of the VAS pain intensity scores through 24, 36, 48, 60, and 72 hours.
- The AUC of the VAS pain intensity scores from 24–48 and 48–72 hours.
- The sum of the pain intensity scores (SPIS) through 24, 48, and 72 hours.

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		

- SPIS from 24–48 and 48–72 hours.
- Total inpatient postsurgical opioid consumption (in mg) through 24 and 72 hours or hospital discharge.
- Total postsurgical opioid consumption (in mg) from hospital discharge through Day 30.
- Percentage of opioid-free subjects through 24, 48, and 72 hours or hospital discharge.
- Time to first opioid rescue through 72 hours or hospital discharge.
- Incidence of the following opioid-related AEs until the discharge order is written: respiratory depression, hypoventilation, hypoxia, dry mouth, nausea, vomiting, constipation, altered mental status, pruritus, urinary retention, and postoperative ileus.
- The OBAS total score at 24, 48, and 72 hours
- Nurse's satisfaction with overall analgesia at 24, 48, and 72 hours or upon hospital discharge.

Health Economic Outcomes Assessments:

The health economic outcomes will include:

- Hospital length of stay (LOS).
- Hospital readmissions.
- Use of skilled nursing facility.
- Use of other health services following hospital discharge (phone calls related to pain, unscheduled visits related to pain, and visits to the emergency department).

Health Economic Outcomes Endpoints:

- Hospital LOS, defined as the time from completion of the wound closure until the hospital discharge order is written or through postsurgical Day 30, whichever is sooner.
- Percentage of subjects meeting the protocol-specified minimum criteria for discharge (ie, no requirement for parenteral pain management, able to tolerate a liquid diet, able to demonstrate safe mobility, not requirement for active wound management) and discharged by time (eg, a “responder analysis”)
- Incidence of hospital readmission through Day 30.
- Incidence of skilled nursing facility use.
- Total time spent in skilled nursing facility.
- Number of phone calls related to postsurgical pain.
- Number of unscheduled visits related to postsurgical pain.
- Number of visits to the emergency department.

Safety Assessment:

- Adverse events from the time the ICF is signed through postsurgical Day 30.

Safety Endpoint:

- Incidence of treatment-emergent AEs (TEAEs) and SAEs through postsurgical Day 30.

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		

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. Superiority of treatment with EXPAREL admixed with bupivacaine HCl (Group 1) versus treatment with bupivacaine HCl (Group 2) will be determined using an analysis of variance (ANOVA) with treatment as the main effect on the AUC of the VAS pain intensity scores through 48 hours. If superiority of pain control is demonstrated, then the total opioid use (in morphine equivalent doses) through 48 hours in Group 1 will be compared to that of Group 2 using an ANOVA. This hierarchical testing procedure will protect the type 1 error rate. Secondary efficacy endpoints will be analyzed using ANOVA, chi-square tests, and log-rank tests, as appropriate. Safety endpoints will be summarized descriptively by treatment group.

Table 1. Time and Events Schedule of Study Procedures

	Screen Visit	D1 Preop	0 min	OR	PACU Arrival	4h	6h	8h	10h	12h	24h	28h	32h	36h	48h	52h	56h	60h	72h	D14 Visit	D30 Call
Time Window	**Within 30 days**					**±15 min**	**±30 min**	**±30 min**	**±1h**	**±1h**	**±1h**	**±2h**	**±2h**	**±2h**	**±2h**	**±2h**	**±2h**	**±2h**	**±4h**	**±3d**	**±3d**
Obtain signed ICF	X																				
Assess/confirm eligibility	X	X[a]																			
Record medical and surgical history	X	X[a]																			
Record demographics and baseline characteristics	X																				
Conduct pregnancy test for WOCBP	X	X[a]																			
Conduct urine drug screen	X	X[a]																			
Alcohol breath test	X																				
Perform physical examination	X																			X	
Measure vital signs (temperature, heart rate, respiratory rate and blood pressure)	X	X[a]																			
Clinical labs (direct bilirubin and either GGT and LDH or ALT and AST)	X																				
Perform 12-lead ECG	X																				
Record VAS pain intensity score[1,2,3,4]		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Randomize subject, prepare study drug		X																			
Administer scheduled presurgical medications[5]		X																			
Administer study drug according to randomization schedule; record start and stop times			X																		
Record intraoperative opioids administered and doses				X																	
Record surgery start and stop times				X																	
Record times and doses of all opioid rescue medication administered					◄- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - - ►
Administer scheduled postsurgical analgesics[1,6]					◄- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - - ►		
Complete OBAS questionnaire[4]											X				X				X		
Nurse's satisfaction with postsurgical pain control[4]											X				X				X		
Pain Interference Scale		X																		X	
Record date and time of actual discharge															◄- - -	- - -	- - -	- - -	- - - ►		
Document any hospital readmissions																				X	X
Document use of skilled nursing facility																				X	X
Document any unscheduled phone calls or office visits related to pain after discharge																				X	X
Document any unscheduled visits to the ER after discharge																				X	X
Record prior and concomitant medications[7]	◄- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - - ►
Record AEs (beginning at the time ICF is signed)[8]	◄- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - - ►

Abbreviations: AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; d = day; D = day; ECG = electrocardiogram; ER = emergency room; GGT=Gamma-glutamyl transpeptidase; h = hours; ICF = informed consent form; LDH = lactate dehydrogenase; min = minutes; OBAS = overall benefit of analgesia score; OR = operating room; PACU = post-anesthesia care unit; Preop = preoperative; q12h = every 12 hours; VAS = visual analog scale; WOCBP = women of childbearing potential.

a: If the Screening Visit is conducted within 10 days of the date of surgery, the following Day-1 pre-op assessments are not required: assess/confirm eligibility; record medical and surgical history; conduct pregnancy test for WOCBP; conduct urine drug screen; and measure vital signs (temperature, heart rate, respiratory rate and blood pressure)

* Postsurgical assessments will be conducted at the timepoints specified after the end of surgery. All assessments conducted after baseline (ie, study drug administration) will be timed from the end of surgery, defined as the time of last suture/staple. **At timepoints when multiple assessments coincide, the VAS pain intensity assessment will be conducted first**.

1 Timepoints shown through 72 hours. Note: if discharge occurs before 72 hours, the study coordinator must stress to the patient the importance of completing the scheduled pain intensity assessments up to 72 hours. These assessments should be recorded by the patient in the patient log provided upon discharge.

2 The preoperative pain intensity assessment should be conducted prior to administration of any premedication.

3 Also record VAS pain intensity scores immediately prior to each administration of rescue pain medication, and just prior to hospital discharge.

4 And just prior to hospital discharge. Note: if discharge occurs before 72 hours, the study coordinator must stress to the patient the importance of completing the scheduled OBAS questionnaire up to 72 hours. Completion of the questionnaire should be recorded by the patient in the patient log provided upon discharge.

5 Administer presurgical analgesics (ie, acetaminophen 975-1000 mg orally (PO), celecoxib 200 mg PO [or naproxen 500 mg PO twice a day or meloxicam 7.5 mg PO once a day in case of allergy], and gabapentin up to 900 mg PO).

6 Administer scheduled post-surgical analgesics (ie, acetaminophen 975-1000 mg PO every 8 hours (q8h) [maximum of 3000 mg per day; acetaminophen IV can be used if the patient is unable to tolerate oral acetaminophen], celecoxib 200 mg PO every 12 hours up to 48 hours (q12h; or naproxen 500 mg PO twice a day or meloxicam 7.5 mg PO once a day in case of allergy), cyclobenzaprine 10 mgq8h, and gabapentin up to 900 mg PO q8h).

7 Instruct subject to discontinue prohibited medications. Record date and time of all medications starting at least 30 days prior to study drug administration until hospital discharge. Record medications administered for treatment of an AE through Day 30.

8 If a cardiac AE (eg, chest pain [angina, myocardial infarction], abnormal/irregular heart rate [bradycardia, tachycardia, extrasystoles], or shortness of breath), neurological AE (eg, altered mental status/altered sensorium, dizziness, dysarthria, hyperesthesia, metallic taste, peroral numbness, seizure, tinnitus, tremors, visual disturbance, muscular twitching or rigidity beyond 72 hours postdose, or tingling/paresthesia beyond 72 hours postdose), or serious AE (SAE) occurs during the study, a 12-lead ECG, vital signs, PK draw, and any appropriate clinical laboratory tests should be conducted as close as possible to when the event occurs.

3. TABLE OF CONTENTS

LIST OF TABLES

4. LIST OF ACRONYMS/ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
ASA	American Society of Anesthesiology
AST	Aspartate transaminase
AUC	Area under the plasma concentration-versus-time curve
BMI	Body mass index
CFR	Code of Federal Regulations
C_{max}	The maximum observed bupivacaine plasma concentration obtained directly from the experimental data without interpolation
CRF	Case Report Form
CSF	Cerebrospinal Fluid
ECG	Electrocardiogram
ER	Emergency room
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
LDH	Lactate dehydrogenase
LIA	Local infiltration analgesia
LOS	Length of stay
MPADSS	Modified Post-Anesthesia Discharge Scoring System
NDA	New Drug Application
NRS	Numeric rating scale

NRS-R	Neurobehavioral rating scale-revised
NSAID	Non-steroidal anti-inflammatory drug
OBAS	Overall Benefit of Analgesia Score
PACU	Post-anesthesia care unit
PCA	Patient-controlled analgesia
PK	Pharmacokinetic
PMR	Postmarketing Requirement
PLIF	Posterior lumbar interbody fusion
PO	Oral
PRN	As needed
PTAE	Pretreatment adverse event
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
sNDA	Supplemental New Drug Application
SNRI	Serotonin and norepinephrine reuptake inhibitor
SPIS	Sum of the pain intensity scores
SSRI	Selective serotonin reuptake inhibitor
$t_{1/2}$	The apparent terminal elimination half-life calculated as $0.693/\lambda_z$
TEAE	Treatment-emergent adverse event
TKA	Total Knee Arthroplasty
TLIF	Transdoraminal lumbar interbody fusion
TXA	Tranexemic acid
US	United States (of America)
VAS	Visual analog scale
WHO	World Health Organization

5. ETHICS

5.1. Institutional Review Board/Independent ethics committee

Prior to enrolling 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 Practices (GCP) and/or the United States (US) Food and Drug Administration (FDA) Title 21 Code of Federal Regulations (CFR) Part 56. 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, and the ICH GCP. Study documents will be maintained in accordance with applicable regulations.

5.3. Subject Information, Consent, and Assent

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 Informed Consent Form (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 enroll. The subject and the study staff with whom he or she discusses the ICF will sign and date the ICF. A copy of the fully signed ICF will be given to the subject.

The Investigator will explain to the subject that they are completely free to decline entering the study and to 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) will be 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, non-steroidal anti-inflammatory drugs (NSAIDs), and/or acetaminophen provided through a variety of routes including intravenous (IV), transdermal patch, and oral (PO) administration. Opioids are widely used and considered some of the most powerful analgesics; however, they also have considerable drawbacks including time and resources required for monitoring opioid-related side effects. A reduction in the use of postoperative opioids is desirable to decrease the incidence and severity of opioid-induced adverse effects, such as respiratory depression, nausea, vomiting, constipation, somnolence, pruritus, and urinary retention.

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

Opioid analgesics have long been established to be the most effective agents used for the management of moderate to severe postoperative pain, and are currently considered the mainstay of treatment. However, AEs related to opioid administration (eg, nausea, vomiting, ileus, confusion) 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.

7.4. Summary of Human Experience with EXPAREL

7.4.1. Wound Infiltration New Drug Application (NDA)

During the original clinical development program (wound infiltration), Pacira conducted 21 clinical studies and 1observational follow-up study to investigate EXPAREL (formerly known as SKY0402™). Across these studies, a total of 1307 adult human subjects received EXPAREL at doses ranging from 9-665 mg 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 ≤266 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 ≤266 mg group through 72 hours postdose. Fewer subjects in the EXPAREL ≤266 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 ≤266 mg group (7.94 mg) compared to the bupivacaine HCl group (15.84 mg); $p<0.0001$. The EXPAREL >266 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 >266 mg group.

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

7.4.1.1. Nerve Block Supplemental NDA

A total of 335 adult human subjects received EXPAREL as a nerve block in 6 clinical studies (SKY0402-002, SKY0402-C-111, SKY0402-C-203, SKY0402-C-211, 402-C-322, and 402-C-323) involving 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 (sNDA). Additional nerve block studies are ongoing.

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 intercostal nerve block using EXPAREL compared with placebo in subjects undergoing posterolateral thoracotomy.

While 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, a treatment effect was evident through 12 to 24 hours based upon a post hoc analysis. Intercostal nerve block with EXPAREL was well tolerated these subjects with similar numbers of TEAEs between the treatment groups, most of which were mild or moderate in severity. 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), none of which were considered by the Investigator to be related to the study drug. Two of these subjects in the EXPAREL group (none were considered related to the study drug) and four of these subjects in the placebo group died.

Study 402-C-323 was a Phase 2/3, multicenter, randomized, double-blind, parallel-group, placebo-controlled, dose-ranging study in subjects undergoing primary unilateral total knee arthroscopy (TKA) under general or spinal anesthesia. Part 1 evaluated 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 subsequently selected a single therapeutic dose of EXPAREL from the three dose levels to be tested in Part 2. 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.

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

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

7.5. Postmarketing Exposure

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

8. OBJECTIVES

8.1. Primary Objective

The primary objective of this study is to compare postsurgical pain control following local infiltration analgesia (LIA) with EXPAREL admixed with bupivacaine HCl versus LIA with bupivacaine HCl in adult subjects undergoing open lumbar posterior spinal fusion surgery.

8.2. Secondary Objectives

The secondary objectives of this study are to compare additional efficacy, safety, and health economic outcomes following LIA with EXPAREL admixed with bupivacaine HCl versus LIA with bupivacaine HCl in adult subjects undergoing open lumbar posterior spinal fusion surgery

9. OVERALL STUDY DESIGN AND PLAN

9.1. Overall Study Design and Plan

9.1.1. Study Design

This is a Phase 4, multicenter, randomized, double-blind, controlled study in approximately 194 adult subjects undergoing primary, 1-2 level, open lumbar spinal fusion surgery under general anesthesia.

Subjects will be screened within 30 days prior to study drug administration.

If a subject can only be screened on the day of surgery, the consent process must have started prior to the day of surgery to give ample time for the subject to review the consent. Screening procedures that are standard of care (SOC) at the institution may be completed prior to written informed consent, however any screening procedures that are not SOC, must be completed after written informed consent, and prior to surgery.

During the screening visit, 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, a medical history, surgical history, physical examination, 12-lead electrocardiogram (ECG), vital sign measurements, urine drug screen, alcohol breath test, and urine pregnancy test for women of childbearing potential will be conducted.

On Day 1, all eligible subjects will receive the following medications within 4 hours prior to surgery:

- Acetaminophen 975-1000 mg, orally (PO)
- Celecoxib 200 mg, PO
    - If a subject has an allergy to celecoxib, naproxen 500 mg PO twice a day or meloxicam 7.5 mg PO once a day may be used.

- Gabapentin (eg, Neurontin) up to 900 mg, PO
- TXA 1 gm (PO or IV) may be used at the start of surgery at the physician's discretion
- Versed 1-2 mg IV for anxiety may be used pre-operatively per physician discretion

Subjects will be randomized 1:1 to two treatment groups and stratified by surgery type (1-Level or 2-Level). Screw type (pedicle or cortical screws) will be recorded in the CRF. Subjects in Group 1 will receive LIA with EXPAREL admixed with bupivacaine HCl and subjects in Group 2 will receive LIA with bupivacaine HCl. For subjects in Group 1 undergoing 1-Level procedures, EXPAREL 266 mg in 20 mL will be admixed with bupivacaine HCl 0.5% in 20 mL and expanded in volume with 20 mL normal saline for a total volume of 60 mL, while for subjects undergoing 2-Level procedures EXPAREL 266 mg in 20 mL will be admixed with bupivacaine HCl 0.5% in 20 mL and expanded in volume with 50 mL normal saline for a total volume of 90 mL. Subjects in Group 2 undergoing 1-Level procedures will receive LIA with bupivacaine HCl 0.5% in 20 mL expanded in volume with 40 mL normal saline for a total volume of 60 mL, while subjects undergoing 2-Level procedures will receive LIA with bupivacaine HCl 0.5% in 20 mL expanded in volume with 70 mL normal saline for a total volume of 90 mL. Trained and qualified Investigators will use their usual surgical technique to perform the surgery. The following medications are permitted during surgery:

- Propofol for induction and/or intraoperatively.
- Lidocaine without epinephrine (0.5% or 1%) pre-incision to anaesthetize the incisional area
    - Must precede the use of EXPAREL or bupivacaine HCl by at least 20 minutes.
- Fentanyl or short-acting analogues
- Any medication for nausea/vomiting prevention can be given at the physician's discretion.

Intraoperative administration of other opioids or any other analgesic, local anesthetics, or anti-inflammatory agents will be prohibited in both groups, unless needed to treat an AE.

Study drug, approximately 1-2 mL every 1.0-1.5 cm, will be administered using 20- or 22-gauge needles prior to wound closure. The tissue should visibly expand with minimal leakage. Study drug should be injected in the prescribed locations based on the areas of highest nerve density to include the muscular (above and below the fascia) and subdermal layers. Approximately 2/3 of study drug will be placed subfascial circumferentially above and below the paraspinous muscles, the remainder subdermal and subcutaneously. Drains may be used at the surgeon's discretion.

If the surgery extends beyond 3 hours and the patient received TXA at the beginning of surgery, an additional 1 gm TXA may be dosed at the end of surgery.

In addition to LIA, all study participants will receive a standardized approach for managing postsurgical pain that includes a scheduled multimodal pain regimen including adjunctive analgesics, NSAIDs. Result analgesics will be available as needed.

Postsurgically, all subjects are required to receive the following scheduled medications until hospital discharge:

- Acetaminophen 975-1000 mg PO every 8 hours (q8h). The total daily dose of acetaminophen is not to exceed 3000 mg. Acetaminophen IV can be used if the patient is unable to tolerate oral acetaminophen
- Celecoxib 200 mg PO every 12 hours (q12h) up to 48 hours post surgery.
    - If a subject has an allergy to celecoxib, naproxen 500 mg PO twice a day or meloxicam 7.5 mg PO once a day may be used.
- Gabapentin (eg, Neurontin) up to 900 mg PO q8h
- Cyclobenzaprine (eg, Flexeril) 10 mg PO x1 dose (PRN at surgeon discretion)

A prewritten order sheet with the scheduled medications will be given to the nurses for the subjects in this study.

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 up to 10 mg. The subject may re-dose, per physician judgment, as needed (PRN), if the initial rescue medication fails. If a subject cannot tolerate PO medication or has repeated failure of the rescue medication with oxycodone (PO), 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**. No other rescue analgesic agents, including NSAIDs, are permitted until hospital discharge. After discharge, the analgesic regimen may be adjusted for each subject individually as deemed appropriate by the physician responsible for the postsurgical care.

Postsurgical Assessments

Postsurgical clinical assessments will include pain intensity scores using a 10-cm VAS (see Appendix 1); OBAS questionnaire (see Appendix 2); total postsurgical opioid consumption; predefined opioid-related AEs; and nurse's satisfaction with overall analgesia (see Appendix 3).

Adverse events will be recorded from the time the ICF is signed through Day 30. If a cardiac AE (eg, chest pain [angina, myocardial infarction], abnormal/irregular heart rate [bradycardia, tachycardia, extrasystoles], or shortness of breath), neurological AE (eg, altered mental status/altered sensorium, dizziness, dysarthria, hyperesthesia, metallic taste, peroral numbness, seizure, tinnitus, tremors, visual disturbance, muscular twitching or rigidity beyond 72 hours postdose, or tingling/paresthesia beyond 72 hours postdose), or SAE occurs during the study, a 12-lead ECG, vital signs, and any appropriate clinical laboratory tests should be conducted.

Postsurgical health economic outcome assessments will include hospital length of stay (LOS), use of skilled nursing facility, hospital readmissions, and use of other health services following discharge (phone calls related to postsurgical pain, unscheduled visits related to postsurgical pain, and visits to emergency department) through Day 30.

A follow-up visit will be scheduled for all subjects on postsurgical Day 14. A follow-up phone call will be made on Day 30 to all subjects who received study drug to assess for AEs.

9.1.2. 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.

9.1.3. 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).

The Pacira Medical Monitor and Pharmacovigilance team review all SAEs reported from Pacira clinical studies on an ongoing basis and in real time (ie, as the events are reported). The Medical Monitor is responsible for temporarily halting the study if the type, frequency, or seriousness/severity of such events suggest a potential threat to the safety of the study participants. If such action is taken, a thorough review of all available data will be conducted and may include unblinded data review by an Independent Safety Monitoring Committee. Based on the results of this review and discussions with investigators and/or regulatory authorities as warranted, the study may be restarted or permanently terminated.

In addition, 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 4 study is designed to compare postsurgical pain control and total opioid consumption following LIA with EXPAREL admixed with bupivacaine HCl versus LIA with bupivacaine HCl in adult subjects undergoing open posterior lumbar spinal fusion surgery.

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

If a cardiac or neurological AE of special interest or SAE occurs during the study, a 12-lead ECG, vital signs, and any appropriate clinical laboratory tests must be conducted as close as possible to when the event occurs.

10. STUDY POPULATION

Subjects must meet all eligibility criteria to be enrolled in this study.

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. Primary surgical indication is lumbar pain, radiculopathy, disc degeneration, disc herniation, foraminal stenosis, or 1-2 level spondylolisthesis or deformity.
3. Scheduled to undergo primary, 1-2 level, open spine fusion under general anesthesia.
4. American Society of Anesthesiologists (ASA) physical status 1, 2, or 3.
5. Female subjects 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, or transdermal, contraceptive approved by the FDA for greater than 2 months prior to screening. All women of childbearing potential (ie, premenopausal without permanent sterilization) must commit to the use of an acceptable form of birth control for the duration of the study and for 30 days after completion of the study.
6. Able to 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. Serious spinal conditions (to include cauda equina syndrome, infection, tumor, fracture, or severe osteoporosis [ie, if taking bisphosphonate or TNF-α blockers]).
3. Planned anterior or lateral incisions
4. Previous spinal surgery at the same level other than microdiscectomy or hemilaminectomy (eg, bi-lateral laminectomy, fusion).
5. Planned concurrent surgical procedure.
6. Identification of a dural tear during surgery will be an intra-operative exclusion unless it is well repaired (no evidence of CSF leak with Valsalva and no plan to restrict activity post-operatively). Any injury to the nerve root occurring during surgery will also be considered an intra-operative exclusion.
7. 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 spinal surgery and which may confound the postsurgical assessments.
8. Comorbidity impacting current physical function or Investigator opinion that it may impact postsurgical rehabilitation.
9. Allergy, hypersensitivity, or contraindication to any of the study medications (ie, bupivacaine, oxycodone, morphine, hydromorphone, gabapentin, acetaminophen, or cyclobenzaprine) for which an alternative medication is not provided in the protocol.

10. Use of any of the following medications within the times specified before surgery: long-acting opioid medication (eg, morphine including MS Contin®, hydromorphone [Dilaudid®], oxycodone [Oxycontin®], methadone) daily for more than 3 months duration or within 3 days of surgery. Patients receiving short-acting opioids or NSAIDs should be at a steady or plateau dose. Such patients should require or receive no more than 40 mg morphine (oral) equivalents (eg, approximately 5 mg oxycodone) within 24 hours of surgery.
11. 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), 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.
12. Current use of systemic glucocorticosteroids within 1 month of enrollment in this study.
13. Use of dexmedetomidine HCl (Precedex) within 3 days of study drug administration.
14. History of coronary or vascular stent placed within the past 3 months (may be extended to 1 year if medically indicated per physician discretion).
15. Have been treated for a deep vein thrombosis, pulmonary embolism, myocardial infarction, or ischemic stroke within the past 6 months (may be extended to 1 year if medically indicated per physician discretion).
16. Severely impaired renal (eg, serum creatinine clearance ≤ 30) or hepatic function (eg, serum AST level >3 x ULN or serum ALT level >3 x ULN).
17. Any neurologic or psychiatric disorder that might impact postsurgical pain or interfere with study assessments.
18. Malignancy in the last 2 years, per physician discretion.
19. History of misuse, abuse, or dependence on opioid analgesics, other prescription drugs, illicit drugs, or alcohol as defined in DSM-IV. Dependence or chronic opioid use will be defined as use of more than 30 morphine equivalents per day during the prior 90 days.
20. Failure to pass the alcohol breath test or urine drug screen positive for illicit drugs.
21. Body weight <50 kg (110 pounds) or a body mass index >44 kg/m^2.
22. Subjects receiving Worker's compensation for a disability or who are involved in litigation.
23. Previous participation in an EXPAREL study.
24. 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. Subjects who withdraw from the study after receiving study drug should undergo safety assessments through the end of the study (Day 30).

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 visit should be performed so that the subject's study participation can be terminated in a safe and orderly manner.

Otherwise, the subject will be instructed to notify the study personnel of any abnormalities during the intervals between study visits and to come to the study site if medical evaluation is needed and the urgency of the situation permits. Any subject exhibiting undesirable side effects will receive appropriate treatment at the discretion of the Investigator.

This study involves a single administration of study drug; therefore, subjects should not be terminated from the ongoing study assessments as long as they are willing and able to continue with the follow-up schedule according to the protocol. For emergencies and other unscheduled visits to a medical facility other than the study site, medical records will be obtained by the Investigator.

10.3.2. Voluntary or Study Investigator Withdrawal

Subjects are free to discontinue participation in 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 (temperature, resting heart rate, respiratory rate, and blood pressure) 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 Day 30.

11. TREATMENTS

11.1. Treatments to be Administered

Study Drug (Group 1)

Subjects randomized to EXPAREL will receive LIA with EXPAREL admixed with bupivacaine HCl. For subjects undergoing 1-Level procedures, EXPAREL 266 mg in 20 mL will be admixed with bupivacaine HCl 0.5% in 20 mL and expanded in volume with 20 mL normal saline for a total volume of 60 mL, while for subjects undergoing 2-Level procedures EXPAREL 266 mg in 20 mL will be admixed with bupivacaine HCl 0.5% in 20 mL and expanded in volume with 50 mL normal saline for a total volume of 90 mL.

Active Comparator (Group 2)

Subjects randomized to bupivacaine will receive LIA with bupivacaine HCl. Subjects undergoing 1-Level procedures will receive LIA with bupivacaine HCl 0.5% in 20 mL expanded in volume with 40 mL normal saline for a total volume of 60 mL, while subjects undergoing 2-Level procedures will receive LIA with bupivacaine HCl 0.5% in 20 mL expanded in volume with 70 mL normal saline for a total volume of 90 mL.

Postsurgical Pain Management

The use of postsurgical pain medication in cases of insufficient analgesia is permitted per the institution's standard of care. The Investigator must record all pain management medications provided to the subjects through Day 30.

11.1.1. Administration Instructions/Procedures

Study drug should be injected in the prescribed locations based on the areas of highest nerve density. Study drug will be administered using syringes with 20- or 22-gauge needles prior to wound closure. The Investigator must document the size of the incision. Each infiltration site should be spaced 1.0-1.5 cm apart and should deliver approximately 1-2 mL into both deep and superficial areas (para-spinous fascia, muscle, and subcutaneous layers). Total volume administered will be depended on the number of levels of dissection, as described below. Following infiltration, the tissue should visibly expand with minimal leakage.

Total Volume of Expansion

The Investigator must document the total volume used for each surgery.

1-Level Procedures

Group 1: EXPAREL 266 mg in 20 mL + bupivacaine HCl 0.5% in 20 mL + 20 mL normal saline = total volume of 60 mL

Group 2: Bupivacaine HCl 0.5% in 20 mL + 40 mL normal saline = total volume of 60 mL

2-Level Procedures

Group 1: EXPAREL 266 mg in 20 mL + bupivacaine HCl 0.5% in 20 mL + 50 mL normal saline = total volume of 90 mL

Group 2: Bupivacaine HCl 0.5% in 20 mL + 70 mL normal saline = total volume of 90 mL

11.1.2. Study Drug Administration Considerations

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

EXPAREL may not be administered to a subject if the vial has been open for more than 4 hours. 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 other than bupivacaine HCL 0.5% in 20 mL.

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

Bupivacaine HCl is a long-acting local anesthetic, used for surgical anesthesia and acute pain management. It is an alternative to NSAIDs and opioids. A multimodal approach of pain management with the use of a long-acting local anesthetic can reduce the total consumption of NSAIDs and opioids during the critical first 12 hours post-surgery.

11.2.3. Description of Diluents

Normal saline (0.9% sodium chloride solution) for injection will be used for the dilution (volume expansion) of study drug.

11.3. Method of Assigning Subjects to Treatment

11.3.1. Randomization Scheme

Subjects will be randomized 1:1 to two treatment groups and stratified by surgery level (1-Level or 2-level). Screw type (pedicle or cortical screws) will be recorded in the CRF. Subjects in Group 1 will receive LIA with EXPAREL admixed with bupivacaine HCl and subjects in Group 2 will receive LIA with bupivacaine HCl. For subjects in Group 1 undergoing 1-Level procedures, EXPAREL 266 mg in 20 mL will be admixed with bupivacaine HCl 0.5% in 20 mL and expanded in volume with 20 mL normal saline for a total volume of 60 mL, while for subjects undergoing 2-Level procedures EXPAREL 266 mg in 20 mL will be admixed with bupivacaine HCl 0.5% in 20 mL and expanded in volume with 50 mL normal saline for a total volume of 90 mL. Subjects in Group 2 undergoing 1-Level procedures will receive LIA with bupivacaine HCl 0.5% in 20 mL expanded in volume with 40 mL normal saline for a total volume of 60 mL, while subjects undergoing 2-Level procedures will receive LIA with bupivacaine HCl 0.5% in 20 mL expanded in volume with 70 mL normal saline for a total volume of 90 mL. The volume of study drug to be used will be the same for both screw types.

The stratification is to ensure equal representation of the treatment groups within each level of stratification. The sample size within a stratification is not fixed. It is not expected that there will be sufficient subjects test within all strata.

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 authorized site staff 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 withdrawn from the study before receiving study drug 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.

11.4. Selection of Doses in the Study

During the clinical development of EXPAREL, single doses ranging from 2 mg to 665 mg have been safely administered via various routes. Pharmacokinetic studies have shown that because EXPAREL releases bupivacaine gradually as the lipid structure breaks down, administration of EXPAREL 266 mg results in a maximum plasma concentration (C_{max}) equivalent to that seen with standard bupivacaine HCl 100 mg. EXPAREL 266 mg, the FDA-approved and marketed dose, was selected for this study.

11.5. Blinding

11.5.1. Blinding Procedures

Subjects will be randomized using central interactive response technology (IRT) and treatment assignment will be known to the Investigator performing the surgery. However, the subject will be blinded to their treatment assignment, as will be any study personnel performing study evaluations. Routine medical review of the treated subject data will be conducted by the Pacira Medical Monitoring Team on a bi-weekly basis, or as needed, throughout the conduct of this study (as described in Section 9.1.3), which will evaluate all reported AEs for severity, seriousness, and relationship to the study drug.

To maintain the double-blind study design, only the 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.

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

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 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

Any medications for the condition for which the procedure is being performed administered within 30 days prior to study drug administration will be recorded on the case report form (CRF), as well all medications through Day 30 after study drug administration or until the subject is withdrawn from the study, whichever is sooner. Additionally, any medications administered in association with an AE will be recorded through Day 30.

11.6.1. Before Study Drug Administration

<u>Permitted Prior Medications and Therapy</u>

Prophylactic antibiotics are permitted, according to the surgeon's preference.

Gabapentin (Neurontin) or pregabalin (Lyrica) is permitted pre-operatively if the duration has been less than 6 weeks.

On the day of surgery (Day 1), all eligible subjects will receive the following medications:

- Acetaminophen 975-1000 mg PO
- Celecoxib 200 mg, PO
    - If a subject has an allergy to celecoxib, naproxen 500 mg PO twice a day or meloxicam 7.5 mg PO once a day may be used
- Gabapentin up to 900 mg, PO
- TXA 1 gm (PO or IV) may be used at the start of surgery at the physician's discretion
- Versed 1-2 mg IV for anxiety may be used pre-operatively per physician discretion

<u>Restricted Prior Medications and Therapy</u>

Before screening

- Bupivacaine and any other local anesthetic are not permitted within 7 days of screening

Within 3 days pre-op

- Long-acting opioid medication (eg, morphine including MS Contin, hydromorphone [Dilaudid], oxycodone [Oxycontin], methadone) daily for more than 3 months duration or within 3 days pre-op
- Patients receiving short-acting opioids or NSAIDs should be at a steady or plateau dose. Such patients should require or receive no more than 20 mg morphine equivalents (eg, 4 Percocet) within 24 hours of surgery.
- Dexmedetomidine HCl (Precedex)

Within 1 month pre-op

- Selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), or Duloxetine (Cymbalta).
    - Note: 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.
- Dermal or systemic glucocorticosteroids (eg, Decadron) are prohibited within 1 month of enrollment in this study.
- Use 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 is not permitted.

11.6.2. During Surgery

Permitted

- Propofol for induction and/or intraoperatively.
- Lidocaine without epinephrine (0.5% or 1%) pre-incision to anaesthetize the incisional area
    - Must precede the use of EXPAREL or bupivacaine HCl by at least 20 minutes.
- Fentanyl or short-acting analogues
- Any medication for nausea/vomiting prevention can be given at the physician's discretion.

Restricted

- No drugs are to be admixed with study drug other that bupivacaine HCl (eg, epinephrine, dexamethasone, clonidine).

- Local anesthetics other than lidocaine (as described above) will not be permitted to be locally administered during surgery because they are known to interact with EXPAREL resulting in the displacement of bupivacaine and elevated plasma levels.
- The use of long-acting opioids (eg, morphine, hydromorphone HCl), acetaminophen/ paracetamol, ketorolac, or other NSAIDs will not be permitted intraoperatively except for emergency use to treat an AE.
- Decadron is not permitted for nausea/vomiting prevention

11.6.3. After Surgery

Permitted

- Acetaminophen 975-1000 mg PO q8h. The total daily dose of acetaminophen is not to exceed 3000 mg. Acetaminophen IV can be used if the patient is unable to tolerate oral acetaminophen
- Celecoxib 200 mg PO q12h up to 48 hours post-surgery
    - If a subject has an allergy to celecoxib, naproxen 500 mg PO twice a day or meloxicam 7.5 mg PO once a day may be used.
- Gabapentin (eg, Neurontin) up to 900 mg PO q8h
- Cyclobenzaprine (eg, Flexeril) 10 mg PO x1 dose (PRN at surgeon discretion)

Restricted

- No other analgesics, including fentanyl, are permitted up to 72 hours after study drug administration or discharge from the hospital.
- PCA is not permitted.
- Anesthetics in the "caine" family, which may interfere with the bupivacaine PK profile, are prohibited through Day 14.

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

11.7. Treatment Compliance

Not applicable because the study drug (EXPAREL or bupivacaine HCl) 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. Drug allocations will also be logged in the IRT which will maintain records. 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 Measurements

The following efficacy measurements will be conducted:

- Pain intensity scores using the VAS on Day 1, pre-operative; upon arrival at the post-anesthesia care unit (PACU); at 4, 6, 8, 10, 12, 24, 28, 32, 36, 48, 52, 56, 60, and 72 hours; immediately prior to each administration of rescue pain medication; and just prior to hospital discharge (see Appendix 1). Note: if the subject is sleeping, do not wake him or her for an assessment of pain at 24 or 48 hours after surgery. If he or she awakens within the assessment window (ie, 1 hour for the 24-hour assessment and 2 hours for the 48-hour assessment), a pain score may be collected then.

  †: If discharge occurs prior to any of the scheduled VAS assessments collected at 4 to 72 hours postsurgery or scheduled OBAS assessments collected at 24 to 72 hours, the study coordinator must stress to the subject the importance of completing the scheduled VAS and OBAS assessments. These assessments should be recorded by the subject in the patient log provided upon discharge.
- Amount of all opioid rescue analgesics taken through Day 30.
- Predefined treatment-emergent opioid-related AEs.
- The OBAS questionnaire at 24, 48, and 72 hours (see Appendix 2). Note: if discharge occurs before 72 hours, the study coordinator must stress to the patient the importance of completing the scheduled OBAS questionnaire up to 72 hours. Completion of the questionnaire should be recorded by the patient in the patient log provided upon discharge.
- Nurse's satisfaction with overall analgesia will be assessed at 24, 48, and 72 hours or upon hospital discharge (see Appendix 3).

12.2. Efficacy Endpoints

The efficacy endpoints listed below will be assessed based on the efficacy measurements conducted at the times specified after the end of surgery.

Primary Efficacy Endpoint:

The co-primary efficacy endpoints are the AUC of the VAS pain intensity scores from 12–48 hours and the total opioid consumption (in IV morphine equivalents) from 0–48 hours.

Secondary Endpoints:

- Proportion of subjects who are pain free (defined as a VAS pain intensity score of ≤1.5 and no prior rescue medication) at each assessed timepoint.
- The VAS pain intensity scores at each assessed timepoint.
- The AUC of the VAS pain intensity scores through 24, 36, 48, 60, and 72 hours.
- The AUC of the VAS pain intensity scores from 24–48 and 48–72 hours.
- The sum of the pain intensity scores (SPIS) through 24, 48, and 72 hours.
- SPIS from 24–48 and 48–72 hours.
- Total inpatient postsurgical opioid consumption (in mg) through 24 and 72 hours or hospital discharge.
- Total postsurgical opioid consumption (in mg) from hospital discharge through Day 30.
- Percentage of opioid-free subjects through 24, 48, and 72 hours or hospital discharge.
- Time to first opioid rescue through 72 hours or hospital discharge.
- Incidence of the following opioid-related AEs until the discharge order is written: respiratory depression, hypoventilation, hypoxia, dry mouth, nausea, vomiting, constipation, altered mental status, pruritus, urinary retention, and postoperative ileus.
- The OBAS total score at 24, 48, and 72 hours. Note: if discharge occurs before 72 hours, the study coordinator must stress to the patient the importance of completing the scheduled OBAS questionnaire up to 72 hours. Completion of the questionnaire should be recorded by the patient in the patient log provided upon discharge.
- Pain interference pre-operative and at Day 14.
- Nurse's satisfaction with overall analgesia at 24, 48, and 72 hours or upon hospital discharge.

12.3. Health Economic Outcomes Assessments

The health economic outcomes will include:

- Hospital LOS.
- Hospital readmissions.
- Use of skilled nursing facility.
- Use of other health services following hospital discharge (phone calls related to pain, unscheduled visits related to pain, and visits to the emergency department).

12.4. Health Economic Outcomes Endpoints

- Hospital LOS, defined as the time from completion of the wound closure until the hospital discharge order is written or through Day 30, whichever is sooner.
- Percentage of subjects meeting the protocol-specified minimum criteria for discharge (ie, no requirement for parenteral pain management, able to tolerate a liquid diet, able to demonstrate safe mobility, not requirement for active wound management) and discharged by time (eg, a "responder analysis").
- Incidence of hospital readmission through Day 30.
- Incidence of skilled nursing facility use.
- Total time spent in skilled nursing facility.
- Number of phone calls related to postsurgical pain.
- Number of unscheduled visits related to postsurgical pain.
- Number of visits to the emergency department.

12.5. Safety Assessments

The following safety measurements will be conducted at the timepoints specified after the end of study drug administration:

- Adverse events from the time the ICF is signed through Day 30.

12.6. Safety Endpoints

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

- Incidence of TEAEs and SAEs through Day 30.

12.7. Appropriateness of Measures

Endpoints selected for this study are based on validated methodologies and other well established clinical measurements used in other peer-reviewed studies in both the peer reviewed literature and at regulatory authorities.

13. STUDY PROCEDURES

A time and events schedule for study procedures is provided in Table 1.

13.1. Instructions for Conducting Procedures and Measures

Day 1 is defined as the day on which study drug is administered. The beginning of surgery is defined as the time of the first incision. All assessments conducted after baseline (ie, study drug administration) will be timed from the end of surgery, defined as the time of the last suture/staple. Postsurgical is defined as after the end of surgery.

Subjects can be discharged based on current clinical practice but, at a minimum, should:

- No longer require parenteral pain management
- Be able to tolerate a liquid diet
- Demonstrate safe mobility as determined with occupational therapy/physical therapy input per hospital standards

13.1.1. Pain Intensity Assessment

Pain intensity will be assessed using a 10-cm VAS (Carlsson 1983, McCormack 1988, and Scott 1976) at baseline (on Day 1 prior to surgery and prior to any premedication); upon arrival at the PACU; at 4, 6, 8, 10, 12, 24, 28, 32, 36, 48, 52, 56, 60, and 72 hours; and immediately prior to each administration of postoperative rescue opioid pain management medication through 72 hours or hospital discharge (see Appendix 1).

13.1.2. Clinical Laboratory Tests

The following select clinical laboratory tests will be conducted at screening:

1. Direct bilirubin
2. Gamma-glutamyl transpeptidase (GGT) and lactate dehydrogenase (LDH)
   OR
   Alanine transaminase (ALT) and aspartate transaminase (AST).

Clinical laboratory tests, as appropriate, may also be conducted if a subject experiences an AE of special interest (ie, cardiac AE or neurological AE) or an SAE (see Section 13.1.5).

13.1.3. Vital Signs

The scheduled vital signs (temperature, resting heart rate, respiratory rate, and blood pressure) will be measured at screening; baseline (on Day 1 prior to surgery; Note: the Day-1 pre-op assessment is not required if the Screening Visit occurred within 10 days of the surgery) and if a subject experiences an AESI (ie, cardiac AE or neurological AE) or an SAE (see Section 13.1.5).

13.1.4. Physical Examination

A full physical examination will be conducted at screening, including a 12-lead ECG and urine pregnancy test. Superficial abnormalities that may interfere with participation in the study will be noted. A targeted physical examination will be conducted on Day 14 and will include examination of the surgical site.

13.1.5. Adverse Events of Special Interest

If a cardiac or neurological AESI or SAE occurs during the study a 12-lead ECG, vital signs, PK draw, and any appropriate clinical laboratory tests must be conducted.

Cardiac AEs of special interest include:

- Chest pain (angina, myocardial infarction)
- Abnormal/irregular heart rate (bradycardia, tachycardia, extrasystoles)

- Shortness of breath requiring intervention.

Neurologic AEs of special interest include:

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

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

- Dizziness
- Hyperesthesia
- Muscular twitching
- Tingling/paresthesia

13.2. Screening Procedures

- Explain study purpose and procedures.
- Obtain written informed consent/assent before performing any study-related procedures.
- Assess eligibility including urine drug screen and alcohol breath test.
- Record relevant medical/surgical history, demographics, and baseline characteristics.
- Conduct urine pregnancy test for women of childbearing potential.
- Perform physical examination.
- Conduct the following clinical laboratory tests:
  1. Direct bilirubin
  2. Gamma-glutamyl transpeptidase (GGT) and lactate dehydrogenase (LDH)
     OR
     Alanine transaminase (ALT) and aspartate transaminase (AST).

- Measure vital signs (temperature, resting heart rate, respiratory rate, and blood pressure).
- Conduct 12-lead ECG after subject has rested in a supine position.
- Record concomitant medications.
- Record AEs starting at the signing of the ICF.

All subjects who are screened for enrollment, but do not meet eligibility criteria, or who decline to participate will be documented on a screening log with the reason for non-participation.

13.3. Baseline Procedures (Day 1 Prior to Surgery)

- Confirm eligibility including urine drug test (Note: this assessment is not required if the Screening Visit occurred within 10 days of the surgery).
- Update relevant medical and surgical history (Note: this assessment is not required if the Screening Visit occurred within 10 days of the surgery).
- Conduct urine pregnancy test for women of childbearing potential (Note: this assessment is not required if the Screening Visit occurred within 10 days of the surgery). A negative pregnancy test result must be available before surgery.
- Record baseline VAS pain intensity score prior to any premedication (see Appendix 1).
- Measure vital signs (temperature, resting heart rate, respiratory rate, and blood pressure) (Note: this assessment is not required if the Screening Visit occurred within 10 days of the surgery).
- Include Pain Interference questionnaire.
- Record changes to concomitant medications since screening.
- Record AEs and any treatment(s) for the events.
- Administer required pre-operative medications

13.4. Intraoperative Procedures

- Confirm eligibility.
- Administer study drug per randomization.
- Record start and stop times of study drug administration.
- Record dosage of study drug administered and total volume.
- Record surgery start and stop times.
- Record concomitant medications.
- Record AEs and any treatment(s) for the events.

- Refer to Section 13.1.5 for additional procedures in the event a cardiac or neurological AESI or SAE occurs.

13.5. Postoperative Assessments Through Hospital Discharge

- Record VAS pain intensity score upon arrival at the PACU; at 4, 6, 8, 10, 12, 24, 28, 32, 36, 48, 52, 56, 60, and 72 hours; and immediately prior to each administration of postoperative rescue medication (see Appendix 1). Note: if the subject is sleeping, do not wake him or her for an assessment of pain at 24 or 48 hours after surgery. If he or she awakens within the assessment window (ie, 1 hour for the 24-hour assessment and 2 hours for the 48-hour assessment), a pain score may be collected then.

  †: If discharge occurs prior to any of the scheduled VAS assessments collected at 4 to 72 hours postsurgery or scheduled OBAS assessments collected at 24 to 72 hours, the study coordinator must stress to the subject the importance of completing the scheduled VAS and OBAS Assessments. These assessments should be recorded by the subject in the patient log provided upon discharge.

- Include OBAS questionnaire (24, 48 and 72 hours). Note: if discharge occurs before 72 hours, the study coordinator must stress to the patient the importance of completing the scheduled OBAS questionnaire up to 72 hours. Completion of the questionnaire should be recorded by the patient in the patient log provided upon discharge
- Obtain nursing likert scale (24, 48 and 72 hours) or until hospital discharge
- Administer postoperative rescue medication upon request, as needed (see Section 11.1).
- Administer scheduled post-op meds
- Record other concomitant medications.
- Record AEs and any treatment(s) for the events.
- Refer to Section 13.1.5 for additional procedures in the event a cardiac or neurological AESI or SAE occurs.
- Record date and time of discharge.
- Provide patient with patient log for recording of daily opioid pain management medication use and remind patient that the completed patient log should be brought to the Day-14 Visit

13.6. Day 14 Visit

- Perform targeted physical examination of the surgical site.
- Include Pain Interference questionnaire.

- Record date and amount of all opioid pain management medication used up to Day 14. Note: upon discharge, the patient will record daily opioid pain management medication use in the provided patient log.
- Document any unscheduled phone calls, unscheduled office visits, or emergency room (ER) visits related to pain after discharge.
- Record concomitant medications.
- Record AEs and any treatment(s) for the events.
- Refer to Section 13.1.5 for additional procedures in the event a cardiac or neurological AE of special interest or SAE occurs.

13.7. Day 30 Phone Call

- Document any unscheduled phone calls, unscheduled office visits, or ER visits related to pain since the Day 14 visit.
- Record AEs and any treatment(s) for the events.
- Record times and doses of all analgesic medication administered since the postsurgical Day 14 visit.
- Record concomitant medications.

14. ADVERSE EVENT REPORTING

Consistent with the current regulatory guidance provided by the US FDA CFR Part 312 and the ICH GCP, AE and SAE 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 (AE)*:* 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 through 30 days 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. For the purposes of Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and 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 Day 30 must be recorded regardless of whether or not they are considered related to study drug. Whenever feasible, AE terms should be documented as medical diagnoses (highest possible level of integration); otherwise, the AEs should 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 should 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 should be recorded and the symptoms collapsed (removed; ie, lined through and initialed). Whenever possible, abnormal laboratory results should be reported as their clinical corollary (eg, low potassium should be recorded as hypokalemia).

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

In general, the severity of an AE should 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 will 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 in the CRF.)

14.2. Serious Adverse Events

14.2.1. Definition of a Serious Adverse Event

Definition of an 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 should 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 should 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 should 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 should 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 Day 30, 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 should 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 should be obtained and all subject-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 Day 30, these should 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:

$$H_0: AUC_{(0\text{-}72)VAS,EXPAREL} = AUC_{(0\text{-}72)VAS,Placebo}$$

The primary alternative hypothesis is:

$$H_A: AUC_{(0\text{-}72)VAS,EXPAREL} \neq AUC_{(0\text{-}72)VAS,Placebo}$$

15.2. Study Endpoints

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

15.3. Determination of Sample Size

The sample size was calculated based on VAS pain and total opioid results reported in Hughes et al (2016) and length of stay reported in the paper by Zheng et al (2002). Based on the reported efficacy for VAS pain intensity scores and assuming a 2-sided 0.05 alpha and a common SD of 70, a sample size of 50 subjects per treatment group should have at least 80% power to detect a 40-unit treatment difference. For total opioid consumption assuming a 2-sided 0.05 alpha and common standard deviation of the log-dose of 0.6 and 80% power a sample size of 64 subjects per treatment group is needed to detect a 30% difference in total opioid consumption through 48 hours. For length of stay assuming a 2-sided 0.05 alpha and common standard deviation of 2.4 and 80% power a sample size of 92 subjects per treatment group is needed to detect a 1 day difference in length of stay. Allowing for a 5% drop-outs rate a sample size of 97 subjects per treatment group should be enrolled to ensure 92 subjects provide length of stay data. A total study sample size of 184 evaluable subjects will provide 80% power to detect a 1-day difference in length of stay; 92% power to detect a 30% difference in total opioid consumption; and 97% power to detect a 40 point difference in VAS-$AUC_{(0\text{-}72)}$.

15.4. Analysis Populations

The safety analysis set will include all subjects who receive study drug. All analyses based on the safety set will be by actual treatment received.

The efficacy analysis set will include all subjects in the safety analysis set who undergo the planned surgery. All analyses based on the efficacy analysis set will be by randomized treatment regardless of treatment actually received.

The per-protocol efficacy analysis set will include all subjects in the efficacy analysis set and do not have any major protocol violations.

15.5. Handling Subject Dropouts and Discontinuations

Subjects who discontinue after dosing will not be replaced.

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

Continuously valued data will be summarized using descriptive statistics (n [number of subjects contributing data], mean, SD, median, minimum, and maximum). Discretely valued data will be tabulated (n and percent) by category. The denominator for all percentages will be the number of subjects who underwent the planned surgery.

15.6.1. Efficacy Analyses

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

15.6.1.1. Primary Efficacy Analyses

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.

15.6.2. 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 24, 48 and 72 hours will be converted to morphine equivalents and analyzed using the same ANOVA model as the primary endpoint. Percentage of opioid-free subjects through 24, 48 and 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. The treatment difference in time to first opioid will be tested using the Gehan-Wilcoxon test.

The VAS $AUC_{(12-24)}$, $AUC_{(12-72)}$, $AUC_{(24-48)}$ and $AUC_{(48-72)}$ will be analyzed in the same manner as the primary efficacy endpoint [$AUC_{(0-72)}$].

The OBAS total score and nurse's satisfaction with overall analgesia at 24, 48 and 72 hours will be analyzed using an ANOVA.

Hospital LOS will be analyzed using an ANOVA.

The incidence of hospital readmission and skilled nursing facility use will be analyzed using a CMH test stratified by site.

15.6.3. Safety Analyses

15.6.3.1. 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 each treatment group. All incidence rates will be categorized and displayed by system organ class and preferred term.

15.7. Significance Testing

The primary efficacy endpoint will be tested at the 0.05 alpha level.

If the primary efficacy endpoint is statistically significant the secondary endpoints will be tested at the 0.05 alpha level in a family-wise sequential hierarchical testing procedure. The exact procedure will be detailed in the SAP.

16. REFERENCES

American Society of Anesthesiologists Task Force on Pain Management. Practice guidelines for acute pain management in the postoperative setting: A report by the American Society for Anesthesiologist Task Force on Pain Management Acute Pain Section. *Anesthesiology.* 1995;82:1071-1081.

Apfelbaum JL, Chen C, Mehta SS, et al. Postoperative pain experience: Results from a national survey suggests postoperative pain continues to be undermanaged. *Anesth Analg*. 2003;97:535-540.

Apseloff G, Onel E, Patou G. Time to onset of analgesia following local infiltration of liposome bupivacaine in healthy volunteers: a randomized, single-blind, sequential cohort, crossover study. *Int J Clin Pharmacol Ther*. 2013;51:367-373.

Carlsson AM. Assessment of Chronic Pain. I. Aspects of the Reliability and Validity of the Visual Analogue Scale. *Pain*. 1983;16:87-101.

Carroll NV, Miederhoff PA, Cox FM, et al. Costs incurred by outpatient surgical centers in managing postoperative nausea and vomiting. *J Clin Anesth*. 1994;6:364-369.

Chernin T. Painkillers and pill popping. *Drug Topics*. 2001;15:31. Accessed 04 January 2011. Available at: http://drugtopics.modernmedicine.com/drugtopics/PainManagement/ArticleStandard/article/detail/118858.

Chung F. Discharge criteria – A new trend. *Can J Anesth*. 1995;42:1056-1058.

Chung F, Chan VW, Ong D. A post-anesthetic discharge scoring system for home readiness after ambulatory surgery. *J Clin Anesth*. 1995;7(6):500-506.

Joshi GP, Cushner FD, Barrington JW, et al. Best Infiltration Practices: Local Analgesia Infiltration Techniques – Hip & Knee Arthroplasty. 2014. Available online through GuidelineCentral.com http://eguideline.guidelinecentral.com/i/319830-hip-and-knee-arthroplasty-orthopedic-surgery

Guild GN, Galindo RP, Marino J, et al. Periarticular regional analgesia in total knee arthroplasty: A review of the neuroanatomy and injection technique. *Orthop Clin N Am*. 2015;46(1):1–8.

Hu D, Onel E, Singla N, et al. Pharmacokinetic profile of liposome bupivacaine injection following a single administration at the surgical site. *Clin Drug Investig*. 2013;33:109-115.

Hughes J, Chaput CD, Maldonado YM, Rahm MD. Efficacy of liposomal bupivacaine for postoperative pain after spine surgery - retrospective control. NASS 31st Annual Meeting Proceedings. The Spine Journal 16 (2016) S251–S337

Joshi GP, Cushner FD, Barrington JW, et al. Techniques for periarticular infiltration with liposomal bupivacaine for the management of pain after hip and knee arthroplasty: A consensus recommendation. *J Surg Orthop Adv*. 2015;24(1):27-35.

Lehmann N, Joshi GP, Dirkmann D, et al. Development and longitudinal validation of the overall benefit of analgesia score: a simple multi-dimensional quality assessment instrument. *Br J Anasth*. 2010;105(4):511-518. Epub 2010 Aug 6.

McCormack HM, DJ Horne, Sheather S. Clinical applications of visual analogue scales: A critical review. *Psychol Med*. 1988;18(4):1007-1019.

Oderda GM, Said Q, Evans RS, et al. Opioid-related adverse drug events in surgical hospitalizations: Impact on cost and length of stay. *Ann Pharmacother*. 2007;41(3):400-406.

Scott J, Huskinsson EC. Graphic representation of pain. *Pain*. 1976;2(2):175-184.

Viscusi ER. New and emerging treatment options for acute postoperative pain in the inpatient setting: Barriers to effective pain management. Medscape Pharmacists. 15 December 2009. Accessed 04 January 2011. Available at: http://www.medscape.org/viewarticle/713472_2.

Zheng F, Cammisa FP, Sandue HA, Girardi FP, and Khan SN. Factors predicting hospital stay, operative time, blood loss, and transfusion in patients undergoing revision posterior lumbar spine decompression, fusion, and segmental instrumentation. SPINE (2002) Volume 27, Number 8, pp 818–824.

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. 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 Pharmaceuticals, Inc. 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 Pharmaceuticals, Inc. 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 Pharmaceuticals, Inc. and/or the investigational product(s) will be disclosed to the regulatory authorities by Pacira Pharmaceuticals, Inc.

_____ _____

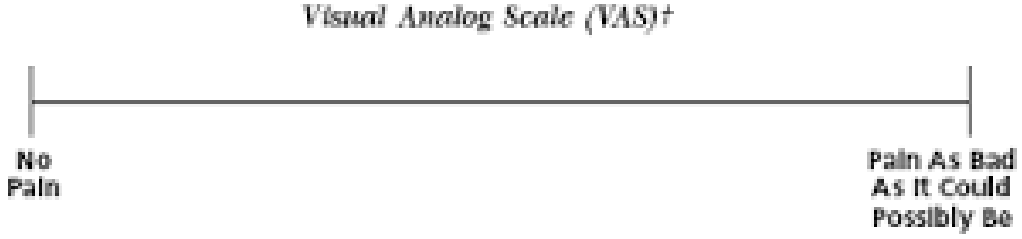
Signature of Investigator

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 surgery and prior to any premedication); upon arrival at the PACU; at, 4, 6, 8, 10, 12, 24,28, 32, 36, 48, 52, 60,and 72; and immediately prior to each administration of rescue medication; and just prior to hospital discharge. Note: if discharge occurs before 72 hours, the study coordinator must stress to the patient the importance of completing the scheduled pain intensity assessments up to 72 hours. These assessments should be recorded by the patient in the patient log provided upon discharge.

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 experience right now.



(For reference only; not for clinical use.)

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

The OBAS questionnaire will be completed at 24, 48, and 72 hours after surgery (Lehmann 2010). Note: if discharge occurs before 72 hours, the study coordinator must stress to the patient the importance of completing the scheduled OBAS questionnaire up to 72 hours. Completion of the questionnaire should be recorded by the patient in the patient log provided upon discharge.

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: Nurse's Satisfaction with Postsurgical Pain Control (Likert Scale)

The nurse's satisfaction with postsurgical pain control will be assessed at 24, 48, and 72 hours after surgery or upon hospital discharge.

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

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

Appendix 4: Pain Interference Scale

PROMIS Item Bank v1.0 – Pain Interference - Short Form 6b

Pain Interference – Short Form 6b

Please respond to each item by marking one box per row.

In the past 7 days…

		Not at all	A little bit	Somewhat	Quite a bit	Very much
PAININ2	How much did pain interfere with your enjoyment of life?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ8	How much did pain interfere with your ability to concentrate?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ9	How much did pain interfere with your day to day activities?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ10	How much did pain interfere with your enjoyment of recreational activities?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ14	How much did pain interfere with doing your tasks away from home (e.g., getting groceries, running errands)?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
PAININ28	How often did pain keep you from socializing with others?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5