FUSION

PACIRA PHARMACEUTICALS, INC.

Clinical Study Protocol

A multicenter, prospective, active controlled, real world, Phase 4 study of EXPAREL in multimodal regimens compared with standard of care for postsurgical pain management in subjects undergoing lumbar posterior spine surgeries (FUSION)

Protocol No.:	402-C-413
IND No.:	Not applicable
EudraCT No.:	Not applicable
Study Phase:	Phase 4
Study Drug:	EXPAREL® (bupivacaine liposome injectable suspension)
Original Protocol Date:	08-November-2018
Amendment 1 Date:	25-February-2019
Study Site(s):	Multicenter study in the United States
Sponsor:	Pacira Pharmaceuticals, Inc. 5 Sylvan Way Parsippany, NJ 07054 Telephone: (973) 254-3560

1. SIGNATURE PAGE

Richard Scranton, MD, MPH Chief Medical Officer	DocuSigned by: Richard Scranton Signer Name: Richard Scranton Signing Reason: I approve this document Signing Time: 2/27/2019 4:42:09 PM EST E9744ABACED3460CADE01BBBB74144EC	27-Feb-2019 Date
Julia Yang, MD Vice President, Clinical Research	DocuSigned by: Julia Yang Signer Name: Julia Yang Signing Reason: I approve this document Signing Time: 2/25/2019 6:14:49 PM EST 5FF2495A4B9D4035A663BB5FCD14592A	25-Feb-2019 Date
Igor Grachev, MD, PhD Senior Medical Director, Clinical Research	DocuSigned by: Igor Grachev Signer Name: Igor Grachev Signing Reason: I approve this document Signing Time: 2/26/2019 6:55:27 AM EST 6B6D484613FC477C89E796A1C812321B	26-Feb-2019 Date
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2. SYNOPSIS

Name of Sponsor/Company: Pacira Pharmaceuticals, Inc. 5 Sylvan Way Parsippany, NJ 07054 (973) 254-3560	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: EXPAREL (bupivacaine liposome injectable suspension); 266 mg in 20 mL		
Name of Active Ingredient: Bupivacaine, 1.3%, 13.3 mg/mL		

Title of Study: A multicenter, prospective, active controlled, real world, Phase 4 study of EXPAREL in multimodal regimens compared with standard of care for postsurgical pain management in subjects undergoing lumbar posterior spine surgeries (FUSION)

Principal Investigator(s): To be determined

Study Center(s): Multicenter study in the United States

Publications (Reference): None

Objectives:

Primary Objective: The primary objective of this study is to compare postsurgical opioid consumption through 72 hours postsurgery in patients receiving local infiltration analgesia (LIA) with EXPAREL and bupivacaine HCl (EXPAREL group) with that of patients receiving standard of care (SOC) (control group) in adult subjects undergoing posterior lumbar spine surgeries where both groups are receiving a multimodal pain regimen.

Secondary Objectives: The secondary objectives of this study are to:

1. Compare safety and effectiveness outcomes following LIA with EXPAREL and bupivacaine hydrochloride (HCl) versus SOC in adult subjects undergoing posterior lumbar spine surgeries through 72 hours, including time to first opioid and opioid-related adverse events (ORAEs).

2. Compare health outcomes following LIA with EXPAREL and bupivacaine HCl versus SOC in adult subjects undergoing posterior lumbar spine surgeries, including discharge readiness, hospital (or other facility) length of stay (LOS), discharge disposition, hospital readmissions, and health service utilization.

Methodology:

This is a Phase 4, multicenter, prospective, active-controlled, real world, study in approximately 225 adult subjects undergoing posterior lumbar spine surgery under general anesthesia.

Screening:

Subjects will be screened within 30 days prior to surgery; screening on the day of surgery will be allowed but is discouraged. If a subject can only be screened on the day of surgery, the informed consent process must still be started at least 24 hours prior to the conduct of any screening procedures that are not considered SOC at the Institution and such procedures may not be performed until written informed consent is provided. All screening procedures that are not SOC must be performed and documented within the 30-day time window (inclusive of the day of surgery for those subjects who can only be screened on the day of surgery) as described here.

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During the screening visit, subjects will be assessed for any past or present medical conditions that in the opinion of the investigator would preclude them from study participation.

After the ICF is signed, the following information will be recorded and procedures done:

- Medical history
- Surgical history
- Medication history
- Opioid use history will be recorded to calculate mean daily mg oral morphine equivalent dosing (MED PO) in the last 30 days
- Demographic and background information, and height, weight, and body mass index (BMI)
- Urine pregnancy test for women of childbearing potential
- Current adverse experiences (AEs), if any

Subjects will be asked questions and/or be asked to complete the following assessments:

- Brief Pain Inventory – short form (BPI-sf)
- 5-item Opioid Compliance Checklist (OCC) (Jamison 2014; Jamison 2016)
- Hospital Anxiety and Depression Scale (HADS)
- Survey of Pain Attitudes (SOPA); single item (7 questions) version
- Numeric Rating Scale (NRS) to assess pain
- Opioid Related Symptoms Distress Scale (OR-SDS)

Based on the planned surgical procedure, subjects will be placed in one of three cohorts:

- Cohort 1 – Open lumbar spinal fusion technique; (“open” cohort)
- Cohort 2 – Minimally invasive tubular and/or percutaneous pedicle screw insertion for lumbar decompression with or without fusion; (“tubular/percutaneous without midline incision” cohort)
- Cohort 3 – Lumbar decompression surgery (LDS) without fusion (discectomy or laminectomy outpatient cohort)

The initial sample size in each study cohort (i.e., cohort 1, cohort 2 and cohort 3) is estimated at 75 subjects (50 subjects with EXPAREL and 25 subjects with Control group), for a total of 225 subjects in all three cohorts. Within each assigned cohort, subjects will be allocated in a 2:1 ratio to the EXPAREL (50 subjects) and Control group (25 subjects).

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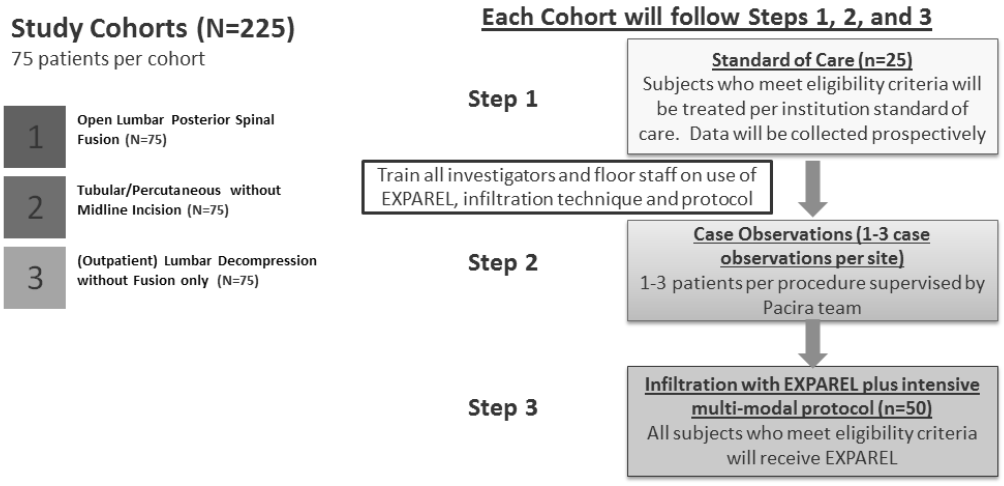
The following sequence will be followed for all cohorts: First, the subjects who meet eligibility criteria will be treated according to the institution's SOC. Their data will be collected prospectively. Next, at each investigational site, the administration of EXPAREL and bupivacaine HCl to the first 1 to 3 subjects in each cohort will be observed to ensure that the correct procedure for infiltration as described in the infiltration guide is being followed. If the infiltration was performed correctly, the subject will be included in the study. If the infiltration was performed incorrectly, the subject will continue in the study but will be removed from statistical analysis and will be replaced to ensure at least 50 evaluable EXPAREL patients are enrolled per cohort. If subjects are discontinued for other reasons, they will be replaced such that a total sample size of 75 fully evaluable subjects is obtained in each study cohort, with 50 in the EXPAREL group and 25 in the Control group. Criteria for fully evaluable will be defined in the statistical analysis plan (SAP).



Blinding

This will be an open-label study and neither subjects nor Investigators will be blinded for study group allocation.

eDiary

Subjects are to record their responses to subject questionnaires on an electronic device (an eDiary) from the time of screening, while in the hospital (or other facility), and after discharge. Every day after discharge through Day 14, subjects are to record any pain medication (date, time, and dose) taken in the prior 24 hours in addition to recording questionnaire responses at the specified time points.

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Study interventions
Control group

Subjects in the Control group represented in each cohort will receive SOC as per the participating institution and Investigators. Subjects in the Control group in all three cohorts (cohort 1, cohort 2 and cohort 3) will receive the following recommended study interventions for analgesia:

Pre-operative oral multimodal analgesia (within approximately 24-48 hours prior to surgery)

a) Tylenol (acetaminophen) 1000 mg orally administered (PO)
b) Gabapentin 300 mg PO
c) Robaxin 750 mg PO

List of recommended pre-operative prophylactic medications (optional) for postoperative nausea and vomiting or pruritus:

For nausea and vomiting:

a) Ondansetron 4 mg intravenously (IV) at approximately 15-30 min before emergence from anesthesia
b) Decadron (dexamethasone) 8-12 mg IV after anesthesia induction
c) Phenergan 25 mg IV PRN
d) Metocopramide 10 mg PO PRN

For pruritus:

a) Diphenhydramine 25 mg PO PRN
b) Nalbuphine 2.5 mg IV PRN

Intra-operative anesthesia and analgesia at the surgical site as per usual care.

Post-operative multimodal analgesia in the control group (within approximately 72 hours postsurgery):

a) Tylenol (acetaminophen) 1000 mg PO three times daily (TID); the total daily dose of acetaminophen is not to exceed 3000 mg. Intravenous (IV) acetaminophen can be used if the subject is unable to tolerate oral acetaminophen.
b) Gabapentin 300 mg PO twice daily (BID); alternative medication is pregabalin 150 mg PO BID
c) Robaxin 750 mg PO BID or TID

The use of additional pre- or postsurgical pain medication (e.g., opioids) in cases of insufficient analgesia is permitted per the institution's SOC.

The investigative staff is responsible for recording all pain medications taken until discharge; the subject will then be responsible for recording their medications in the eDiary through Day 14.

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EXPAREL group

Subjects in the EXPAREL group in all three cohorts (cohort 1, cohort 2 and cohort 3) will receive the following strongly recommended study interventions for analgesia:

1. Pre-operative oral multimodal analgesia (within approximately 24-48 hours prior to surgery)
   a) Tylenol (acetaminophen) 1000 mg PO
   b) Gabapentin 300 mg PO
   c) Robaxin 750 mg PO

2. List of recommended pre-operative prophylactic medications (optional) for postoperative nausea, vomiting, or pruritus:

   For nausea and vomiting:
   a) Ondansetron 4 mg IV at approximately 15-30 min before emergence from anesthesia
   b) Decadron (dexamethasone) 8-12 mg IV after anesthesia induction
   c) Phenergan 25 mg IV PRN
   d) Metocopramide 10 mg PO PRN

   For pruritus:
   a) Diphenhydramine 25 mg PO PRN
   b) Nalbuphine 2.5 mg IV PRN for pruritus

3. Intra-operative anesthesia and analgesia at the surgical site as per usual care.

   Note: Subjects will not be permitted to receive any other local anesthetic for pre-, intra- (i.e., within 20 min before administering EXPAREL), or postoperative analgesia, other than the specified admixed bupivacaine for local infiltration at the surgical site per the infiltration guide. If administering lidocaine or other non-bupivacaine-based local anesthetics is required per the institution's SOC, wait 20 minutes before administering EXPAREL

4. Post-operative scheduled multimodal analgesia (within approximately 72 hours postsurgery):
   a) Tylenol (acetaminophen) 1000 mg PO TID; the total daily dose of acetaminophen is not to exceed 3000 mg. Intravenous (IV) acetaminophen can be used if the subject is unable to tolerate oral acetaminophen
   b) Gabapentin 300 mg PO BID; alternative medication is pregabalin 150 mg PO BID
   c) Robaxin 750 mg PO BID or TID

Postsurgical Pain Management

Subjects should receive opioid and non-opioid rescue pain medications only upon request for breakthrough pain. Rescue medications shall be provided based on the pain scores reported on the NRS. For pain scores of 1 to 3, subjects shall receive nonsteroidal anti-inflammatory drugs (NSAIDs), without exceeding the maximum daily dose. For pain scores of 4 or greater, immediate-release orally-administered (PO) oxycodone shall be administered as a rescue medication. For pain scores of 4 to 7, 5 mg PO oxycodone shall be provided PRN; for pain score of 8 to 10 on the NRS, 10 mg PO oxycodone will be provided PRN.

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If a subject is unable to tolerate PO medication or fails the PO oxycodone rescue, IV morphine (initiated at 1 to 2 mg) or hydromorphone (initiated at 0.3 to 0.5 mg) may be administered PRN. Initial rescue medications can be IV per Investigator's discretion. Use of patient controlled analgesia pumps (PCA) is not recommended.

Postoperative Assessments:

The date, time, and doses of all opioid and non-opioid rescue medications, and all multimodal scheduled medications will be recorded. Additionally, the time that the subject spent in different hospital units (Post-Anesthesia Care Unit [PACU], step down), date and time of discharge, discharge disposition, concomitant medications and AEs (if any) will be recorded.

The following assessments will be made through 72 hours following surgery and, as specified below, at the follow up phone call or visit at 14 days after surgery for all subjects who received study drug as specified below:

- Postsurgical opioid use (i.e., mg MED PO) at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours after the end of surgery, at discharge, and at the 14 day phone call (or visit)
- Pain at the surgical site using an 11-point NRS at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours after the end of surgery, at discharge, and at the 14 day phone call (or visit)
- BPI-sf: administered at screening/baseline; at 24, 48, and 72 hours , at discharge, and at the 14 day phone call (or visit)
- Opioid related symptom distress scale (OR-SDS) at 24, 48, and 72 hours, at discharge, and at the 14 day phone call (or visit)
- Discharge readiness using Modified Post-Anesthesia Discharge Scoring System (MPADSS) at 24, 48, and 72 hours or discharge or until the subject attains a score of 9, whichever occurs first
- Adverse events and medications used to treat AEs

The following are also to be documented:

- Unscheduled phone calls or office visits related to pain (Day 14 call or visit)
- Requests for refills for opioid medication (Day 14 call or visit)
- Hospital readmission(s) related to pain (Day 30 call)
- Hospital readmission(s) for any reason (Day 30 call)
- Unscheduled Emergency Room (ER) visits related to pain (Day 30 call)
- Persistent opioid use by asking the subject at the 30 day (± 3 days) phone call "Are you currently taking opioid medication to manage pain from your spine surgery?"

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Number of Subjects (Planned):
A sufficient number of subjects will be screened to provide a total of 225 evaluable subjects, with 150 in the EXPAREL group and 75 in the Control group.

Interim analyses may be conducted to adjust to variability. Adaptive study design will be used which incorporates adjustment of sample size, cohort sequence, type of surgical procedure, endpoints, etc.

Eligibility Criteria:
Inclusion Criteria:

Subjects must meet all of the following inclusion criteria to be eligible for participation:
1. 18-75 years old at the time of screening
2. Primary surgical indication is related to spinal degenerative disease, including any of the following:
   a) Spinal stenosis
   b) Spondylolisthesis
   c) Radiculopathy/instability disc disorders
   d) Degenerative disc disease
3. Medically cleared for elective spine surgery
4. Scheduled to undergo:
   a) Elective (i.e., not emergency)
   b) Lumbosacral (i.e., L1-S1)
   c) Posterior approach with posterior instrumentation
5. Cohort 1 – Open cohort only: (Open or mini-open surgical technique with):
   a) 1-level (i.e., spanning 2 vertebrae) or 2-level (i.e., spanning 3 contiguous vertebrae)
   b) Primary fusion or revision fusion
   c) Open or mini-open surgical technique
6. Cohort 2 – Tubular or percutaneous cohort only:
   a) 1-level (i.e., spanning 2 vertebrae) or 2-level (i.e., spanning 3 contiguous vertebrae)
   b) Primary fusion or revision fusion
   c) Tubular or percutaneous surgical technique
7. Cohort 3 – Lumbar decompression without fusion outpatient cohort only:
   a) Radiculopathy
   b) Spinal stenosis
8. Able to provide informed consent and adhere to all study assessments and visit schedule

Exclusion Criteria:
Subjects who meet any of the following exclusion criteria will not be eligible for participation in this study:
1. Serious spinal pathology determined by the Investigator that might meaningfully affect postsurgical outcomes, including any of the following:
   a) Suspected cauda equina syndrome (e.g., bowel/bladder involvement)

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b) Infection
c) Tumor
d) Fracture
e) Systemic inflammatory spondyloarthropathy

2. Contraindication to local anesthesia according to the clinical judgment of the Investigator and based on the EXPAREL label.
3. Patients who most likely will require PCA pumps in EXPAREL group
4. Anterior surgical approaches, including <u>any</u> of the following:
   a) Anterior lumbar interbody fusion (ALIF)
   b) Oblique lumbar interbody fusion (OLIF)
   c) Anterior-posterior or 360º fusion
5. Lateral surgical approaches, including any of the following:
   a) Extreme lateral interbody fusion (XLIF)
   b) Direct lateral interbody fusion (DLIF)
6. High-dose presurgical opioid use
   a) Mean daily intake greater than 100 mg mEq PO in the past 30 days
7. Known allergy, hypersensitivity, or contraindication to <u>any</u> of the following study medications:
   a) Bupivacaine
   b) EXPAREL
   c) Tylenol (acetaminophen)
   d) Robaxin
   e) 2 or more NSAIDs
   f) 2 or more gabapentinoids
   g) 2 or more rescue opioids (e.g., oxycodone, morphine, hydromorphone)
   h) 2 or more medications for postoperative nausea, vomiting, or pruritus (e.g., dexamethasone, ondansetron)
8. History of severely impaired renal or hepatic function
9. Severe chronic pain that requires analgesic treatment and, in the opinion of the principal Investigator, is likely to meaningfully affect postsurgical outcomes
10. Subjects that have implanted spinal cord stimulator or intrathecal drug pump
11. Any neurologic or psychiatric disorder that might affect postsurgical pain or interfere with study assessments per Investigator discretion
12. Malignancy in the last 2 years
13. History of misuse, abuse, or dependence on opioid analgesics, other prescription drugs, illicit drugs, or alcohol as defined in DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition). Dependence or chronic opioid use will be defined as use of more than 30 morphine equivalents per day during the prior 90 days
14. Currently pregnant, nursing, or planning to become pregnant during the study or within 1 month after study drug administration
15. Body Mass Index < 17 kg/m^2 or >44 kg/m^2 at screening
16. Subjects receiving Worker's Compensation for disability or who are involved in other litigation related to the

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spine
17. Planned concurrent surgical procedure
18. Previous participation in an EXPAREL study
19. Administration of any 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

In addition, the subject might be excluded from the study prior to study drug infiltration if one of the following criteria during the surgical procedure is met:
a) Unable to place planned surgical instrumentation
b) Poor fixation at the time of surgical instrumentation

In addition, the subject must be considered an early termination if one of the following criteria after the surgical procedure is met:
1. An incision size >20 cm
2. Autograft taken from a harvest site other than surgical site (i.e., iliac crest autograft)
3. Intraoperative complications likely to meaningfully affect postsurgical outcomes, including any of the following:
   a) Clinically significant and prolonged (i.e., >24 hours) neurologic deficit (e.g., foot drop)
   b) Dural tear or suspected dural tear requiring bed rest (exception: subject will be allowed if the dural tear is fixed as per SOC of the institution during surgery)
   c) Extensive bleeding (i.e., >1,000 mL blood loss)
   d) Symptomatic epidural hematoma

Whenever possible, subjects discontinuing the study should complete end of study (EoS) assessments. Subjects discontinuing prior to 72 hours are to complete the 72 hour assessments as EoS assessments. If early termination occurs after discharge but prior to Day 14, Day 14 assessments are to be completed as EoS assessments. If early termination occurs after Day 14 but prior to Day 30, Day 30 assessments are to be completed as EoS assessments.

Test Product, Dose, Mode of Administration, and Lot Number:
EXPAREL group (EXPAREL admixed with Bupivacaine HCl)

	Medication 1	**Medication 2**
Name	EXPAREL (bupivacaine liposome injectable suspension)	Bupivacaine HCl
Active Ingredient	Bupivacaine	Bupivacaine HCl
Dosage	266 mg	150 mg
Lot Number	To be determined	To be determined
Mode of administration	Local infiltration at the surgical site	Local infiltration at the surgical site

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Reference Product, Dose, Mode of Administration, and Lot Number:
Institutional site SOC for postsurgical analgesia.

Duration of Subject Participation in Study:
Participation in the study will begin upon signing the study ICF, which must occur no more than 30 days prior to the expected date of surgery. Follow-up will continue for 30 days (± 3 days) after discharge. Study subjects may therefore participate for a maximum of 63 days.

Efficacy Assessments:
The following assessments will be performed to determine efficacy:

1. Postsurgical opioid use (i.e., mg MED PO) from end of surgery (closure of wound/incision) to 72 hours postsurgery
2. Opioid related adverse events (ORAEs) using the OR-SDS at 24, 48, and 72 hours, at discharge, and at 14 days.
3. BPI-sf, administered at screening/baseline; at 24, 48, and 72 hours, at discharge, and at 14 days.
4. NRS, used to assess pain at the surgical site at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours, at discharge, and at 14 days.

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Efficacy Endpoints:

The endpoints listed below will be assessed based on the efficacy measurements conducted at the times specified after the end of surgery. End of surgery is defined as the time when the last incision/wound is closed. All post-surgical measures/assessments will be recorded from this point forward.

Primary efficacy endpoint:

The primary efficacy endpoint is postsurgical opioid consumption in mg MED PO from 0 hours (end of surgery) to 72 hours postsurgery

Secondary endpoints:

1. Post-surgical opioid consumption in mg MED PO at 14 days after surgery
2. Time to first opioid rescue through 72 hours or discharge
3. Opioid related adverse events will be assessed by using the Opioid Related Symptoms Distress Scale (OR-SDS) at 24, 48, and 72 hours postsurgery, at discharge, and at 14 days

Exploratory endpoints:

1. The NRS pain intensity score at surgical site at each assessed time point during the hospital (or other facility) stay (at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours), at discharge, and at 14 days
2. BPI-sf – short form (BPI-sf) at screening/baseline; daily for the first 3 days (24 hours, 48 hours and 72 hours or discharge), at discharge, and at 14 days.
3. OCC, SOPA and HADS at the baseline visit.
4. The area under the curve (AUC) of the NRS pain intensity scores at surgical site from 0 to 24, 0 to 48, and 0 to 72 hours

Safety Assessments: Adverse events will be monitored and recorded from the time the ICF is signed through Day 30. Safety assessments will be measured at multiple time points throughout the study.

Safety Endpoints:

Any adverse events (AEs) reported while subjects are in the hospital (or other facility), or at any time during the 30 day study follow-up, will be assessed as safety outcomes.

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Health Outcomes Assessments:

1. Time as hours spent in PACU and stepdown unit
2. Total length of stay (i.e., recorded in hours) in the hospital (or other facility)
3. Discharge readiness (measured via the MPADSS) at 24, 48, and 72 hours or discharge or until the subject attains a score of 9, whichever occurs first
4. Discharge disposition (i.e., home, outpatient rehabilitation facility, inpatient rehabilitation facility, skilled nursing facility, other)
5. 30 days all cause readmissions
6. 30 days readmissions related to pain
7. 30 days Emergency Room (ER) visits related to pain
8. 14days office visits related to pain
9. 14 days call to doctor related to pain
10. 30 days persistent opioid use by asking the subject "Are you currently taking opioid medication to manage pain from your spine surgery?"

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 and bupivacaine HCl (EXPAREL group) to treatment with SOC (Control group) will be determined using an analysis of variance (ANOVA) with treatment as the main effect on postoperative opioid consumption through 72 hours. Secondary efficacy endpoints will be analyzed using ANOVA, logistic regression model, chi-square tests, and log-rank tests, as appropriate. Safety endpoints will be summarized descriptively by treatment group.

Interim Analysis
Interim analyses may be conducted to adjust to variability. Adaptive study design (i.e., adjustment of sample size, cohort sequence, type of surgical procedure, endpoints, etc.) will be used.

Table 1. Time and Events Schedule of Study Procedures (Part 1)

Study Procedure	Screening/ Baseline (1-30 days prior to surgery)	Pre-op	Intra-op	PACU	Post-op
Screening and Baseline					
Obtain signed ICF[a]	X				
Record medical and surgical history	X				
Record medication history[b]	X				
Record demographics and baseline characteristics	X				
Record opioid use in last 30 days to determine mg MED PO/day average	X				
Record height, weight, and BMI	X				
Confirm eligibility	X				
Urine pregnancy test (UPT) (for women of childbearing potential)	X				
NRS for pain at the pre-surgical area	X				
Survey of Pain Attitudes (Single-item SOPA)	X				
Brief Pain Inventory – short form (BPI-sf)	X				
Hospital Anxiety and Depression Scale (HADS)	X				
5-item Opioid Compliance Checklist (OCC)[c]	X				
Record AEs and medications to treat AEs from the time ICF was signed	◄	―	―	―	►
Day of surgery					
Confirm eligibility; UPT does not need to be repeated		X			
Administer scheduled presurgical medications		X			
Record surgery start and stop times			X		
Prepare study drug			X		
Administer study drug; record start and stop times			X		
Record intraoperative opioids administered and doses, and all concomitant medications			X		
Record times and doses of all opioid and non-opioid rescue medications administered			X		
Post-surgery[d]					
Record date, time, and dose of rescue postsurgical analgesics					X
Record date, times, and doses of all multimodal scheduled medications administered					X
Record date, time of admission to, and time of discharge from different hospital units (PACU, step-down)				X	
Record concomitant medications		◄	―	―	►

Abbreviations: AE = Adverse event; BMI = Body mass index; BPI-sf = Brief Pain Inventory – short form; HADS = Hospital Anxiety and Depression Scale; ICF = Informed consent form; MED = Morphine equivalent dosing; OCC = 5-item Opioid Compliance Checklist (Jamison 2014; Jamison 2016); PACU = Post-anesthesia care unit; PO = per os (oral); SOC = standard of care; SOPA = Survey of Pain Attitude; UPT = urine pregnancy test.

[a] No more than 30 days should pass between signing of the ICF and performance of the surgery. Subjects will be screened within 30 days prior to surgery; screening on the day of surgery will be allowed but is discouraged. If a subject can only be screened on the day of surgery, the informed consent process must still be started at least 24 hours prior to the

conduct of any screening procedures that are not considered SOC at the institution and such procedures may not be performed until written informed consent is provided. All screening procedures that are not SOC must be performed and documented within the 30-day time window (inclusive of the day of surgery for those subjects who can only be screened on the day of surgery) as described here. During the screening visit, subjects will be assessed for any past or present medical conditions that in the opinion of the investigator would preclude them from study participation.

[b] Record any medications for the condition for which the procedure is being performed that were administered within 30 days prior to screening.

[c] Sources for 5-item OCC are Jamison 2014 and Jamison 2016.

[d] All assessments conducted after baseline (prior to the study drug administration) will be timed from the end of surgery. Postsurgical is defined as a period after the end of surgery. End of surgery is defined as the time (when the last incision/wound is closed).

Table 2. Time and Events Schedule of Study Procedures after PACU Arrival (Part 2)

	From End of Surgery 6-72 Hours[a]									Discharge[b]	Phone call or Visit[a]	Phone call[b]
Time Point ± Time window	**6 hrs ±1 hr**	**12 hrs ±1 hr**	**18 hrs ±1 hr**	**24 hrs ±1 hr**	**30 hrs ±2 hr**	**36 hrs ±2 hr**	**42 hrs ±2 hr**	**48 hrs ±2 hr**	**72 hrs ±4 hr[b]**		**14 days ±3 days[a]**	**30 days ±3 days**
Study Procedure												
NRS for pain at surgical site	X	X	X	X	X	X	X	X	X	X	X	
BPI-sf				X				X	X	X	X	
Record date and time of all opioid and non-opioid rescue medications[a]	←	—	—	—	—	—	—	—	—	—	→	
OR-SDS				X				X	X	X	X	
MPADSS[c]				X				X	X	X[c]		
Record date and time of discharge										X		
Record subject discharge disposition										X		
Document any unscheduled phone calls or office visits related to pain											X	
Document any requests for refills for opioid medication											X	
Record persistent opioid use by asking the subject "Are you currently taking opioid medication to manage pain from your spine surgery?"												X
Document any hospital readmissions related to pain												X
Document hospital readmissions for any cause												X
Document any unscheduled visits to the ER related to pain												X
Record date and time of AEs and medications to treat AEs (with dosage)	←	—	—	—	—	—	—	—	—	—	—	→

Abbreviations: AE=adverse event; BPI-sf = Brief Pain Inventory – short form; ER = Emergency room; hr/hrs = hour(s); MPADSS = Modified Post-Anesthesia Discharge Scoring System; NRS=numeric rating scale; OR-SDS = Opioid-Related Symptom Distress Scale.

[a] Subjects are to record their responses to subject questionnaires on an electronic device (eDiary) at screening, while in the hospital (or other facility), and at Day 14. Every day from discharge through Day 14, subjects are to record in the eDiary any pain medication (date, time, and dose) taken in the prior 24 hours in addition to recording questionnaire responses. Subjects who were lent an eDiary will have to return to the site at 14 days at which time they are to return the device. Subjects who used their own device will have a follow-up phone call at Day 14. All subjects will have a follow up call at 30 days after the surgery.

[b] For all subjects, if discharge occurs prior to 72 hours postsurgery, all Discharge assessments are to be performed at the time of discharge. After discharge, all scheduled assessments should be performed at the scheduled time points (i.e., NRS pain assessments at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours postsurgery; BPI-sf and OR-SDS at 24, 48, and 72 hours; and date, time, and dose of all opioid and non-opioid rescue medications) and recorded in the eDiary.

[c] Discharge readiness via the MPADSS will be assessed at 24, 48, and 72 hours and/or discharge or until the subject attains a score of 9, whichever occurs first.

Note: Early Termination: Whenever possible, subjects discontinuing the study should complete end of study (EoS) assessments. Subjects discontinuing prior to 72 hours are to complete the 72 hour assessments as EoS assessments. If early termination occurs after discharge but prior to Day 14, Day 14 assessments are to be completed as EoS assessments. If early termination occurs after Day 14 but prior to Day 30, Day 30 assessments are to be completed as EoS assessments.

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4. LIST OF ABBREVIATIONS

AE	Adverse event
ALIF	Anterior lumbar interbody fusion
ALT	Alanine transaminase
ANOVA	Analysis of variation
AST	Aspartate transaminase
AUC	Area under the plasma concentration-versus-time curve
BID	Bis in die (twice a day)
BMI	Body mass index
BPI-sf	Brief Pain Inventory-short form
CFR	Code of Federal Regulations
C_{max}	Maximum plasma concentration
Cm	Centimeters
CRF	Case Report Form
CV	Coefficient of variation
DLIF	Direct lateral interbody fusion
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EoS	End of study
ER	Emergency room
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
HADS	Hospital Anxiety and Depression Scale
HCl	Hydrochloride
ICF	Informed consent form
ICH	International Council for Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
JCAHO	Joint Commission on Accreditation of Healthcare Organizations

L	Lumbar (e.g., L5 vertebra)
LDS	Lumbar decompression surgery
LIA	Local infiltration analgesia
LOS	Length of stay
MCID	Minimum clinically important difference
MED	Morphine equivalent dosing
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
MPADSS	Modified Post-Anesthesia Discharge Scoring System
NRS	Numeric rating scale
NSAIDs	Non-steroidal anti-inflammatory drugs
OCC	Opioid compliance checklist
OLIF	Oblique lumbar interbody fusion
OR-SDS	Opioid Related Symptoms Distress Scale
ORAE	Opioid related adverse event
PACU	Post-anesthesia care unit
PCA	Patient controlled analgesia
PO	Per os (orally administered)
POD	Postoperative day
PRN	Pro re nata (as needed)
PTAE	Pretreatment adverse event
S	Sacral (e.g., S5 vertebra)
SAE	Serious adverse event
SAP	Statistical analysis plan
SNRIs	Serotonin and norepinephrine reuptake inhibitors
SOC	Standard of care
SOPA	Survey of Pain Attitudes
SSRIs	Selective serotonin reuptake inhibitors
TAP	Transversus abdominis plane
TEAE	Treatment-emergent adverse event
TID	Ter in die (three times a day)
ULN	Upper limit of normal
UPT	Urine pregnancy test
US	United States (of America)
XLIF	Extreme lateral lumbar interbody fusion

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) that complies with the International Council for 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 (if applicable) 312, and the ICH GCP. Study documents will be maintained in accordance with applicable regulations.

5.3. Subject Information and Consent

Before a subject undergoes any study-specific screening procedures, the Investigator or designee will thoroughly explain to the subject the purpose of the study, the associated procedures, and any expected effects and potential adverse reactions. A copy of the IRB-approved 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 participate. The subject, and the study staff with whom he or she discusses the ICF, will sign and date the ICF. A photocopy of the signed ICF will be given to the subject.

The Investigator will explain to the subject that he or she is completely free to decline entry into the study and may withdraw from the study at any time, for any reason, without risking his or her medical care. Similarly, the Investigator and/or Pacira Pharmaceuticals, Inc. (Pacira) 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 IRBs/IECs and regulatory agencies.

7. INTRODUCTION

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). Current therapies have a variety of side effects (see Section 7.2) and there is an unmet medical need for agents that provide better and safer postsurgical pain control.

EXPAREL® (bupivacaine liposome injectable suspension) is a long-acting, non-opioid, analgesic. Bupivacaine, the active pharmaceutical ingredient in EXPAREL, is a local anesthetic that has been used to produce local analgesia via a field block (also referred to as infiltration) and to produce regional analgesia via a peripheral nerve block for decades in the United States (US) and around the world.

7.1. Indication

EXPAREL was initially approved by the US Food and Drug Administration (FDA) in 2011 for single-dose administration into the surgical site to produce postsurgical analgesia. The indication was amended and approved by the US FDA in 2018 to read: "EXPAREL is indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus block to produce postsurgical regional analgesia. Safety and efficacy have not been established in other nerve blocks."

Since its approval, EXPAREL has been administered to over 4 million patients in the US.

7.2. Current Therapies/Treatments

Current modalities of postoperative analgesia include wound infiltration and nerve block with local anesthetics, 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; 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 (e.g., delay in regaining bowel function or an inability to tolerate liquid and solid oral intake, etc.), and conserves healthcare resources. As such, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) requires that all healthcare

facilities practice safe and quality pain management, promote safe opioid prescribing and use, minimize the risks associated with treatment (The Joint Commission), 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. Opioid-only regimens are common and intravenous (IV) patient-controlled analgesia is a widely used delivery system for morphine sulfate. AEs related to opioid administration (e.g., nausea, vomiting, ileus, confusion), however, represent one important reason that there is a need to develop opioid-sparing strategies. Indeed, fear of gastrointestinal side effects such as nausea and vomiting, as well as respiratory depression, present major limitations for the widespread use of opioid analgesics. (Chernin 2001 and Viscusi 2009) Furthermore, management of opioid-related events often requires medical attention (e.g., opioid antagonists, antiemetic agents) and increased pharmacy/nursing time, which may raise healthcare expenses (Carroll 1994).

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

EXPAREL could provide physicians with a long-acting analgesic for procedures that are more amenable to brachial plexus nerve block than field block, an indication for which EXPAREL has an extensive history of safe and effective use in over 4 million patients in the US. Moreover, the analgesic effects of a local anesthetic when administered as a brachial plexus nerve block could be prolonged via a single-shot technique without the risks and difficulty of placing 1 or more continuous nerve block catheters. Finally, this approach also has the potential to reduce the exposure of surgical patients to opioids and their associated AEs, as well as reduce the number of opioids available for abuse and diversion in the community.

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 (Balocco 2018). EXPAREL (Pacira Pharmaceuticals, Inc., Parsippany, New Jersey) is a bupivacaine liposome injectable suspension. It consists of microscopic spherical, multivesicular liposomes (DepoFoam® drug delivery system), organized in a honeycomb-like structure comprising numerous non-concentric internal aqueous chambers containing a bupivacaine base at a concentration of 13.3 mg/mL. Each chamber is separated from adjacent chambers by lipid membranes. The lipids (phospholipids, cholesterol, and triglycerides) are naturally occurring or close analogs of endogenous lipids. Bupivacaine is slowly released from the DepoFoam particles by a complex mechanism involving

reorganization of the barrier lipid membranes and subsequent diffusion of the drug over an extended period of time. A small amount of extra-liposomal bupivacaine (i.e., not bound within the DepoFoam particles) enables EXPAREL to have a similar onset of action to standard bupivacaine hydrochloride (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 to 2 hours and a second peak at approximately 24-48 hours (Hu 2013).

Following the initial approval of EXPAREL, numerous clinical studies were conducted in which EXPAREL was administered via various routes of administration, including infiltration into the transversus abdominis plane (TAP) (Sternlicht 2014, Feierman 2014).

Please see the EXPAREL Full Prescribing Information (2018) for complete safety information regarding EXPAREL (liposome bupivacaine injectable suspension): https://www.exparel.com/hcp/prescriptioninformation.pdf.

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 EXPAREL – has a slightly different mixture of lipid components than DepoCyt.

7.4. Summary of Human Experience with EXPAREL

The EXPAREL clinical development program, which includes 31 clinical studies (13 Phase 1, 7 Phase 2, and 11 Phase 3), assessed the efficacy and safety across a wide range of body regions and applications, investigating its use in pain management when administered as a peripheral nerve block for regional analgesia and as a field block for local analgesia. A total of 3,644 subjects were studied in these 31 clinical studies, of which 2,141 subjects received EXPAREL.

In terms of efficacy, 5 positive Phase 3 studies, 316, 317, 323, 327, and 331 demonstrated statistically significant improvements in pain intensity scores compared to placebo or IR bupivacaine in the postoperative period. All 5 studies also showed a statistically significant reduction compared to placebo or bupivacaine in total opioid consumption; Studies 327, 316, 317, and 331 additionally showed a significantly higher percentage of opioid-free subjects and a significantly longer time to first opioid use compared to placebo or IR bupivacaine.

The safety of EXPAREL was evaluated in 10 randomized, double-blind, local administration into the surgical site clinical studies involving 823 subjects undergoing various surgical procedures.

Subjects were administered a dose ranging from 66 to 532 mg of EXPAREL. In these studies, the most common adverse reactions (incidence ≥10%) following EXPAREL administration were nausea, constipation, and vomiting. The common adverse reactions (incidence ≥2% to <10%) following EXPAREL administration were pyrexia, dizziness, edema peripheral, anemia, hypotension, pruritus, tachycardia, headache, insomnia, anemia postoperative, muscle spasms, hemorrhagic anemia, back pain, somnolence, and procedural pain.

The less common/rare adverse reactions (incidence <2%) following EXPAREL administration were chills, erythema, bradycardia, anxiety, urinary retention, pain, edema, tremor, dizziness, postural, paresthesia, syncope, incision site edema, procedural hypertension, procedural hypotension, procedural nausea, muscular weakness, neck pain, pruritus generalized, rash pruritic, hyperhidrosis, cold sweat, urticaria, palpitations, sinus bradycardia, supraventricular extrasystoles, ventricular extrasystoles, ventricular tachycardia, hypertension, pallor, anxiety, confusional state, depression, agitation, restlessness, hypoxia, laryngospasm, apnea, respiratory depression, respiratory failure, body temperature increased, blood pressure increased, blood pressure decreased, oxygen saturation decreased, urinary incontinence, vision blurred, tinnitus, drug hypersensitivity, and hypersensitivity.

Across the 31 completed studies in the clinical program, safety data were collected on 3,644 subjects (2,141 subjects received EXPAREL, 850 subjects received IR bupivacaine alone, and 653 subjects received placebo). Doses administered ranged from 10 mg to 750 mg. There were adequate numbers in the ≥65 years of age category (171 subjects) as well as the American Society of Anesthesiologists Class 3-4 category (135 subjects). Overall, the type and frequency of safety events were consistent across various surgical procedures performed and with the well-established safety profile of local anesthetics. The safety of EXPAREL was also assessed for any evidence of neurotoxicity, impaired wound healing, and the potential for systemic local anesthetic toxicity. There is no evidence of any local adverse effects specific to EXPAREL.

Please refer to the Investigator's Brochure for additional information regarding the completed studies. Please see the EXPAREL Full Prescribing Information for complete safety information regarding EXPAREL (liposome bupivacaine injectable suspension) in the setting of wound infiltration (https://www.exparel.com/hcp/prescriptioninformation.pdf).

7.5. Postmarketing Exposure

The extensive supportive safety database generated by 4 million exposures (as of 07 May 2018) in the US supports the safety profile of EXPAREL.

8. OBJECTIVES

8.1. Primary Objective

The primary objective of this study is to compare postsurgical opioid consumption through 72 hours postsurgery in patients receiving local infiltration analgesia (LIA) with EXPAREL and bupivacaine

HCl (EXPAREL group) with that of patients receiving standard of care (SOC) (control group) in adult subjects undergoing posterior lumbar spine surgeries where both groups are receiving a multimodal pain regimen.

8.2. Secondary Objective(s)

The secondary objectives are to:

1. Compare safety and effectiveness outcomes following LIA with EXPAREL and bupivacaine hydrochloride (HCl) versus SOC in adult subjects undergoing posterior lumbar spine surgeries through 72 hours, including time to first opioid, opioid-related adverse events (ORAEs).
2. Compare health outcomes following LIA with EXPAREL and bupivacaine HCl versus SOC in adult subjects undergoing posterior lumbar spine surgeries, including discharge readiness, hospital (or other facility) length of stay (LOS), discharge disposition, hospital readmissions, and health service utilization.

9. OVERALL STUDY DESIGN AND PLAN

9.1. Study Design

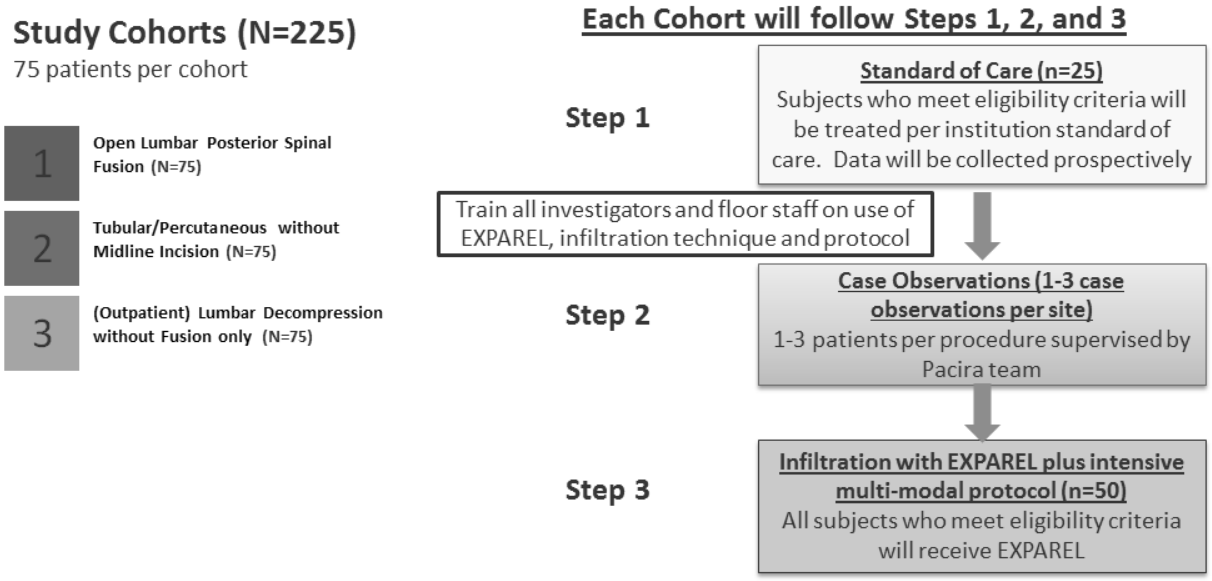
This is a Phase 4, multicenter, prospective, active-controlled, real world study in approximately 225 adult subjects undergoing posterior lumbar spine surgeries under general anesthesia. This will be an open-label study and neither subjects nor Investigators will be blinded for study group allocation. This study will include three cohort groups: cohort 1 – open lumbar spinal fusion technique ("open"); cohort 2 – minimally invasive tubular and/or percutaneous pedicle screw insertion for lumbar decompression with or without fusion ("tubular/percutaneous without midline incision"); and cohort 3 – lumbar decompression surgery (LDS) without fusion (discectomy or laminectomy) outpatient cohort.

The initial sample size in each study cohort (i.e., cohort 1, cohort 2 and cohort 3) is estimated at 75 subjects (50 subjects with EXPAREL and 25 subjects with Control group), for a total of 225 subjects in all three cohorts. Within each assigned cohort, subjects will be allocated in a 2:1 ratio to the EXPAREL (50 subjects) and Control group (25 subjects).

The following sequence will be followed for all cohorts: First, the subjects who meet eligibility criteria will be treated according the institution's SOC. Their data will be collected prospectively. Next, at each investigational site, the administration of EXPAREL and bupivacaine HCl to the first 1 to 3 subjects in each cohort will be observed to ensure that the correct procedure for infiltration as described in the infiltration guide is being followed. If the infiltration was performed correctly, the subject will be included in the study. If the infiltration was performed incorrectly, the subject will continue in the study but will be removed from statistical analysis and will be replaced to ensure at least 50 evaluable EXPAREL patients are enrolled per cohort. If subjects are discontinued for other

reasons, they will be replaced such that a total sample size of 75 fully evaluable subjects is obtained in each study cohort, with 50 in the EXPAREL group and 25 in the Control group. Criteria for fully evaluable will be defined in the statistical analysis plan (SAP).

Figure 1 Study Schema



Obtaining Informed Consent

Potential participants may provide informed consent up to 30 days before their scheduled surgery. Subjects will be screened within 30 days prior to surgery; screening on the day of surgery will be allowed but is discouraged. If a subject can only be screened on the day of surgery, the informed consent process must still be started at least 24 hours prior to the conduct of any screening procedures that are not considered SOC at the institution and such procedures may not be performed until written informed consent is provided. All screening procedures that are not SOC must be performed and documented within the 30-day time window (inclusive of the day of surgery for those subjects who can only be screened on the day of surgery) as described here. During the screening visit, subjects will be assessed for any past or present medical conditions that in the opinion of the investigator would preclude them from study participation.

Screening

Subjects will be screened within 30 days prior to surgery. During the screening visit, subjects will be assessed for past or present 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, medication history, opioid use history, and current adverse experiences (if any) will be collected. Height, weight, and BMI will be recorded, and a urine pregnancy test (UPT) for women of childbearing potential will be conducted.

Subjects will be asked questions and/or be asked to fill forms to complete the following assessments:

- Brief Pain Inventory – short form (BPI-sf)
- 5-item Opioid Compliance Checklist (OCC) (Jamison 2014; Jamison 2016)
- Hospital Anxiety and Depression Scale (HADS)
- Survey of Pain Attitudes (SOPA); single item (7 questions) version
- Numeric rating scale (NRS) to assess pain
- Opioid Related Symptoms Distress Scale (OR-SDS)

Day of Surgery

Control Group: Subjects in the Control group will receive SOC as per the participating institutions and Investigators. Subjects in the Control group in all three cohorts (cohort 1, cohort 2, and cohort 3) will receive the following recommended study interventions for analgesia:

Pre-operative oral multimodal analgesia (within approximately 24-48 hours prior to surgery)

a) Tylenol (acetaminophen) 1000 mg PO
b) Gabapentin 300 mg PO
c) Robaxin 750 mg PO

List of recommended pre-operative prophylactic medications (optional) for postoperative nausea and vomiting or pruritus:

Nausea and vomiting:

a) Ondansetron 4 mg IV at approximately 15-30 min before emergence from anesthesia
b) Decadron (dexamethasone) 8-12 mg IV after anesthesia induction
c) Phenergan 25 mg PRN
d) Metocopramide 10 mg PO PRN

Pruritus:

a) Diphenhydramine 25 mg PO PRN
b) Nalbuphine 2.5 mg IV PRN for pruritus

Intra-operative anesthesia and analgesia at the surgical site as per usual care.

Post-operative multimodal analgesia in the control group (within approximately 72 hours postsurgery):

a) Tylenol (acetaminophen) 1000 mg PO TID; the total daily dose of acetaminophen is not to exceed 3000 mg. Intravenous (IV) acetaminophen can be used if the subject is unable to tolerate oral acetaminophen.
b) Gabapentin 300 mg PO BID; alternative medication is pregabalin 150 mg PO BID

c) Robaxin 750 mg PO BID or TID

The use of additional pre- or postsurgical pain medication (e.g., opioids) in cases of insufficient analgesia is permitted per the institution's SOC.

The investigative staff is responsible for recording all pain medications taken until the hospital (or other facility) discharge; the subject will then be responsible for recording their medications in the eDiary through Day 14.

EXPAREL Group: All eligible subjects in EXPAREL group will receive the following strongly recommended study interventions for analgesia:

1. Pre-operative oral multimodal analgesia (within approximately 24-48 hours prior to surgery):
   a) Tylenol (acetaminophen) 1000 mg PO
   b) Gabapentin 300 mg PO
   c) Robaxin 750 mg PO

2. List of recommended pre-operative prophylactic medications (optional) for postoperative nausea and vomiting or pruritus:
   Nausea and vomiting:
   a) Ondansetron 4 mg IV at approximately 15-30 min before emergence from anesthesia
   b) Decadron (dexamethasone) 8-12 mg IV after anesthesia induction
   c) Phenergan 25 mg PRN
   d) Metocopramide 10 mg PO PRN

   Pruritus:
   a) Diphenhydramine 25 mg PO PRN
   b) Nalbuphine 2.5 mg IV PRN for pruritus

3. Intraoperative anesthesia and analgesia at the surgical site as per usual care
   Note: Subjects will not be permitted to receive any other local anesthetic for preoperative, intraoperative (i.e., within 20 min before administering EXPAREL), or postoperative analgesia, other than the specified admixed bupivacaine for local infiltration at the surgical site per the infiltration guide. If administering lidocaine or other non-bupivacaine-based local anesthetics is required per the institution's SOC, wait 20 min before administering EXPAREL.

<u>Post-operative Medications</u>

Postsurgically, all eligible subjects from the EXPAREL group are required to receive the following scheduled postoperative multimodal analgesia (within approximately 72 hours postsurgery):

- Tylenol (acetaminophen) 1000 mg PO TID; the total daily dose of acetaminophen is not to exceed 3000 mg. Intravenous (IV) acetaminophen can be used if the subject is unable to tolerate oral acetaminophen.

- Gabapentin 300 mg PO BID; alternative medication is pregabalin 150 mg PO BID.
- Robaxin 750 mg PO BID or TID

No additional skeletal muscle relaxants should be used in the hospital in the EXPAREL group. 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 receive opioid and non-opioid rescue pain medications only upon request for breakthrough pain.

Rescue medications shall be provided based on the pain scores reported on the NRS. For pain scores of 1 to 3, subjects shall receive nonsteroidal anti-inflammatory drugs (NSAIDs), without exceeding the maximum daily dose. For pain scores of 4 or greater, immediate- release orally-administered (PO) oxycodone shall be administered as a rescue medication. For pain scores of 4 to 7, 5 mg PO oxycodone shall be provided as needed (PRN); for pain score of 8 to 10 on the NRS, 10 mg PO oxycodone will be provided PRN.

If a subject is unable to tolerate PO medication or fails the PO oxycodone rescue, IV morphine (initiated at 1 to 2 mg) or hydromorphone (initiated at 0.3 to 0.5 mg) may be administered PRN.

Optional: The initial rescue medication can be IV per Investigator's discretion.

Post-discharge Analgesia
Upon discharge from the hospital (or other facility), subjects will receive prescriptions for 30 tablets of Tylenol (acetaminophen) 500 mg (1000 mg up to TID; not to exceed 3000 mg or 6 tablets daily) and 30 tablets of oxycodone 5 mg (PRN, not to exceed 3 tablets per day). If refills for opioid medication are requested by subjects from discharge up to Day 14, the time and date of the request(s) will be noted as one of the outcomes measured in this study related to postsurgical opioid use.

The subject should record pain medication taken (date, time and dose) in the eDiary from discharge through Day 14.

Postoperative Assessments
The date, time, and doses of all opioid and non-opioid rescue medications (if needed) and all multimodal scheduled medications will be recorded. Additionally, the time that the subject spent in different hospital units (Post-Anesthesia Care Unit [PACU], step down), date and time of discharge, discharge disposition, concomitant medications and AEs (if any) will be recorded.

The following assessments will be made through 72 hours following surgery and, as specified below, at the follow up phone call or visit at 14 days after surgery for all subjects who received study drug as specified below:

- Postsurgical opioid use (i.e., mg MED PO) at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours after the end of surgery, at discharge, and at the 14 day phone call (or visit)
- Pain at the surgical site using an 11-point NRS at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours after the end of surgery, at discharge, and at the 14 day follow-up call (or visit) (see Appendix 1)
- BPI-sf: administered at screening/baseline; at 24, 48, and 72 hours, at discharge, and at the 14 day follow-up phone call (or visit)
- Opioid related symptom distress scale (OR-SDS) at 24, 48, and 72 hours, at discharge, and at the 14 day follow-up call (or visit) (see Appendix 3)
- Discharge readiness using Modified Post-Anesthesia Discharge Scoring System (MPADSS) at 24, 48, and 72 hours or discharge or until the subject attains a score of 9, whichever occurs first
- Adverse events and medications used to treat AEs through Day 30

The following are also to be documented:

- Unscheduled phone calls or office visits related to pain (Day 14 call or visit)
- Requests for refills for opioid medication (Day 14 call or visit)
- Hospital readmission(s) related to pain (Day 30 call)
- Hospital readmission(s) for any reason (Day 30 call)
- Unscheduled Emergency Room (ER) visits related to pain (Day 30 call)
- Adverse events and medications used to treat AEs
- Persistent opioid use by asking the subject at the 30 day (± 3 days) phone call "Are you currently taking opioid medication to manage pain from your spine surgery?"

Follow-up Visit and Phone calls

Two follow up phone calls will be scheduled at 14 days (±3 days) and 30 days (±3 days) after the surgery for all subjects. Subjects who were lent an eDiary will have to return to the site at 14 days at which time they are to return the device; they will have a follow-up phone call at 30 days. Subjects who used their own device will have follow-up phone calls at 14 and 30 days after the surgery.

9.1.1. Duration of the Study and Subject Participation

Participation in the study will begin upon signing the study ICF, which must occur no more than 30 days prior to the expected date of surgery. Follow-up will continue for 30 days (± 3 days) after the discharge. Study subjects may therefore participate for up to 63 days from ICF to the final study follow-up.

9.1.2. Study Stopping Rules

If Pacira, the Investigator, or officials from regulatory authorities discover conditions during the study that indicate that the study or study site should be terminated, this action may be taken after Pacira has consulted with appropriate regulatory authorities and notified the Investigator(s).
The Pacira Medical Monitor and Pharmacovigilance team review all serious adverse events (SAEs) reported from Pacira clinical studies on an ongoing basis and in real time (i.e., 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 suggests a potential threat to the safety of the study participants. If such action is taken, a thorough review of all available data will be done. 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, multicenter, active-controlled study is designed to compare postsurgical opioid consumption following local infiltration with EXPAREL with bupivacaine HCl versus SOC in adult subjects undergoing posterior lumbar spine surgeries.

This study is designed to assess the effectiveness of EXPAREL infiltration in a multimodal setting to reduce total postsurgical opioid consumption. All subjects in the study will be eligible to receive a non-opioid or opioid analgesic, if needed, to control breakthrough postsurgical pain as part of the multimodal approach to pain management.

Adverse events (AEs) and SAEs will be recorded by the investigator or staff from the time the ICF is signed through postoperative Day (POD) 30.

10. STUDY POPULATION

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

10.1. Inclusion Criteria

Subjects must meet <u>all</u> of the following criteria to be eligible for study entry:

1. Subjects 18-75 years old at time of screening
2. Primary surgical indication is related to spinal degenerative disease, including <u>any</u> of the following:
    a) Spinal stenosis
    b) Spondylolisthesis
    c) Radiculopathy/instability disc disorders
    d) Degenerative disc disease

3. Medically cleared for elective spine surgery
4. Scheduled to undergo:
   a) Elective (i.e., not emergency)
   b) Lumbosacral (i.e., L1-S1)
   c) Posterior approach with posterior instrumentation
5. Cohort 1- Open only:
   Open or mini-open surgical technique with:
   a) 1-level (i.e., spanning vertebrae) or 2-level (i.e., spanning 3 contiguous vertebrae)
   b) Primary fusion or revision fusion
   c) Open or mini-open surgical technique
6. Cohort 2- Tubular or percutaneous cohort only:
   a) 1-level (i.e., spanning 2 vertebrae) or 2-level (i.e., spanning 3 contiguous vertebrae)
   b) Primary fusion or revision fusion
   c) Tubular or percutaneous surgical technique
7. Cohort 3- Lumbar decompression without fusion outpatient cohort only:
   a) Radiculopathy
   b) Spinal stenosis
8. Able to provide informed consent and adhere to all study assessments and visit schedule

10.2. Exclusion Criteria

Subjects who meet any of the following exclusion criteria will not be eligible for participation in this study:

1. Serious spinal pathology determined by the Investigator that might meaningfully affect postsurgical outcomes, including any of the following:

   a) Suspected cauda equina syndrome (e.g., bowel/bladder involvement)
   b) Infection
   c) Tumor
   d) Fracture
   e) Systemic inflammatory spondyloarthropathy

2. Contraindication to local anesthesia according to the clinical judgment of the Investigator and based on the EXPAREL label.
3. Patients who most likely will require patient-controlled analgesia (PCA) pumps in EXPAREL group
4. Anterior surgical approaches, including any of the following:

   a) Anterior lumbar interbody fusion (ALIF)
   b) Oblique lumbar interbody fusion (OLIF)
   c) Anterior-posterior or 360º fusion

5. Lateral surgical approaches, including any of the following:
   a. Extreme lateral interbody fusion (XLIF)
   b. Direct lateral interbody fusion (DLIF)
6. High-dose presurgical opioid use
   a. Mean daily intake greater than 100 mg mEq PO in the past 30 days
7. Known allergy, hypersensitivity, or contraindication to any of the following study medications:

   a) Bupivacaine
   b) EXPAREL
   c) Tylenol (acetaminophen)
   d) Robaxin
   e) 2 or more NSAIDs
   f) 2 or more gabapentinoids
   g) 2 or more rescue opioids (e.g., oxycodone, morphine, hydromorphone)
   h) 2 or more medications for postoperative nausea, vomiting, or pruritus (e.g., dexamethasone, ondansetron)
8. History of severely impaired or hepatic function
9. Severe chronic pain that requires analgesic treatment, and in the opinion of the principal Investigator, is likely to meaningfully affect postsurgical outcomes
10. Subjects that have implanted spinal cord stimulator or intrathecal drug pump
11. Any neurologic or psychiatric disorder that might affect postsurgical pain or interfere with study assessments per Investigator discretion
12. Malignancy in the last 2 years
13. History of misuse, abuse, or dependence on opioid analgesics, other prescription drugs, illicit drugs, or alcohol as defined in DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition). Dependence or chronic opioid use will be defined as use of more than 30 morphine equivalents per day during the prior 90 days
14. Currently pregnant, nursing, or planning to become pregnant during the study or within 1 month after study drug administration
15. Body Mass Index < 17 kg/m^2 or >44 kg/m^2 at screening
16. Subjects receiving Worker's Compensation for disability or who are involved in other litigation related to the spine
17. Planned concurrent surgical procedure
18. Previous participation in an EXPAREL study
19. Administration of any 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

In addition, the subject might be excluded from the study prior to study drug infiltration if one of the following criteria during the surgical procedure is met:

a) Unable to place planned surgical instrumentation
b) Poor fixation at the time of surgical instrumentation

In addition, the subject must be considered an early termination if one of the following criteria after the surgical procedure is met:

1. An incision size >20 cm
2. Autograft taken from a harvest site other than surgical site (i.e., iliac crest autograft)
3. Intraoperative complications likely to meaningfully affect postsurgical outcomes, including any of the following:
   a) Clinically significant and prolonged (i.e., >24 hours) neurologic deficit (e.g., foot drop)
   b) Dural tear or suspected dural tear requiring bed rest (exception: subject will be allowed if the dural tear is fixed as per SOC of the institution during surgery)
   c) Extensive bleeding (i.e., >1,000 mL blood loss)
   d) Symptomatic epidural hematoma

10.3. Removal of Subjects from Therapy or Assessment

Every reasonable effort shall be made to maintain subject compliance and participation in the study. Reasons for discontinuation of any subject from the study will be recorded. If a subject withdraws from the study and has an ongoing AE, the subject may be monitored for safety through Day 30 or until satisfactory resolution is obtained at the investigator's discretion. Whenever possible, subjects discontinuing the study should complete EoS assessments. Subjects discontinuing prior to 72 hours are to complete the 72 hour assessments as EoS assessments. If early termination occurs following discharge but prior to Day 14, the subject will be asked to complete the Day 14 assessments as EoS assessments. If early termination occurs after Day 14 but prior to Day 30, the subject will be asked to complete the Day 30 assessments as EoS assessments.

Subject might be excluded from the study prior to study drug infiltration if one of the following criteria during the surgical procedure is met:

a) Unable to place planned surgical instrumentation
b) Poor fixation at the time of surgical instrumentation

If any clinically significant event or condition is uncovered during or after the surgery, such as the ones listed below, the subject should be withdrawn from the study and the event or condition should be reported as an AE or SAE:

1. An incision size >20 cm
2. Autograft taken from harvest site other than surgical site (i.e., iliac crest autograft)
3. Intraoperative complications likely to meaningfully affect postsurgical outcomes, including any of the following:
   a) Clinically significant and prolonged (i.e., >24 hours) neurologic deficit (e.g., foot drop)
   b) Dural tear or suspected dural tear requiring bed rest

c) Extensive bleeding (i.e., >1,000 mL blood loss)
d) Symptomatic epidural hematoma

10.3.1. Withdrawal Secondary to Adverse Events

If a subject experiences an AE that renders him/her incapable of continuing with the remaining study assessments, then he/she will be discontinued from further participation in the study. If such a subject discontinues prior to 72 hours, all assessments to be conducted at 72 hours should be completed. If such a subject discontinues following discharge but prior to Day 14, the subject will be asked to complete the Day 14 assessments. If the subject withdraws after Day 14 but before Day 30, the subject will be asked to complete the Day 30 assessments.

Any subject who discontinues because of an AE should be instructed to notify the study personnel of any abnormalities 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 infiltration 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 must be obtained by the Investigator and appropriate information captured in the subject's case report form (CRF).

10.3.2. Voluntary or Study Investigator Withdrawal

Subjects are free to discontinue from the study at any time, without prejudice to future treatment. Nevertheless, subjects will be encouraged to complete the end of study 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 EoS assessments. If the subject withdraws before 72 hours postsurgery, he or she will be asked to complete the 72 hour assessments as EoS assessments. If the subject withdraws following discharge but prior to Day 14, he or she will be asked to complete the Day 14 assessments as EoS assessments. If the subject withdraws after Day 14 but before Day 30, he or she will be asked to complete the Day 30 assessments as EoS assessments.

After termination from the study, the subject may be monitored for safety including monitoring of AEs through Day 30 at the investigator's discretion.

11. TREATMENTS

11.1. Treatment to be Administered

11.1.1. Control Group

Subjects in the Control group in each cohort will receive SOC as per the participating institution and Investigators. Subjects in the Control group in all three cohorts (cohort 1, cohort 2 and cohort 3) will receive the following recommended study interventions for analgesia:

Pre-operative oral multimodal analgesia (within approximately 24 to 48 hours prior to surgery):

a) Tylenol (acetaminophen) 1000 mg PO

b) Gabapentin 300 mg PO

c) Robaxin 750 mg PO

Intra-operative anesthesia and analgesia at the surgical site as per usual care.

List of recommended pre-operative prophylactic medications (optional) for postoperative nausea and vomiting or pruritus:

For nausea and vomiting:

a) Ondansetron 4 mg intravenously (IV) at approximately 15-30 min before emergence from anesthesia
b) Decadron 8-12 mg IV after anesthesia induction
c) Phenergan 25 mg IV PRN
d) Metocopramide 10 mg PO PRN

For pruritus:

a) Diphenhydramine 25 mg PO PRN
b) Nalbuphine 2.5 mg IV PRN

Post-operative multimodal analgesia in the control group:

a) Tylenol (acetaminophen) 1000 mg PO TID; the total daily dose of acetaminophen is not to exceed 3000 mg. Intravenous (IV) acetaminophen can be used if the subject is unable to tolerate oral acetaminophen.

b) Gabapentin 300 mg PO BID; alternative medication is pregabalin 150 mg PO BID

c) Robaxin 750 mg PO BID or TID

The use of additional pre- or postsurgical pain medication (e.g., opioids) in cases of insufficient analgesia is permitted per the institution's SOC.

The investigative staff is responsible for recording all pain medications taken until the discharge; the subject will then be responsible for recording their medications in the eDiary.

Postsurgical Pain Management

Subjects should receive opioid and non-opioid rescue pain medications only upon request for breakthrough pain.

Rescue medications shall be provided based on the pain scores reported on the NRS. For pain scores of 1 to 3, subjects shall receive additional unscheduled nonsteroidal anti-inflammatory drugs (NSAIDs), without exceeding the maximum daily dose. For pain scores of 4 or greater, immediate-release orally-administered (PO) oxycodone shall be administered as a rescue medication. For pain scores of 4 to 7, 5 mg PO oxycodone shall be provided; for pain score of 8 to 10 on the NRS, 10 mg PO oxycodone will be provided.

If a subject is unable to tolerate PO medication or fails the PO oxycodone rescue, IV morphine (initiated at 1 to 2 mg) or hydromorphone (initiated at 0.3 to 0.5 mg) may be administered PRN. Initial rescue medication can be IV per Investigator's discretion. Use of patient controlled analgesia pumps (PCA) is not recommended.

The investigative staff is responsible for recording all pain medications taken until discharge; the subject will then be responsible for recording their medications in the eDiary from discharge through Day 14.

11.1.2. EXPAREL Group

Subjects in the EXPAREL group in all three cohorts (cohort 1, cohort 2 and cohort 3) will receive the following strongly recommended study interventions for analgesia:

1. Pre-operative oral multimodal analgesia (within approximately 24-48 hours prior to surgery)

    a) Tylenol (acetaminophen) 1000 mg PO

    b) Gabapentin 300 mg PO

    c) Robaxin 750 mg PO

2. List of recommended pre-operative prophylactic medications (optional) for postoperative nausea and vomiting or pruritus:

    For nausea and vomiting:

a) Ondansetron 4 mg intravenously (IV) at approximately 15-30 min before emergence from anesthesia
b) Decadron 8-12 mg IV after anesthesia induction
c) Phenergan 25 mg IV PRN
d) Metocopramide 10 mg PO PRN

For pruritus:
a) Diphenhydramine 25 mg PO PRN
b) Nalbuphine 2.5 mg IV PRN

3. Intra-operative anesthesia and analgesia at the surgical site as per usual care (Note: Subjects will not be permitted to receive any other local anesthetic for pre-, intra- (i.e., within 20 min. before administering EXPAREL), or postoperative analgesia, other than the specified admixed bupivacaine for local infiltration at the surgical site per infiltration guide. If administering lidocaine or other non-bupivacaine-based local anesthetics is required per the institution's SOC, wait 20 min before administering EXPAREL).

4. Post-operative scheduled multimodal analgesia (within approximately 72 hours postsurgery):

a) Tylenol (acetaminophen) 1000 mg PO TID; the total daily dose of acetaminophen is not to exceed 3000 mg. Intravenous (IV) acetaminophen can be used if the subject is unable to tolerate oral acetaminophen.

b) Gabapentin 300 mg PO BID; alternative medication is pregabalin 150 mg PO BID

c) Robaxin 750 mg PO BID or TID

Postsurgical Pain Management

Subjects should receive opioid and non-opioid rescue pain medications only upon request for breakthrough pain.

Rescue medications shall be provided based on the pain scores reported on the NRS. For pain scores of 1 to 3, subjects shall receive nonsteroidal anti-inflammatory drugs (NSAIDs), without exceeding the maximum daily dose. For pain scores of 4 or greater, immediate- release orally-administered (PO) oxycodone shall be administered as a rescue medication. For pain scores of 4 to 7, 5 mg PO oxycodone shall be provided PRN; for pain score of 8 to 10 on the NRS, 10 mg PO oxycodone will be provided PRN.

If a subject is unable to tolerate PO medication or fails the PO oxycodone rescue, IV morphine (initiated at 1 to 2 mg) or hydromorphone (initiated at 0.3 to 0.5 mg) may be administered PRN.

Initial rescue medication can be IV per Investigator's discretion. Use of patient controlled analgesia pumps (PCA) is not recommended.

The investigative staff is responsible for recording all pain medications taken until the discharge; the subject will then be responsible for recording their medications in the eDiary from discharge through Day 14.

11.2. Administration Instructions/Procedures

Please refer to cohort-specific infiltration guide for technique.

11.2.1. EXPAREL Administration Considerations

Because of the potential risk of severe adverse effects associated with the administration of bupivacaine, the study sites must be equipped to manage subjects with any evidence of cardiac, neurological, or respiratory toxicity.

Subjects will not be permitted to receive any other local anesthetic for pre-, intra- (i.e., within 20 min before administering EXPAREL), or postoperative analgesia, other than the specified admixed bupivacaine for local infiltration at the surgical site per the infiltration guide. If administering lidocaine or other non-bupivacaine-based local anesthetics is required per the institution's SOC wait 20 min before administering EXPAREL.

EXPAREL may not be administered to a subject if the vial has been open for more than 4 hours. In order to prevent EXPAREL from settling, gently inverting and re inverting the syringe prior to administration is recommended.

11.3. Identity of the Investigational Products

11.3.1. Description of EXPAREL

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

11.3.2. Description of Reference Product

The reference therapy will be the institutional site's SOC for post-surgical analgesia.

11.3.3. Description of Diluents

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

11.4. Method of Assigning Subjects to Treatment

11.4.1. Two-step Subject Allocation

This study will not have a randomized design, but rather two-step subject allocation. Study subjects will be allocated in a 2:1 ratio to the EXPAREL or SOC group. This study will be done in 2 steps: step 1 – including 25 subjects managed by institutional SOC (Control group), and step 2 – including 50 subjects managed by multimodal regimen with local infiltration of EXPAREL and bupivacaine HCl into the surgical site (EXPAREL group).

11.4.2. Replacement of Subjects

Given that this study will have a case observation period for the first 1 to 3 subjects in EXPAREL group, the total number of subjects included in this group may further increase when accounting for the number of subjects that will be excluded from data analysis if the infiltration guide was not properly followed. Subjects enrolled to replace those excluded subjects from data analysis will be assigned unique subject numbers.

11.5. 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 100 mg. Clinical studies have shown that for wound infiltration a total dose of 266 mg (20 mL) of EXPAREL is safe and efficacious. Based on this experience, the FDA-approved marketed dose of 266 mg was deemed appropriate for this study.

11.6. Blinding

This will be an open-label study and neither subjects nor Investigators will be blinded for study group allocation.

11.7. Prior and Concomitant Therapy and Medications

Any medications for the condition for which the procedure is being performed administered within 30 days prior to screening will be recorded on the case report form (CRF), as well all medications though Day 14 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.

11.7.1. Prior Therapy and Medications

The following multimodal pain regimen will be used for all cohorts that receive EXPAREL:

Permitted Prior Medications and Therapy

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

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

- Tylenol (acetaminophen) 1000 mg PO; the total daily dose of acetaminophen is not to exceed 3000 mg. Intravenous acetaminophen can be used per investigator's discretion if the subject is unable to tolerate oral acetaminophen.
- Gabapentin 300 mg PO; alternative medication is pregabalin 150 mg PO
- Robaxin 750 mg PO

List of recommended pre-operative prophylactic medications (optional) for postoperative nausea and vomiting or pruritus:

For nausea and vomiting:

a) Ondansetron 4 mg intravenously (IV) at approximately 15-30 min before emergence from anesthesia
b) Decadron 8-12 mg IV after anesthesia induction
c) Phenergan 25 mg IV PRN
d) Metocopramide 10 mg PO PRN

For pruritus:

a) Diphenhydramine 25 mg PO PRN
b) Nalbuphine 2.5 mg IV PRN

Restricted Prior Medications and Therapy

Use of the medications listed below is restricted or prohibited within the specified time frames. Subjects will not be permitted to receive any other local anesthetic for pre-, intra-, or postoperative analgesia, other than admixed bupivacaine HCl for local infiltration at the surgical site.

Before screening

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

Within 3 days pre-op

- Long-acting opioid medication (e.g., morphine including MS Contin (morphine sulfate extended-release tablets), hydromorphone [Dilaudid], oxycodone [Oxycontin], methadone) daily for more than 3 months duration or within 3 days pre-op
- NSAIDs, aspirin (except for low-dose aspirin used for cardioprotection), or acetaminophen within 3 days pre-op.
- Dexmedetomidine HCl (Precedex) within 3 days post-op

Note: 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 (e.g., 4 Percocet) within 24 hours of surgery.

Within 1 month pre-op

Initiation of treatment with any of the following medications is prohibited within 1 month of study drug administration or if the medication(s) are being given to control pain:

- Selective serotonin reuptake inhibitors (SSRIs), serotonin and selective norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin (Lyrica), 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 (e.g., 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.

11.7.2. Permitted and Restricted Therapy and Medications During Surgery

Permitted Medications and Therapy

- Propofol for induction and/or intraoperatively
- Fentanyl or short-acting analogues
- Any medication for nausea/vomiting or pruritus prevention can be given at the physician's discretion.

Restricted Medications and Therapy

- As described in the EXPAREL package insert, no drugs are to be admixed with study drug other that bupivacaine HCl (e.g., epinephrine, dexamethasone, clonidine).
- When a topical antiseptic is applied to the surgical site, the solutions are not to come in contact with each other (e.g., the area must be dry before EXPAREL is administered).
- The use of long-acting opioids (e.g., morphine, hydromorphone HCl), acetaminophen/ paracetamol, ketorolac, or other NSAIDs will not be permitted intraoperatively except for emergency use to treat an AE.

- Avoid additional use of local anesthetics within 96 hours following administration of EXPAREL.

Upon discovering use of any prohibited therapy and/or medication during or after surgery, the Investigator should document all events that led to the deviation, write a note to file, and notify the Pacira Medical Monitor accordingly.

11.7.3. Permitted and Restricted Therapy or Medications After Surgery

Permitted Medications and Therapy

- Tylenol (acetaminophen) 1000 mg PO TID; the total daily dose of acetaminophen is not to exceed 3000 mg. Intravenous acetaminophen can be used if the subject is unable to tolerate oral acetaminophen.
- Gabapentin 300 mg PO BID; alternative medication is pregabalin 150 mg PO BID.
- Robaxin 750 mg BID or TID.

Postsurgical Pain Management

Subjects should receive opioid and non-opioid rescue pain medications only upon request for breakthrough pain.

Rescue medications shall be provided based on the pain scores reported on the NRS. For pain scores of 1 to 3, subjects shall receive nonsteroidal anti-inflammatory drugs (NSAIDs), without exceeding the maximum daily dose. For pain scores of 4 or greater, immediate- release orally-administered (PO) oxycodone shall be administered as a rescue medication. For pain scores of 4 to 7, 5 mg PO oxycodone shall be provided PRN; for pain score of 8 to 10 on the NRS, 10 mg PO oxycodone will be provided PRN.

If a subject is unable to tolerate PO medication or fails the PO oxycodone rescue, IV morphine (initiated at 1 to 2 mg) or hydromorphone (initiated at 0.3 to 0.5 mg) may be administered PRN. The initial rescue medication can be IV per Investigators' discretion.

Use of patient controlled analgesia pumps (PCA) is not recommended.

Restricted Medications and Therapy

- No other analgesics, including fentanyl, are permitted up to 72 hours after study drug administration or discharge from the hospital (or other facility).

- Anesthetics in the “caine” family, which may interfere with the bupivacaine pharmacokinetic profile, are prohibited through 96 hours following administration of EXPAREL .

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

11.8. Treatment Compliance

Study drug will be administered by the study staff and, thus, treatment compliance is ensured.

11.9. Accountability of Study Drug

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

12. STUDY ENDPOINTS AND MEASUREMENTS

12.1. Efficacy Assessments

The following efficacy measurements will be conducted:

1. Postsurgical opioid use in milligrams of oral morphine equivalent dosing (i.e., mg MED PO) from the end of surgery (closure of wound/incision) until 72 hours postsurgery. Although pre-operative and intra-operative opioids will be recorded for study subjects, they will not be included in the definition of this primary outcome.
2. Opioid related adverse events (ORAEs) will be assessed by using the Opioid Related Symptoms Distress Scale (OR-SDS) (see Appendix 3) at 24, 48, and 72 hours, discharge, and at 14 days.
3. BPI-sf will be administered at screening/baseline; at 24, 48, and 72 hours, discharge, and at 14 days (see Appendix 2).
4. NRS: The pain intensity score at surgical site will be assessed using an 11-point NRS during the hospital (or other facility) stay at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours, discharge, and then once at 14 days (see Appendix 1).

For all subjects, if discharge occurs prior to 72 hours postsurgery, all Discharge assessments are to be performed at the time of discharge. After discharge, all scheduled assessments should be performed at the scheduled time points (i.e., NRS pain assessments at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours postsurgery; BPI-sf and OR-SDS at 24, 48, and 72 hours; and date, time, and dose of all opioid and non-opioid rescue medications) and recorded in the eDiary.

Note: if the subject is sleeping, do not wake him or her for an assessment of pain. If he or she awakens within the assessment window (i.e., ±1 hour for all time points up to 24 h, ±2 hours for the 30 to 48 hour assessments, and ±4 hours for the 72-hour assessment), a pain score may be collected then.

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. End of surgery is defined as the time when the last incision/wound is closed.

Primary efficacy endpoint: The primary efficacy endpoint is postsurgical opioid consumption in mg MED PO from 0 hours (end of surgery) to 72 hours postsurgery.

Secondary endpoints:

1. Post-surgical opioid consumption in mg MED PO at 14 days after surgery
2. Time to first opioid rescue through 72 hours or discharge
3. Opioid related adverse events will be assessed by using the Opioid Related Symptoms Distress Scale (OR-SDS) at 24, 48, and 72 hours postsurgery, at discharge, and at 14 days.

Exploratory endpoints:

1. The NRS pain intensity score at surgical site at each assessed time point during the hospital (or other facility) stay (at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours), at discharge, and then once at 14 days (±3 days)
2. Brief Pain Inventory – short form (BPI-sf) at screening/baseline, daily for the first 3 days (24 hours, 48 hours, and 72 hours), at discharge, and at 14 days (±3 days).
3. OCC, SOPA and HADS at the baseline visit.

4. The area under the curve (AUC) of the NRS pain intensity scores at surgical site from 0 to 24, 0 to 48, and 0 to 72 hours

12.3. Pharmacokinetic Measurements (Not Applicable)

Not Applicable.

12.4. Pharmacokinetic Endpoints (Not Applicable)

Not Applicable.

12.5. Health Outcomes Assessments

- Time in hours spent in PACU and stepdown unit
- Total length of stay (i.e., recorded in hours) in the hospital (or other facility)
- Discharge readiness, measured via the Modified Post-Anesthesia Discharge Scoring System (MPADSS) at 24, 48 and 72 hours or discharge or until the subject attains a score of 9, whichever occurs first (see Appendix 7)
- Discharge disposition (i.e., home, outpatient rehabilitation facility, inpatient rehabilitation facility, skilled nursing facility, other)
- 30 days readmissions related to pain
- 30 days all cause readmissions
- 30 days Emergency Room (ER) visits related to pain
- 14 days office visits related to pain
- 14 days call to doctor related to pain
- 30 days "Are you currently taking opioid medication to manage pain from your spine surgery?"

12.6. Safety Assessments

Adverse events will be monitored and recorded from the time the ICF is signed through Day 30 or until termination from the study. Safety assessments will be measured at multiple time points throughout the study. Treatment-emergent AEs should be managed per the Investigator's discretion and the site's SOC.

12.7. Safety Endpoints

Any adverse events (AEs) reported while subjects are in the hospital (or other facility), at any time up to the Day 30 visit, or until termination from the study, will be assessed as safety outcomes.

12.8. 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 all study procedures is provided in Table 1 and Table 2.

13.1. Instructions for Conducting Procedures and Measures

Baseline is when the first assessments are done after informed consent is obtained, and is defined for statistical analyses purposes as the last non-missing assessment of a given endpoint prior to first dose of trial drug unless otherwise specified. 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 (prior to the study drug administration) will be timed from the end of surgery. Postsurgical is defined as a period after the end of surgery. End of surgery is defined as the time when the last incision/wound is closed.
Subjects can be discharged from the hospital (or other facility) 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 (or other facility) standards

The study will not require limitations with respect to hospitalization duration. Study staff will monitor and record postsurgical analgesia and will collect study data (other than subject assessments/questionnaires) through discharge. Following discharge, the subject will record use of pain medication, if any, in the eDiary. Additionally, the subject will record pain at surgical site using the NRS pain scale in the eDiary daily through 72 hours postoperation, at discharge, and at Day 14. The subject will record responses to the BPI-sf in the eDiary at 24, 48, and 72 hours, at discharge, and at Day 14.

13.1.1. eDiary

Subjects are to record their responses to subject questionnaires on an electronic device (an eDiary) at screening, while in the hospital (or other facility), and after discharge. Every day after discharge through Day 14, subjects are to record any pain medication (date, time, and dose) taken in the prior 24 hours in addition to recording questionnaire responses at the specified time points. Subjects can use their own device or be lent a device from the time of the screening visit.

13.1.2. Pain Intensity Assessments

Pain intensity scores at the surgical site will be assessed using an 11-point NRS at screening/baseline; at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours after surgery, at discharge, and at Day 14 (Carlsson 1983; McCormack 1988, and Scott 1976) (see Appendix 1). For all subjects, if discharge occurs prior to 72 hours postsurgery, all Discharge assessments are to be performed at the time of discharge. After discharge, all scheduled assessments should be performed at the scheduled time points (i.e., NRS pain assessments at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours postsurgery; BPI-sf and OR-SDS at 24, 48, and 72 hours; and date, time, and dose of all opioid and non-opioid rescue medications) and recorded in the eDiary.

13.1.3. Brief Pain Inventory-short form (BPI-sf)

The BPI-sf (See Appendix 2) will be completed at the screening/baseline visit; daily for the first 3 days (24, 48 and 72 hours), at discharge, and on Day 14 (Tan 2004). For all subjects, if discharge occurs prior to 72 hours postsurgery, all Discharge assessments are to be performed at the time of discharge. After discharge, all scheduled assessments should be performed at the scheduled time points (i.e., NRS pain assessments at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours postsurgery; BPI-sf and OR-SDS at 24, 48, and 72 hours; and date, time, and dose of all opioid and non-opioid rescue medications) and recorded in the eDiary.

13.1.4. Opioid Related Symptoms Distress Scale (OR-SDS)

Opioid related adverse events will be assessed by using the Opioid Related Symptoms Distress Scale (OR-SDS) (See Appendix 3) at 24, 48, and 72 hours after surgery, at discharge, and at 14 days (Apfelbaum 2004 and Yadeau 2011). For all subjects, if discharge occurs prior to 72 hours postsurgery, all Discharge assessments are to be performed at the time of discharge. After discharge, all scheduled assessments should be performed at the scheduled time points (i.e., NRS pain assessments at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours postsurgery; BPI-sf and OR-SDS at 24, 48, and 72 hours; and date, time, and dose of all opioid and non-opioid rescue medications) and recorded in the eDiary.

13.1.5. Hospital Anxiety and Depression Scale (HADS)

Hospital anxiety and depression will be assessed using Hospital Anxiety and Depression Scale (HADS) at the screening/baseline visit (Turk 2015) (See Appendix 4).

13.1.6. Survey of Pain Attitudes (SOPA)

Pain attitudes will be assessed using Survey of Pain Attitudes (SOPA) (See Appendix 5) at the screening/baseline visit (Jensen 2003).

13.1.7. 5-item Opioid Compliance Checklist (OCC)

5-item Opioid Compliance Checklist (See Appendix 6) will be assessed at the screening/ baseline visit (Jamison 2014; Jamison 2016).

13.1.8. Vital Signs

Height, weight, and body mass index (BMI) will be recorded at screening/baseline.

13.1.9. Clinical Laboratory Tests

Clinical laboratory evaluations are to be conducted as per SOC of the institution.

13.1.10.Discharge Readiness

The subject's discharge readiness will be assessed using the Modified Post-Anesthesia Discharge Scoring System criteria (MPADSS) (Chung 1995a; Chung 1995b) (see Appendix 7). The discharge readiness assessment will be used for data collection only and is not intended to interfere with the investigational site's policy for determining when the subject should be discharged from the hospital (or other facility). Discharge readiness will be assessed at 24, 48, and 72 hours or discharge or until the subject attains a score of 9, whichever occurs first.

13.2. Obtaining Informed Consent

Potential participants may provide informed consent up to 30 days before their scheduled surgery, and at least 1 day prior to surgery, in order to ensure ample time for the subject to review the ICF and have all his or her questions answered by the Investigator/study staff prior to providing informed consent. Screening procedures that are SOC at the institution may be completed prior to written informed consent. Any screening procedures that are not SOC must be completed after written informed consent is provided and prior to surgery. (See Section 13.3- Screening/Baseline Procedures)

13.3. Screening/Baseline Procedures

Subjects will be screened within 30 days prior to surgery. If a subject can only be screened on the day of surgery, the informed consent process must still be started at least 24 hours prior to the conduct of any screening procedures that are not considered SOC at the institution and such procedures may not be performed until written informed consent is provided. All screening procedures that are not SOC must be performed and documented within the 30-day time window (inclusive of the day of surgery for those subjects who can only be screened on the day of surgery) as described here. During the screening visit, subjects will be assessed for any past or present medical conditions that in the opinion of the investigator would preclude them from study participation.

The following screening/baseline procedures should be performed within 30 days prior to surgery:

- Explain study purpose and procedures
- Obtain written informed consent before performing any study-related procedures.
- Assess and confirm eligibility
- Record medical and surgical history
- Record any prior and concomitant medications (medication history) for the condition for which the procedure is being perform administered within 30 days prior to screening
- Record demographics and baseline characteristics
- Explain to the subject that he or she is to use an electronic diary (eDiary) into which he or she will be expected to capture specific information at screening and at specified time points after surgery, including recording pain medications every day from discharge through Day 14.
- Measure height, weight, and BMI
- Conduct urine pregnancy test for women of childbearing potential
- Record AEs starting when the ICF is signed
- Record concomitant medications for treatment of AEs
- 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.
- Record baseline NRS pain intensity score prior to any premedication (see Appendix 1).
- Record opioid use history (i.e., to calculate mean daily mg MED PO in the last 30 days)
- Complete Brief Pain Inventory-short form (BPI-sf) (Appendix 2)
- Complete Hospital Anxiety and Depression Scale (HADS) (Appendix 4)
- Complete Survey of Pain Attitudes (SOPA) (Appendix 5)
- Complete 5-item Opioid Compliance Checklist (OCC) (Appendix 6)

13.4. Preoperative procedures

Control Group

- Confirm eligibility; UPT does not need to be repeated
- Record AEs and medications used to treat them from the time ICF is signed

- Administer recommended pre-operative medications (within approximately 24 to 48 hours of procedure) in all 3 cohorts (cohort 1, cohort 2, and cohort 3):

  a) Tylenol (acetaminophen) 1000 mg PO
  b) Gabapentin 300 mg PO
  c) Robaxin 750 mg PO

Intra-operative anesthesia and analgesia at the surgical site as per usual care.

- List of recommended pre-operative prophylactic medications (optional) for postoperative nausea and vomiting or pruritus:

For nausea and vomiting:

a) Ondansetron 4 mg intravenously (IV) at approximately 15-30 min before emergence from anesthesia
b) Decadron 8-12 mg IV after anesthesia induction
c) Phenergan 25 mg IV PRN
d) Metocopramide 10 mg PO PRN

For pruritus:

a) Diphenhydramine 25 mg PO PRN
b) Nalbuphine 2.5 mg IV PRN

EXPAREL Group

- Confirm eligibility; UPT does not need to be repeated
- Record AEs and medications used to treat them from the time ICF is signed
- Administer the following strongly recommended study interventions for analgesia to subjects in all three cohorts (cohort 1, cohort 2 and cohort 3):

  - Pre-operative oral multimodal analgesia (within approximately 24-48 hours prior to surgery)

    a) Tylenol (acetaminophen) 1000 mg PO

    b) Gabapentin 300 mg PO

    c) Robaxin 750 mg PO

  - List of recommended pre-operative prophylactic medications (optional) for postoperative nausea and vomiting or pruritus:

    For nausea and vomiting:

    a) Ondansetron 4 mg intravenously (IV) at approximately 15-30 min before emergence from anesthesia
    b) Decadron 8-12 mg IV after anesthesia induction
    c) Phenergan 25 mg IV PRN
    d) Metocopramide 10 mg PO PRN

    For pruritus:

    a) Diphenhydramine 25 mg PO PRN
    b) Nalbuphine 2.5 mg IV PRN

13.5. Intra-operative Procedures:

Note: Subjects will not be permitted to receive any other local anesthetic for pre-, intra- (i.e., within 20 min before administering EXPAREL), or postoperative analgesia, other than the specified admixed bupivacaine for local infiltration at the surgical site per infiltration guide. If administering lidocaine or other non-bupivacaine-based local anesthetics is required per the institution's SOC wait 20 min before administering EXPAREL.

- Prepare study drug (no earlier than 4 hours before administration)
- Record surgery start and stop times
- Administer study drug; Record start and stop times of study drug administration
- Record dosage of study drug administered and total volume
- Record all intraoperative medications
- Record times and doses of all opioid and non-opioid rescue medications administered
- Record AEs and any treatment(s) for the events

If an AE or SAE occurs during the study, the event should be managed per the Investigator's discretion and the site's SOC.

13.6. Postoperative Procedures Through Discharge from the Hospital (or Other Facility)

For all subjects, if discharge occurs prior to 72 hours postsurgery, all Discharge assessments are to be performed at the time of discharge. After discharge, all scheduled assessments should be performed at the scheduled time points (i.e., NRS pain assessments at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours postsurgery; BPI-sf and OR-SDS at 24, 48, and 72 hours; and date, time, and dose of all opioid and non-opioid rescue medications) and recorded in the eDiary.

Control Group:

- Administer the following scheduled multimodal analgesia within approximately 72 hours postsurgery):
    a) Tylenol (acetaminophen) 1000 mg PO TID; the total daily dose of acetaminophen is not to exceed 3000 mg. Intravenous (IV) acetaminophen can be used if the subject is unable to tolerate oral acetaminophen.
    b) Gabapentin 300 mg PO BID; alternative medication is pregabalin 150 mg PO BID Robaxin 750 mg PO BID or TID

- Administer additional postsurgical pain medication (e.g., opioids) in cases of insufficient analgesia as permitted per your institution's SOC.
- Record times and doses of all multimodal scheduled medication administered

EXPAREL Group

- Administer the following postoperative scheduled multimodal analgesia (within approximately 72 hours postsurgery):

    a) Tylenol (acetaminophen) 1000 mg PO TID; the total daily dose of acetaminophen is not to exceed 3000 mg. Intravenous (IV) acetaminophen can be used if the subject is unable to tolerate oral acetaminophen.

    b) Gabapentin 300 mg PO BID; alternative medication is pregabalin 150 mg PO BID

    c) Robaxin 750 mg PO BID or TID

- Record times and doses of all multimodal scheduled medication administered
- Administer rescue postsurgical analgesics

Both Treatment Groups

- Record dates, times, and doses of all opioid and non-opioid rescue medications administered
- Record all pain medications taken until discharge
- Complete OR-SDS questionnaire at 24, 48 and 72 hours after the surgery, and at discharge
- Record NRS pain intensity score upon arrival at the PACU; at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours; at discharge; 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. If he or she awakens within the assessment window (i.e., 1 hour for all time points up to 24 hours, 2 hours for the 30 to 48 hour assessments, and 4 hours for the 72-hour assessment), a pain score may be collected then.
- Complete BPI-sf at 24, 48, and 72 hours after the surgery and at discharge
- Administer postoperative rescue medication only upon request, as needed (see Section 11.1- Treatment to be Administered)
- Record other concomitant medications

- Record time of admission to and discharge from the PACU
- Record time of admission to and discharge from the step-down unit
- Complete MPADSS at 24, 48 and 72 hours after the surgery or discharge or until the subject attains a score of 9, whichever occurs first
- Record date and time of discharge
- Record discharge disposition (home, outpatient rehabilitation facility, inpatient rehabilitation facility, and skilled nursing facility)
- Instruct the subject about use of the eDiary to record daily opioid pain management medication use, pain scores, and BPI-sf responses. If the subject is being provided an eDiary, remind the subject that the completed eDiary should be returned to the clinic at the end of their participation in the study.
- Record AEs or SAEs and any treatment(s) for the events
- If an AE and/or SAE occurs during the study, the event should be managed per the Investigator's discretion and the site's SOC.

13.7. After Discharge from the Hospital (or Other Facility)

- Subject is to record the use of pain medication, if any, in the eDiary daily from discharge through Day 14
- Assessments to be completed on Day 14 are presented in Section 13.8
- Assessments to be completed on Day 30 are presented in Section 13.9

13.8. Day 14 Phone Call or Visit

- Record pain at surgical site using NRS (Appendix 1)
- Complete BPI-sf (see Appendix 2)
- Complete OR-SDS (see Appendix 3)
- Review and record date and amount of all opioid pain management medication used up to Day 14. (Note: upon discharge, the patient will continue to record daily opioid pain management medication use in the eDiary)
- Document any requests for refills for opioid medication
- Document whether the subject has made any unscheduled phone calls or office visits related to pain
- Record any AEs or SAEs and any treatment(s) for the events
- Collect the eDiary (if the subject was lent an eDiary for the course of the study)

If an AE or SAE occurs during the study, the event should be managed per the Investigator's discretion and the site's SOC.

13.9. Day 30 Phone Call

- Record persistent opioid use by asking the subject "Are you currently taking opioid medication to manage pain from your spine surgery?" (see Appendix 8)
- Document if the subject has had any hospital readmissions for pain
- Document if the subject has had any hospital readmisions for any cause
- Document whether the subject has made any unscheduled visits to the ER related to pain since discharge
- Record any AEs and medications used to treat AEs

If an AE or SAE occurs during the study, the event should be managed per the Investigator's discretion and the site's SOC.

14. ADVERSE EVENT REPORTING

Consistent with the current regulatory guidance provided by the US CFR and the ICH GCP, AE and SAE are defined in Section 14.1.1 and Section 14.2.1, respectively.

The concepts of AE and SAE 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 primarily used 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 an 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 (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (e.g., off-label use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

An AE can be any unfavorable and unintended change in a body structure or body function. Adverse events include any clinically significant deterioration of a subject's medical status. The AE may involve any organ or system and can be represented by the new onset or the deterioration of a disease, a syndrome, a symptom, a physical sign, as well as by findings and results of instrumental examinations and laboratory tests. Any medically relevant and untoward change after the subject

signs the ICF, including frequency or pattern changes for a fluctuating condition (e.g., migraine) is considered an AE.

An AE that occurs after the ICF has been signed and before the start of the study drug administration is identified as a pretreatment AE (PTAE). An AE that occurs after the first administration of a study treatment is considered a treatment emergent adverse event (TEAE). All AEs must be recorded and reported accordingly, whether they appear causally related to the study drug, or not. Adverse events will be followed until the outcome is known or until the Investigator feels no further medical follow-up is warranted.

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 with an onset after the subject signs the ICF (i.e., PTAEs and TEAEs). For the purpose of this study, all AEs that occur through Day 30 after study drug administration must be recorded regardless of whether or not they are considered related to the study drug. Whenever feasible, AEs should be documented as medical diagnoses (highest possible level of integration). Otherwise, when they do not appear clearly interrelated, individual signs or symptoms may be reported as separate AEs. Record one AE per line in the CRF; for example, the AE of nausea and vomiting should be listed as two separate events: the event of nausea and the event of vomiting. Whenever possible, abnormal laboratory results should be reported as their clinical corollary (e.g., low potassium should be recorded as hypokalemia).

All AEs will be followed through progression and regression of their severity. For example, if an AE is reported as mild in severity but changes to moderate, the AE of mild will have an outcome of changed AE characteristic and the AE will be re-entered. The AE with a moderate severity must have the same start date as the mild event stop date. If the AE then becomes mild, the AE with a moderate severity will have an outcome of changed AE characteristic and the AE will be re-entered with a severity of mild; the start date of the mild AE must be the same as the stop date of the moderate AE.

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

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

Information recorded on the appropriate AE CRF will include AE term, the date and time of onset, severity, seriousness, relationship to the study drug, action taken with study drug, action taken for the 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 must assess the relationship of the AE to study drug after careful medical consideration on a case-by-case basis. General guidelines for determining the AE’s causality to the study drug are provided below.

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

Unlikely: A clinical event with a temporal relationship to study drug administration which makes a causal relationship improbable and in which other drugs, chemicals, or underlying disease provide a plausible explanation;

Possible: A clinical event with a reasonable time sequence to administration of the study drug but which could also be explained by a concurrent disease or other drugs or chemicals;

Probable: A clinical event with a reasonable time sequence to administration of the study drug unlikely to be attributed to a concurrent disease or other drugs or chemicals and which follows a clinically reasonable response on withdrawal (dechallenge); or

Definite: The pharmacological properties of the study drug(s) or of the substance class, and the course of the AE after dechallenge and, if applicable, after rechallenge, and/or specific test indicate involvement of the study drug(s) in the occurrence/worsening of the AE, and no indication of other causes exists.

14.1.5. Outcome of Adverse Events

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

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

14.1.6. Action Taken with Subject due to an Adverse Event

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

- None.
- Medication.
- Non-pharmaceutical therapy. (The specific therapy used must be recorded in the CRF.)
- Discontinued from study.

- Other. (The specific action taken must be recorded in the CRF.)

14.2. Serious Adverse Events

14.2.1. Definition of a Serious Adverse Event

Definition of a Serious Adverse Event (SAE): An AE 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 (i.e., 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 by either email (drugsafety@pacira.com) or fax to 858-678-3962 within 24 hours of discovery. 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 patient-identifying information redacted prior to forwarding to Pacira. In the event of a fatal or life-threatening SAE, any required follow-up must be provided to Pacira Drug Safety or designee immediately. The Investigator will follow all SAEs until resolved or the condition stabilizes and further follow-up is not warranted.

If the Investigator is made aware of any SAEs after 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.

Interim analyses may be conducted to adjust to variability. Adaptive study design (i.e., adjustments of sample size, cohort sequence, type of surgical procedure, endpoints, etc.) will be used.

15.1. Study Objective

The primary objective of this study is to compare postsurgical opioid consumption through 72 hours postsurgery in patients receiving local infiltration analgesia (LIA) with EXPAREL and bupivacaine HCl (EXPAREL group) with those receiving SOC (Control group) in adult subjects undergoing posterior lumbar spine surgeries where both groups are receiving a multimodal pain regimen.

15.2. Study Endpoints

The endpoints to be assessed in this study are listed in Section 12.2, Efficacy Endpoints and Section 12.7, Safety Endpoints.

15.3. Determination of Sample Size

The sample size for this study is based on the primary outcome measure of postsurgical opioid use in milligrams of oral morphine equivalent dosing (mg MED PO) from the end of surgery (closure of wound/incision) until 72 hours postsurgery. Based on preliminary data, the coefficient of variation (CV) is approximately 60%. The minimum clinically important difference (MCID) for this outcome was estimated at 40%.

With these parameters and a beta of 0.2 (i.e., 80% power), an alpha of 0.05, a 2-sided test, and allocating subjects in a 2:1 ratio to the EXPAREL group or Control group to minimize barriers to enrolment for an approved and marketed medication, a total sample size of 75 fully evaluable subjects is required in each study cohort, with 50 in the EXPAREL group and 25 in the Control group. The same assumptions are made across all cohorts. Not fully evaluable subjects should be replaced. Criteria for fully evaluable will be defined in SAP. Given that this study will have a case observation period for the first few subjects in EXPAREL group, if observation is deemed correct and infiltration was performed correctly, subject can be included in the study. If observation is deemed incorrect and infiltration was performed incorrectly, subject will continue in the study but will be removed from statistical analysis and will be replaced to ensure at least 50 evaluable EXPAREL arm patients are enrolled per cohort. The total number of subjects in all three cohorts will be 225, with 150 in the EXPAREL group and 75 in the Control group.

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 allocated subjects who undergo the planned surgery. All analyses based on the efficacy analysis set will be by treatment groups.

The per-protocol efficacy analysis set will include all subjects in the efficacy analysis set who do not have any important protocol deviations.

15.5. Handling Subject Dropouts and Discontinuations

Given that this study will have a case observation period for the first few subjects in EXPAREL group, the total number of subjects included in this group may further increase for the number of subjects that will be excluded from data analysis if the infiltration guide was not properly followed.

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

15.6. Statistical Analyses

15.6.1. Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group.

15.6.2. Study Compliance

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

15.6.3. Efficacy Analyses

A comprehensive statistical analysis plan (SAP) will be developed for this study. All efficacy endpoint analyses will be conducted for the efficacy analysis set. The primary efficacy endpoint will also be analyzed using the per-protocol analysis set as a sensitivity analysis.

Summary statistics (n, mean, median, standard deviation, minimum, maximum) will be shown for each continuous measure of efficacy by treatment group. Number and percentage of subjects in each category will be shown for each categorical measure of efficacy by treatment group. For time to event measures of efficacy, medians and Kaplan-Meier estimates will be shown by treatment group.

15.6.4. Safety Analyses

Adverse event verbatim terms will be mapped to preferred terms and related system/organ class using the Medical Dictionary for Regulatory Activities (MedDRA). All summaries of AEs will

include AEs that occur after the beginning of anesthesia. All summaries of AEs will be based on the safety analysis set. Events that start prior to anesthesia will be identified in listings only. Incidence rates of AEs after the start of anesthesia and the proportion of subjects prematurely withdrawn from the study due to an AE will be shown for each treatment group. Incidence rates will also be shown for each treatment group for study drug-related AEs after the start of anesthesia and by severity. Incidence rates of SAEs will also be shown for each treatment group. All incidence rates will be categorized and shown 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.

15.8. Interim Analyses

Interim analyses may be conducted to adjust to variability. Adaptive study design (i.e., adjustment of sample size, cohort sequence, type of surgical procedure, endpoints, etc.) will be used.

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INVESTIGATOR AGREEMENT

Printed Name of Investigator: _____

Printed Title/Position: _____

Printed Institution Address: _____

_____

_____

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

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

_____ _____

Signature of Investigator Date

17. APPENDICES

17.1. Appendix 1: Subject's Reported Pain (Numeric Rating Scale) at Surgical Site

Subjects will be evaluated for pain intensity scores at rest using the 11-point NRS at rest at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours after surgery, at discharge, and then once at 14 days (±3 days). If the subject is sleeping, do not wake him or her for an assessment of pain. If he or she awakens within the assessment window (i.e., ±1 hour for all time points up through 24 h, ±2 hours for the 30- to 48-h assessments, and ±4 hours for the 72-hour assessment), a pain score may be collected then.

The subject will either download the application onto their own device or an eDiary will be lent to the subject following surgery, which will have to be returned on the Day 14 visit. The subject will record pain at surgical site using the NRS pain scale in the eDiary through 72 hours postoperation.

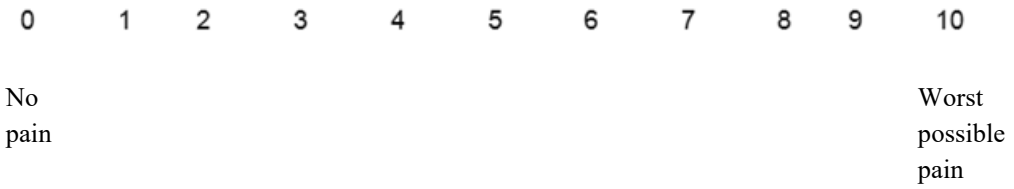
To assess pain intensity (NRS) at rest, the subject should rest quietly in a supine or seated position that does not exacerbate his or her postsurgical pain for 3-5 minutes before entering the pain score.

Subjects are to assess, "How much pain are you experiencing at surgical site right now?" ("surgical site" meaning location on the body where the surgery was performed). They are advised to circle a number on the NRS to indicate the level of pain experienced at the time of assessment, with a number closer to zero (0) meaning little or no pain and a number closer to 10 meaning much pain or pain as bad as it can be.

Subject's Reported Pain NRS

Pain Intensity Scale

On a scale of 0 to 10, where 0 = no pain and 10 = worst possible pain, circle the number that best describes how much pain you are experiencing at the surgical site right now. (Circle one number only)



(**For reference only; not for clinical use**.)

17.2. Appendix 2: Brief Pain Inventory - Short Form (BPI-sf)

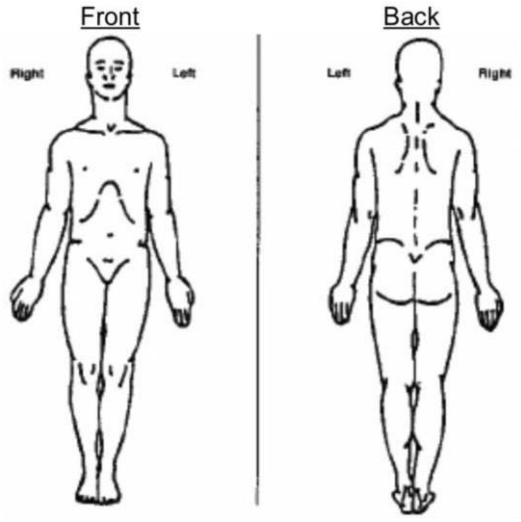
The BPI-sf will be completed at screening/baseline; daily for the first 3 days (24 hours, 48 hours, 72 hours), at discharge; and at Day 14 (± 3 days).

Part A

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

   ☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



Part B

Describe the quality of your pain (0 to 10, where: 0 = no pain and 10 = pain as bad as you can imagine).

3. Please rate your pain by marking the box beside the number that best describes your pain at its **worst** in the last 24 hours.

   ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

   No Pain — Pain As Bad As You can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its **least** in the last 24 hours.

   ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

   No Pain — Pain As Bad As You can Imagine

5. Please rate your pain by marking the box beside the number that best describes you pain on the **average**.

   ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain Pain As Bad As You can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have **right now**.

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain Pain As Bad As You can Imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much **relief** you have received.

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

No relief Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

General Activity

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Does Not Interfere Completely Interferes

Mood

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Does Not Interfere Completely Interferes

Walking ability

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Does Not Interfere Completely Interferes

Normal Work (includes both work outside the home and housework)

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Does Not Interfere Completely Interferes

Relations with other people

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Does Not Interfere Completely Interferes

Sleep

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Does Not Interfere — Completely Interferes

Enjoyment of life

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

Does Not Interfere — Completely Interferes

17.3. Appendix 3: The Opioid Related Symptom Distress Scale (OR-SDS)

Opioid related adverse events will be assessed by using the Opioid Related Symptoms Distress Scale (OR-SDS) at 24 hour postsurgery (postoperative Day [POD] 1), 48 hours postsurgery (POD 2), 72 hours postsurgery (POD 3), at discharge, and at 14 days (± 3 days).

We have listed 10 symptoms below. Read each one carefully. If you have had the symptom during the past 24 hours, let us know how OFTEN you had it, how SEVERE it was usually and how much it DISTRESSED OR BOTHERED you by placing an "X" in the appropriate box. If you DID NOT HAVE the symptoms, please place an "X" in the box marked "Did not have." For the symptoms "retching/vomiting" below, you will indicate the actual **number** of episodes you experienced. During the last 24 hours, did you have any of the following:

Symptoms	Did not have	(If yes), how often did you have it?				(If yes), how severe was it usually?				(If yes), how much did it distress or bother you?				
		Rarely	Occasionally	Frequently	Almost Constantly	Slight	Moderate	Severe	Very Severe	Not at all	A little Bit	Somewhat	Quite a Bit	Very Much
Fatigue	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Drowsiness	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Inability to concentrate	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Nausea	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Dizziness	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Constipation	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Itching	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Difficulty with urination	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Confusion	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Retching/vomiting	☐	_ _ # of episodes				☐	☐	☐	☐	☐	☐	☐	☐	☐

17.4. Appendix 4: Hospital Anxiety and Depression Scale (HADS)

Hospital anxiety and depression will be assessed using Hospital Anxiety and Depression Scale (HADS) at the baseline visit.

Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in my stomach**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Not quite so much now	2		I don't take as much care as I should
	1	Definitely not so much now	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much		2	Quite a lot

D	A		D	A	
		now			
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind			**I look forward with enjoyment of things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not often	2		Not often
	3	Not at all	3		Very seldom

17.5. Appendix 5: Single-item Survey of Pain Attitudes (SOPA)

Pain attitudes will be assessed using Survey of Pain Attitudes (SOPA) at the baseline visit.

Instructions: Please indicate how much you agree with each of the following statements about your pain problem by using the following scale:

0 = This is very untrue for me.

1 = This is somewhat untrue for me.

2 = This is neither true nor untrue for me (or it does not apply to me).

3 = This is somewhat true for me.

4 = This is very true for me.

1. There is little I can do to ease my pain.....0 1 2 3 4
2. My pain does not stop me from leading a physically active life.....0 1 2 3 4
3. The pain I feel is a sign that damage is being done.....0 1 2 3 4
4. There is a connection between my emotions and my pain level.....0 1 2 3 4
5. I will probably always have to take pain medications.....0 1 2 3 4
6. When I am hurting, I deserve to be treated with care and concern.....0 1 2 3 4
7. I trust that doctors can cure my pain.....0 1 2 3 4

17.6. Appendix 6: 5-item Opioid Compliance Checklist

5-item Opioid Compliance Checklist (OCC) will be assessed at the baseline visit.

Over the past month have you:

1. Lost or misplaced your opioid medications? ☐ Yes ☐ No
2. Run out of your pain medication early? ☐ Yes ☐ No
3. Missed any scheduled medical appointments? ☐ Yes ☐ No
4. Used any illegal or unauthorized substances? ☐ Yes ☐ No
5. Been completely honest about your personal drug use? ☐ Yes ☐ No

17.7. Appendix 7: Modified Post-Anaesthetic Discharge Scoring System (MPADSS)

The subject's discharge readiness will be assessed using the Modified Post Anesthesia Discharge Scoring System below (Chung 1995a; Chung 1995b).

The discharge readiness assessment will be used for data collection only and is not intended to interfere with the investigational site's policy for determining when the subject should be discharged from the hospital (or other facility).

Discharge readiness will be assessed at 24, 48, and 72 hours or at discharge, or until the subject attains a score of 9, whichever occurs first. Once a score of 9 is reached, no further discharge readiness assessments are required.

Modified Post Anesthesia Discharge Scoring System

Parameter	Score
Vital Signs: measure systolic blood pressure, heart rate, respiratory rate, temperature	
• All 4 vital signs are within 20% of the preoperative values	2
• Any of the 4 vital signs are within 20%-40% of the preoperative values and none exceeds 40% of the preoperative value	1
• Any of the 4 vital signs are >40% of the preoperative values	0
Ambulation	
• Steady gait/no dizziness	2
• With assistance	1
• None/dizziness	0
Nausea and Vomiting	
• Minimal: no nausea/vomiting or nausea not requiring treatment	2
• Moderate: nausea without vomiting and can tolerate liquids	1
• Severe: nausea/vomiting and unable to tolerate oral liquids	0
Pain	
• Minimal: requiring one or less pain rescue in the prior 12 hours	2
• Moderate: requiring more than one pain rescue in the prior 12 hours	1
• Severe: requiring supplemental IV analgesia for pain rescue	0
Surgical Bleeding	
• Minimal: no action required	2
• Moderate: requires dressing change because it has soaked through or a compressive dressing	1
• Severe: requires a suture or a return to the operating room	0

17.8. Appendix 8: Persistent Opioid Use

To be collected at Day 30 as part of the Day 30 phone call. The subject will be asked the following question:

1. Are you currently taking opioid medications to manage pain from your spine surgery?
    a. Yes
    b. No