Pacira Pharmaceuticals, Inc.

DISCLOSURE: REDACTED CLINICAL STUDY PROTOCOL AMENDMENT 1

Title: A Phase 3, Randomized, Double-Blind, Multicenter, Active-Controlled Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of EXPAREL Admixed with Bupivacaine HCl vs. Bupivacaine HCl Administered via Adductor Canal Block for Postsurgical Analgesia in Subjects Undergoing Primary Unilateral Total Knee Arthroplasty
NCT Number: NCT05139030
Protocol Number: 402-C-335

Clinical Study Protocol Amendment 1, Approval Date: 22-Oct-2021

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Pacira Pharmaceuticals, Inc. or partners, personal information, or to otherwise protect the integrity of the clinical study.

Clinical Study Protocol

Amendment 1

A Phase 3, Randomized, Double-Blind, Multicenter, Active-Controlled Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of EXPAREL Admixed with Bupivacaine HCl vs. Bupivacaine HCl Administered via Adductor Canal Block for Postsurgical Analgesia in Subjects Undergoing Primary Unilateral Total Knee Arthroplasty

Protocol No.:	402-C-335
EudraCT No.:	Not applicable
IND No.:	**069,198**
Study Phase:	Phase 3
Study Drug:	EXPAREL® (bupivacaine liposome injectable suspension)
Original Protocol Date:	23-Sep-2021
Amendment 1 Date:	22-Oct-2021
Study Sites:	Multicenter study in the United States
Sponsor:	Pacira Pharmaceuticals, Inc. 5 Sylvan Way Parsippany, New Jersey 07054 USA Telephone: CCI

1. SIGNATURE PAGE

CCI [redacted] Date

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2. SYNOPSIS

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

Title of Study: A Phase 3, Randomized, Double-Blind, Multicenter, Active-Controlled Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of EXPAREL Admixed with Bupivacaine HCl vs. Bupivacaine HCl Administered via Adductor Canal Block for Postsurgical Analgesia in Subjects Undergoing Primary Unilateral Total Knee Arthroplasty

Principal Investigators: To be determined

Study Centers: Multicenter study in the United States (US)

Publications (Reference): None

Date First Subject Enrolled: To be determined	**Phase of Development:** 3

Objectives:

Primary Objective:

The primary objective is to compare the magnitude of the postsurgical analgesic effect following a single dose of EXPAREL admixed with bupivacaine hydrochloride (HCl) vs. bupivacaine HCl when administered via an adductor canal block in subjects undergoing primary unilateral total knee arthroplasty (TKA)

Secondary Objectives:

The secondary objectives are to:

1. Compare the total postsurgical opioid consumption (in oral morphine equivalents) following a single dose of EXPAREL admixed with bupivacaine HCl vs. bupivacaine HCl
2. Compare the time to first opioid consumption post-surgery, following a single dose of EXPAREL admixed with bupivacaine HCl vs. bupivacaine HCl
3. Characterize and compare the magnitude of the duration of sensory and motor block following a single dose of EXPAREL admixed with bupivacaine HCl and bupivacaine HCl
4. Assess the safety, and pharmacokinetic (PK) profile of EXPAREL admixed with bupivacaine HCl and bupivacaine HCl

Methodology:

This is a Phase 3, multicenter, randomized, double-blind, active-controlled study in approximately 160 subjects undergoing primary unilateral TKA under spinal anesthesia. The study will have 2 cohorts. Both cohorts will enroll in parallel.

Cohort 1 (PK, PD, Efficacy, and Safety):

Cohort 1 will enroll approximately 40 subjects (20 subjects per treatment arm) undergoing primary unilateral TKA under spinal anesthesia to obtain information on PK profile, pharmacodynamics (PD), efficacy, and safety. Subjects will be randomized (1:1) to receive an adductor canal block with a single dose of either

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EXPAREL 10 mL (133 mg) admixed with 10 mL 0.5% bupivacaine HCl (50 mg) or 10 mL 0.5% bupivacaine HCl (50 mg) mixed with 10 mL normal saline. The total dose volume will be consistent (20 mL) for all subjects.

Cohort 2 (Efficacy and Safety):

Cohort 2 will enroll approximately 120 subjects (60 subjects per treatment arm) undergoing primary unilateral TKA under spinal anesthesia to obtain information on efficacy and safety. Subjects in this cohort will be randomized (1:1) to receive an adductor canal block with a single dose of either EXPAREL 10 mL (133 mg) admixed with 10 mL 0.5% bupivacaine HCl (50 mg) or 10 mL 0.5% bupivacaine HCl (50 mg) mixed with 10 mL normal saline. The total dose volume will be consistent (20 mL) for all subjects.

An adaptive study design will be used in this study. An interim analysis to evaluate the sample size assumptions and evaluate futility will occur when a total of approximately 80 subjects (40 in each arm) combined from either Cohort 1 or Cohort 2 have enrolled and provided complete assessment data for the primary efficacy outcome.

Obtaining Informed Consent

Potential subjects undergoing primary unilateral TKA under spinal anesthesia will be approached by the Investigator and/or the study staff for informed consent up to 45 days before the surgery. Subjects may be consented on the day of the surgery, if the consent process is started early with ample time for the subject to review the informed consent form (ICF) and have all questions answered by the Investigator/study staff prior to providing informed consent.

Screening

Subjects may be screened up to 45 days prior to day of surgery but eligibility must be re-confirmed on the day of surgery prior to randomization. Screening procedures that are standard of care at the institution may be completed prior to written informed consent and documented within the 45-day time window.

The following screening procedures will be performed after the ICF is signed (if not standard of care): assess eligibility, record medical/surgical history, record prior and concomitant medications (related to medical history), record demographics and baseline characteristics, record subject height and weight for body mass index (BMI) calculation, assess chronic opioid use in the past 30 days (average ≥30 oral morphine equivalents/day), conduct urine pregnancy test for women of childbearing potential, perform 12-lead EKG, record serious adverse events (SAEs) starting when the ICF is signed and record medications for treatment of SAEs.

Day of Surgery

On the day of surgery, before administration of the block, study staff will review the Pain Rating Guide with the subject and then record the subject's responses to the following pain assessments:

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- Pain intensity scores (using the numeric rating scale; NRS) measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, what was the **worst** pain in your operative knee in the last 30 days?"
- Pain intensity scores (using the NRS) measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, what was the **average** pain in your operative knee in the last 30 days?"

In addition, the following procedures will be conducted: conduct urine drug screen, conduct urine pregnancy test for women of childbearing potential, measure and record vital signs (temperature, resting heart rate, respiratory rate, oxygen saturation and blood pressure) in supine position, record changes to concomitant medications since screening, confirm eligibility and randomize subject, and record AEs/ SAEs and any treatment(s) for the events.

For Cohort 1 only, the following additional procedures will be conducted: obtain PK samples and conduct sensory/ motor function assessments. Sensory and motor function assessments will be conducted by trained blinded study staff.

Treatment Arms:

On the day of surgery, subjects will receive ultrasound-guided adductor canal block with one of the following treatments:

1. **EXPAREL admix arm:** subjects randomized to this treatment arm will receive 10 mL (133 mg) EXPAREL admixed with 10 mL (50 mg) 0.5% bupivacaine HCl
2. **Bupivacaine HCl arm:** subjects randomized to this treatment arm will receive 10 mL (50 mg) 0.5% bupivacaine HCl mixed with 10 mL normal saline

Block Procedure:

Subjects may be lightly sedated with 1 to 2 mg of midazolam intravenously (IV) before the nerve block procedure. The study drug (EXPAREL admixed with bupivacaine HCl or bupivacaine HCl) will be administered under ultrasound guidance 90 min (±30 min) prior to surgery. A peripheral nerve stimulator will be used to confirm nerves in the adductor canal before study drug administration. A confirmatory ultrasound video will be captured during the nerve block procedure (during hydrodissection by saline injection and study drug administration), with needle in place to ensure accurate block placement. The Investigator will provide the video to the sponsor within 24 hours from the end of block procedure that will be reviewed by an independent ultrasound adjudication committee to ensure accuracy of study drug administration. Only two unblinded study drug administrators (anesthesiologist) will be assigned per site to perform the block procedures unless approved in advance in writing by the Sponsor on a case-by-case basis. The designated study drug administrators (anesthesiologist) will not participate in any other study related assessments after randomization.

For all study arms, the total volume of 20 mL will be administered as the adductor canal block.

Pre-Operative Medication

All eligible subjects will also receive the following medication within 4 hours prior to surgery:

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- Celecoxib 200 mg, orally (PO).

No gabapentinoids are allowed for pain control, per protocol.

All subjects in both Cohort 1 and Cohort 2 will receive an infiltration between the popliteal artery and capsule of the knee (IPACK) under ultrasound guidance with 15 mL of 0.25% bupivacaine HCl (37.5 mg) immediately following study drug administration (should be done with the same set-up for the nerve block).

Anesthesia and Intraoperative Medication:

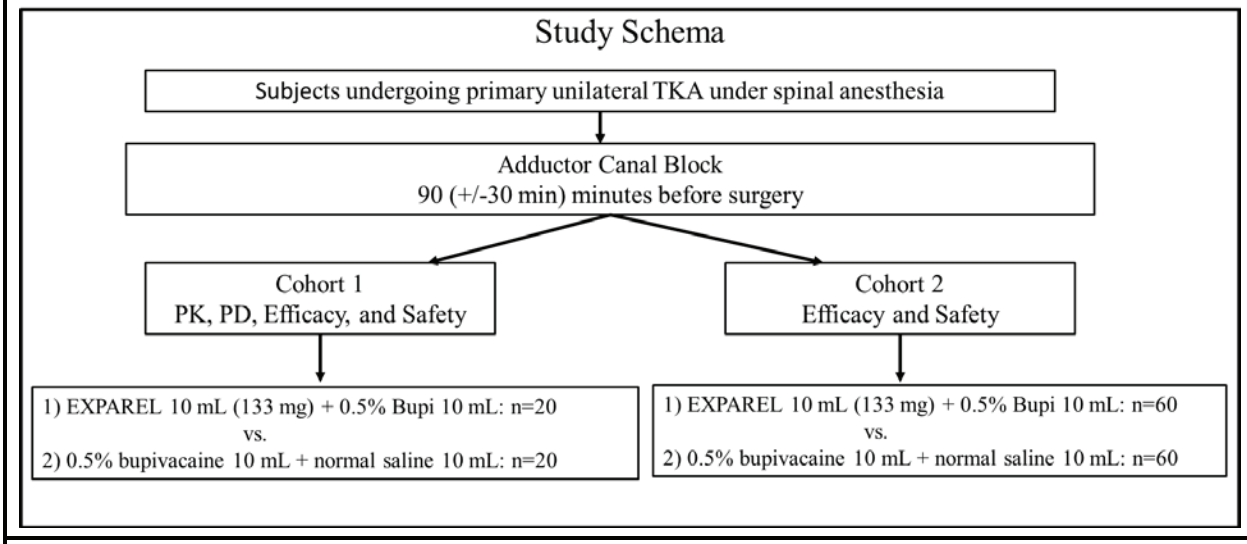
All subjects will receive spinal anesthesia immediately prior to surgery with 0.5% bupivacaine HCl (up to 15 mg). No other medication (including opioids) should be mixed with the bupivacaine for spinal anesthesia. If the spinal fails or cannot be completed, the subject may receive total intravenous anesthesia (TIVA).

No dexamethasone, NSAIDs, or ketamine will be permitted.

All subjects will receive a dose of 1000 mg of intravenous (IV) acetaminophen at the time of surgical incision. Intravenous (IV) Fentanyl will be allowed for intraoperative pain control (Fentanyl dose not to exceed 1 ug/kg unless deemed medically necessary).

Further details on permitted/restricted perioperative medications are included in protocol Sections 11.6.1 and 11.6.2.

Study Schema:



Postsurgical Pain Management:

All opioid and other analgesics (pain medications) administered post-surgery through hospital discharge will be recorded.

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All subjects will receive one post-operative dose of 1000 mg IV acetaminophen, administered approximately 8 hours after the first dose (approximately 8 hours after incision). The maximum total dose will not exceed 2000 mg. No additional acetaminophen is permitted after the second IV acetaminophen dose.

Oxycodone will be administered on an as needed (PRN) basis for breakthrough pain through 96 hours post-surgery; opioids should not be given on a pre-determined schedule. Immediate release oral (PO) oxycodone will be administered in a stepwise approach:

- Initial dose of 5 mg oxycodone may be offered.
- If the initial opioid dose is insufficient for pain relief, an additional 5 mg oxycodone may be offered up to a maximum of 10 mg (total dose).
- If a subject is unable to tolerate PO medication (or the PO oxycodone pain relief is insufficient), IV morphine (initiated at 2 mg) or hydromorphone (initiated at 0.2 mg) may be administered.

No NSAIDs or other opioids including Tramadol are allowed for the breakthrough pain management. No Acetaminophen (other than the scheduled IV acetaminophen) should be used for breakthrough pain.

For study purposes, it is important to standardize pain management modalities during the first 96 hours post-surgery. Therefore, the study staff must adhere closely to the treatment options and requirements noted in the protocol. After 96 hours, the analgesic regimen may be adjusted for each subject individually as deemed appropriate by the physician responsible for the postsurgical care.

Postsurgical Assessments:

The post-surgical assessments are as follows: record pain intensity scores using the Numerical Rating Scale (NRS) (see Appendix 1, Section 18.1) measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, how much pain are you experiencing in your operative knee **right now**?" from the end of surgery to 96 hours post-surgery at the designated timepoints. Additional assessments include: record pain intensity scores using the NRS measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, what was the **worst** pain in your operative knee in the last 24 hours?" and "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, what was the **average** pain in your operative knee in the last 24 hours?" and subject satisfaction with pain management using the subject satisfaction questionnaire (at 96 h).

Vital signs will be measured and recorded as follows:

- Upon arrival in the Post-anesthesia Care Unit (PACU) (±5 min)
- At PACU discharge (±5 min)
- Every 6 hours from the end of surgery until 96 hours post-surgery: 6 h (±2 h), 12 h (±2 h), 18 h (±2 h), 24 h (±2 h), 30 h (±2 h), 36 h (±2 h), 42 h (±2 h), 48 h (±2 h), 54 h (±2 h), 60 h (±2 h), 66 h (±2 h), 72 h (±2 h), 78 h (±3 h), 84 h (±3 h), 90 h (±3 h), 96 h (±3 h), and at hospital discharge
- Additionally, for Cohort 1 subjects: 120 h (±3 h), 144 h (±3 h), and 168 h (±3 h)

A 12-lead EKG will be performed at:

- 24 h (±2 h), 48 h (±2 h), 72 h (±2 h), and 96 h (±3 h).

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- Additionally, for Cohort 1 subjects: 120 h (±3 h), 144 h (±3 h), and 168 h (±3 h)

Other postsurgical assessments include: record adverse events (AEs)/ SAEs and concomitant medications.

For Cohort 1 only, additional assessments include: collect scheduled PK blood samples, perform sensory and motor function assessments.

Post operatively the subject will progress to full weight bearing as tolerated per the surgeon's standard of care. A walker is recommended for physical therapy until the fall risk is minimized and the subject can transfer and ambulate safely.

In case an AE of special interest (AESI) or serious AE (SAE) occurs during the study, if the investigator or medical monitor considers that the event may be related to study treatment or suggests the possible occurrence of local anesthetic systemic toxicity (LAST; with or without the need for treatment [e.g., intralipids]), an unscheduled PK blood sample, 12-lead EKG, and vital signs must be collected. Neurological assessments will be conducted according to the study site's standard of care at least once daily until resolution of symptoms.

Health Care Facility Discharge:

Subjects in Cohort 1 and Cohort 2 will be discharged after the completion of the 168 h and 96 h assessments, respectively.

Post-operative Day (POD) 14 Phone call follow-up:

For the assessment of AEs/SAEs and concomitant medication use, a final follow-up phone call will be made on POD 14 ± 3 days.

Number of Subjects (Planned):

A total of approximately 160 subjects undergoing primary unilateral TKA will be enrolled in the study. Approximately 40 subjects are planned for Cohort 1 and will be randomized 1:1 to either the EXPAREL admix arm or bupivacaine HCI arm.

Approximately 120 subjects are planned for Cohort 2 and will be randomized 1:1 to either the EXPAREL admix arm or bupivacaine HCI arm.

Eligibility Criteria:

Inclusion Criteria:

1. Male or female, ages 18 or older at screening.
2. Indicated to undergo primary unilateral total knee arthroplasty under spinal anesthesia.
3. Primary indication for TKA is degenerative osteoarthritis of the knee.
4. American Society of Anesthesiologists (ASA) physical status 1, 2, or 3 (see Appendix 5, Section 18.5).
5. Able to provide informed consent, adhere to the study schedule, and complete all study assessments.
6. Body Mass Index (BMI) ≥18 and <40 kg/m^2.

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Exclusion Criteria:

1. Allergy, hypersensitivity, intolerance, or contraindication to any of the study medications for which an alternative is not named in the protocol (e.g., amide-type local anesthetics, opioids, bupivacaine HCl, NSAIDs).
2. Planned concurrent surgical procedure (e.g., bilateral TKA).
3. Undergoing unicompartmental TKA or revision TKA.
4. Concurrent painful physical condition (e.g., arthritis, fibromyalgia, cancer) that may require analgesic treatment with NSAIDs or opioids in the post dosing period for pain that is not strictly related to the knee surgery and which, in the Investigator's opinion, may confound the post dosing assessments.
5. Inadequate sensory function below the knee as assessed by the Investigator.
6. History of contralateral TKA within 1 year.
7. Previous open knee surgery on the knee being considered for TKA. Prior arthroscopy is permitted.
8. History of, suspected, or known addiction to or abuse of illicit drug(s), prescription medicine(s), or alcohol within the past 2 years.
9. Administration of an investigational drug within 30 days or 5 elimination half-lives of such investigational drug, whichever is longer, prior to study drug administration, or planned administration of another investigational product or procedure during the subject's participation in this study.
10. Previous participation in an EXPAREL study.
11. Uncontrolled anxiety, schizophrenia, or other psychiatric disorder that, in the opinion of the Investigator, could interfere with study assessments or compliance.
12. Currently pregnant, nursing, or planning to become pregnant during the study.
13. Clinically significant medical disease that, in the opinion of the Investigator, would make participation in a clinical study inappropriate. This includes diabetic neuropathy, coagulation or bleeding disorders, severe peripheral vascular disease, renal insufficiency, hepatic dysfunction, or other conditions that would constitute a contraindication to participation in the study.
14. Currently on a neuromodulating agent (e.g., gabapentin, pregabalin [Lyrica], duloxetine [Cymbalta], etc.)].
15. Current use of systemic glucocorticoids within 30 days of randomization in this study.
16. Use of dexmedetomidine HCl (Precedex®) or clonidine within 3 days of study drug administration.
17. Any use of marijuana [including Tetrahydrocannabinol (THC) and Cannabidiol (CBD)] within 30 days prior to randomization, or planned use during the course of the study.
18. Chronic opioid use (average ≥30 oral morphine equivalents/day) within 30 days prior to randomization.

Given the COVID-19 pandemic, if there is a concern about a subject's recent or potential exposure to COVID-19, or if the subject is not medically fit/cleared for surgery due to suspected COVID-19 illness/symptoms, the subject must be excluded per Exclusion criterion #13.

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Name of Active Ingredient: Bupivacaine, 1.3%, 13.3 mg/mL		

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

Name: EXPAREL (bupivacaine liposome injectable suspension)

Active ingredient: Bupivacaine 1.3%, 13.3 mg/mL

Dosage:

- **EXPAREL admix arm:** single administration of 10 mL (133 mg) EXPAREL admixed with 10 mL (50 mg) 0.5% bupivacaine HCl

Lot number: To be determined

Mode of administration: Adductor canal block

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

Name: 0.5% Bupivacaine HCl

Active ingredient: Bupivacaine HCl

Dosage:

- **Bupivacaine arm:** single administration of 10 mL (50 mg) 0.5% bupivacaine HCl mixed with 10 mL normal saline.

Lot number: To be determined

Mode of administration: Adductor canal block

Duration of Subject Participation in the Study:

Participation will begin upon signing of the ICF. No more than 45 days should pass between signing the ICF and study drug administration. Study drug administration will be on the same day of surgery. A follow-up phone call will occur on POD 14 (±3 days). Therefore, each subject may participate in the study for up to a maximum of 62 days.

Efficacy Assessments:

- Pain intensity score using the NRS as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, how much pain are you experiencing in your operative knee **right now**?" will be assessed by the study staff:
  - Upon arrival in the Post-anesthesia Care Unit (PACU) (±5 min)
  - Every 15 minutes in the PACU (±5 min)
  - At PACU discharge (±5 min)
  - Every 6 hours from the end of surgery until 96 hours post-surgery: 6 h (±2 h), 12 h (±2 h), 18 h (±2 h), 24 h (±2 h), 30 h (±2 h), 36 h (±2 h), 42 h (±2 h), 48 h (±2 h), 54 h (±2 h), 60 h (±2 h), 66 h (±2 h), 72 h (±2 h), 78 h (±3 h), 84 h (±3 h), 90 h (±3 h), and 96 h (±3 h)
- An unscheduled pain intensity score using NRS as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, how much pain are you experiencing in your operative knee **right now**?" will be obtained immediately prior to administration of any breakthrough pain medication until 96 hours post-surgery.

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- Pain intensity using the NRS at 24 (±2 h), 48 (±2 h), 72 (±2 h), and 96 (±3 h) post-surgery, measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, what was the **worst** pain in your operative knee in the last 24 hours?"
- Pain intensity using the NRS at 24 (±2 h), 48 (±2 h), 72 (±2 h), and 96 (±3 h) post-surgery, measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, what was the **average** pain in your operative knee in the last 24 hours?"

Subjects will be instructed to focus all NRS pain intensity ratings on the operative knee, and no other locations where they may be experiencing pain.

In addition, subject satisfaction with pain management using 1 question from the International Pain Outcome (IPO) questionnaire will be recorded at 96 hours (±3 h) post-surgery.

Efficacy Endpoints:

Primary Efficacy Endpoint:

- The area under the curve (AUC) of the NRS pain intensity scores from 0 to 96 hours post-surgery.

Secondary Efficacy Endpoints:

- Total postsurgical opioid consumption in oral morphine equivalents (OMED) from 0 to 96 hours post-surgery.
- Time to first opioid consumption post-surgery.
- Worst and average NRS pain intensity scores at 24h, 48h, 72h, and 96h from the end of surgery.

Safety Assessments:

The following safety assessments will be conducted by blinded study staff at the time points specified:

- SAEs will be recorded from the time of informed consent and AEs will be recorded from the time of randomization through POD 14.

Safety Endpoint:

- Incidence of treatment-emergent AEs and SAEs from the start of the nerve block procedure through POD 14.

Pharmacokinetic and Pharmacodynamic Assessments (Cohort 1 Subjects Only):

Blood samples for PK assessment and the sensory/ motor function assessments will be assessed at scheduled timepoints in Cohort 1 subjects only (See Table 2).

Pharmacokinetic Endpoints: The following PK endpoints will be determined:

- Area under the plasma concentration-versus-time curve (AUC)
- Maximum plasma concentration (C_{max}) and time of C_{max} (T_{max})
- The apparent terminal elimination half-life ($t_{1/2el}$)
- Apparent clearance (CL/F)

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- Apparent volume of distribution (Vd)

Pharmacodynamic Endpoints: The following pharmacodynamics endpoints will be determined:

- Median time to onset of sensory block and motor block
- Median duration of sensory block and motor block

Statistical Methods:

The total sample size was calculated based on the primary outcome measure of NRS pain intensity scores. A total sample size of 160 subjects (1:1 randomization, 80 EXPAREL admixed with bupivacaine HCl: 80 Bupivacaine HCl) provides at least 80% power to detect a treatment difference of 80 units in the AUCs (SD=180) comparing EXPAREL admix arm with bupivacaine HCl arm at one-sided 0.025 significance level.

AUC of NRS pain intensity scores from 0-96 hours post-surgery will be analyzed using the Analysis of Covariance (ANCOVA) model. The main contrast of interest to assess treatment effect will be the difference between EXPAREL admix arm with bupivacaine HCl arm in the AUC of pain score's Least Square Means.

Total postsurgical opioid consumption in oral morphine equivalents (OMED) from 0 to 96 hours will be analyzed using the ANCOVA model. Time to first postsurgical opioid medication will be analyzed using the Kaplan-Meier survival method. Worst and average NRS pain intensity scores through 24h, 48h, 72h, and 96h from the end of surgery will be summarized by treatment arm.

Descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum) will be provided for continuous data. Tabulations (number and percentage of subjects) by category will be provided for categorical data. Safety analyses will be summarized descriptively by treatment arms.

An interim analysis to evaluate the sample size assumptions and evaluate futility will occur when a total of approximately 80 subjects (40 subjects in EXPAREL admix arm and 40 subjects in bupivacaine HCl arm) combined from either Cohort 1 or Cohort 2 have enrolled and provided complete assessment data for the primary efficacy outcome.

Table 1: Time and Events Schedule of Study Procedures (Screening through POD 14)

	Screen-ing Visit[1]	Day of Surgery (Prior to Surgery)	OR	PACU	Time from End of Surgery (h)																120-168 ±3[2]	Health Care Facility Discharge[3]	POD 14 Call ±3 days
					6 ±2	12 ±2	18 ±2	24 ±2	30 ±2	36 ±2	42 ±2	48 ±2	54 ±2	60 ±2	66 ±2	72 ±2	78 ±3	84 ±3	90 ±3	96 ±3			
Obtain ICF*	X																						
Assess/confirm eligibility*	X	X[4]																					
Record medical/ surgical history*[5]	X																						
Collect height/weight for BMI calculation*	X																						
Demographics and baseline characteristics*	X																						
Record prior and concomitant Medications[5]	X	X[4]	◄		- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - - ►
Urine pregnancy test for WOCBP	X	X[4]																					
Urine drug screen		X[4]																					
Perform 12-lead EKG[6]	X							X				X				X				X	X		
Review Pain Rating Guide		X[4]																					
Record *worst* and *average* pain (NRS) in the last 30 days		X[4]																					
Randomize subject; prepare study drug		X																					
Record block start/ end times[7]		X																					
Capture ultrasound video for the nerve block and send to Sponsor		X																					
Record IPACK start/end times		X																					
Record surgery start and end times			X																				

	Screening Visit[1]	Day of Surgery (Prior to Surgery)	OR	PACU	Time from End of Surgery (h) 6 ±2	12 ±2	18 ±2	24 ±2	30 ±2	36 ±2	42 ±2	48 ±2	54 ±2	60 ±2	66 ±2	72 ±2	78 ±3	84 ±3	90 ±3	96 ±3	120-168 ±3[2]	Health Care Facility Discharge[3]	POD 14 Call ±3 days
	Screening Visit[1]	Day of Surgery (Prior to Surgery)	OR	PACU	Time from End of Surgery (h) 6 ±2	12 ±2	18 ±2	24 ±2	30 ±2	36 ±2	42 ±2	48 ±2	54 ±2	60 ±2	66 ±2	72 ±2	78 ±3	84 ±3	90 ±3	96 ±3	120-168 ±3[2]	Health Care Facility Dis-charge[3]	POD 14 call ±3 days
Record intra-op medication administered			X																			
Record Pre-op and post-op scheduled analgesic medication[8]		X	◄	---►																		
Record PACU time in and out				X																		
Record **scheduled** NRS scores[9,10]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Measure and record vital signs[11]		X[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Record ***worst*** and ***average*** NRS scores (24-hour recall)[9,10]								X				X				X				X		
Record **unscheduled** NRS immediately prior to breakthrough pain medication[12]				◄	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	►		
Record breakthrough pain medication[12]				◄	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	►		
Record day and time of HCF admission and discharge		X																			X	
Record AEs/SAEs[13]	◄	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	►
Perform unscheduled neurological assessment[14]		◄	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	►

	Screen-ing Visit[1]	Day of Surgery (Prior to Surgery)	OR	PACU	Time from End of Surgery (h)																120-168 ±3[2]	Health Care Facility Discharge[3]	POD 14 Call ±3 days
					6 ±2	12 ±2	18 ±2	24 ±2	30 ±2	36 ±2	42 ±2	48 ±2	54 ±2	60 ±2	66 ±2	72 ±2	78 ±3	84 ±3	90 ±3	96 ±3			
Subject's satisfaction questionnaire (IPO)																				X			

Abbreviations: AE=adverse event; BMI=Body Mass Index; h=hour(s); HCF=health care facility; ICF=informed consent form; IPO=International Pain Outcome; min=minute(s); NRS=numeric rating scale; NSAID=nonsteroidal anti-inflammatory drug; OR=Operating Room; PACU=Post-Anesthesia Care Unit; POD=Post-operative Day; SAE=serious adverse event; WOCBP=women of childbearing potential.

* No more than 45 days before scheduled surgery day

1. Subjects may be screened on the same day as health care facility admission/surgery (with ample time for the informed consent process) or up to 45 days prior to surgery, but eligibility will be re-confirmed on the day of surgery prior to randomization. Screening procedures that are standard of care 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 obtained.
2. For Cohort 1 subjects only: A 12-lead EKG will be performed, and vital signs will be measured and recorded at additional time points: 120 (±3h), 144 (±3h), and at 168 (±3h).
3. Subjects in Cohort 1 and Cohort 2 will be discharged after 168 h and 96 h assessments, respectively.
4. Eligibility criteria, prior medication, urine pregnancy test, and urine drug screen to be assessed prior to randomization; review of Pain Rating Guide and worst and average pain scores over the previous 30 days to be assessed prior to study drug administration.
5. Relevant medical/surgical history within the last 5 years (including all ongoing history, regardless of start date) should be recorded, with the exception of history that is relevant to the TKA surgery, in which case all years should be recorded. Prior medications taken within 30 days of randomization (including all ongoing medications, regardless of start date) will be recorded.
6. A baseline 12-lead EKG must be performed at screening visit. A 12-lead EKG must be performed if a subject experiences an AESI or an SAE (see footnote 15)
7. Block to be administered 90 min (±30 min) prior to surgery.
8. Record all pre-operative and post-operative scheduled analgesic medication (celecoxib and acetaminophen)
9. The NRS pain intensity assessment should not be completed after any physical activity, including the motor block assessment (for Cohort 1 subjects). If that is not possible, to assess pain intensity at rest, the subject should rest quietly in a supine or seated position that does not exacerbate subject's postsurgical pain for 5-10 minutes before assessing the pain score using the NRS. If a subject is asleep, the subject will not be awakened to assess pain. If the subject awakens within the assessment window, a pain score will be collected then.
10. Pain scores (24 hr recall) once daily (i.e., worst/average pain) will be collected at 24 (±2 h), 48 (±2 h), 72 (±2 h), and 96 (±3 h) post-surgery. Pain scores (current pain) will be collected by the study staff beginning at PACU admission (±5 min); q15 min in PACU (±5 min); at PACU discharge (±5 min) ; then q6h (±2 h) from end of surgery to 72 hours post-surgery and q6h (±3 h) from 78-96 hours post-surgery.
11. Vital signs (temperature, resting heart rate, respiratory rate, oxygen saturation and blood pressure) will be measured after the subject has rested in a supine position for at least 5 minutes. Vital signs will be measured before study drug administration, upon arrival in the PACU (±5 min), at PACU discharge (±5 min), then q6h (±2 h) from end of surgery to 72 hours post-surgery and q6h (±3 h) from 78-96 hours post-surgery, and at hospital discharge. Additionally, for Cohort 1 subjects: 120 h (±3 h), 144 h (±3 h), and 168 h (±3 h). Vital signs must be measured and recorded if a subject experiences an AESI or an SAE (see footnote 15)
12. Oxycodone will be administered on an as needed (PRN) basis for breakthrough pain through 96 hours post-surgery; opioids should not be given on a pre-determined schedule. Immediate release oral (PO) oxycodone will be administered in a stepwise approach:
    - Initial dose of 5 mg oxycodone may be offered.
    - If the initial opioid dose is insufficient for pain relief, an additional 5 mg oxycodone may be offered up to a maximum of 10 mg (total dose).

If a subject is unable to tolerate PO medication (or the PO oxycodone pain relief is insufficient), IV morphine (initiated at 2 mg) or hydromorphone (initiated at 0.2 mg) may be administered.

13. Document all AEs with an onset after the subject is randomized and SAEs with an onset after the subject signs the ICF.
14. An unscheduled neurological assessment will be conducted once daily if a subject experiences an AESI or an SAE, until resolution of symptoms (see footnote 15).
15. In case an AE of special interest (AESI) or serious AE (SAE) occurs during the study, if the investigator or medical monitor considers that the event may be related to study treatment or suggests the possible occurrence of local anesthetic systemic toxicity (LAST; with or without the need for treatment [e.g., intralipids]), an unscheduled PK blood sample, 12-lead EKG, and vital signs must be collected. Neurological assessments will be conducted according to the study site's standard of care at least once daily until resolution of symptoms.

Table 2: Pharmacokinetic and Pharmacodynamic Assessments (Cohort 1 Subjects only)

		Post-study Drug Administration[a]															
		Day of Study Drug Administration to Post-operative Day 4 (POD 4)													POD 5	POD 6	POD 7
Time Window	**Up to 15 mins before blocks**	**15m**	**30m**	**45m**	**1h**	**2h**	**8h**	**12h**	**24h**	**30h**	**48h**	**60h**	**72h**	**84h**	**96h**	**120h**	**144h**	**168h**
		±5m	**±5m**	**±5m**	**±15m**	**±30m**	**±30m**	**±30m**	**±1h**	**±1h**	**±1h**	**±2h**	**±2h**	**±2h**	**±3h**	**±3h**	**±3h**	**±3h**
Collect PK blood sample; Record date and time of blood sample[b]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess and record sensory and motor function[c,d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: h=hour; m=minute; PK=pharmacokinetic

a. All timepoints are from end of block administration.
b. An unscheduled PK sample must be collected if a subject experiences an AESI or an SAE (see footnote 15 in Table 1)
c. Once the offset of light touch sensation is recorded and documented in both locations, no further scheduled sensory assessments are required. Once the offset of motor block is recorded and documented, no further scheduled motor assessments are required. Pharmacodynamic assessments must be performed by blinded, trained, licensed medical staff (e.g., Physician, Registered Nurse, Physician Assistant) and documented on the investigator's study delegation log. A limited number of study staff should perform the sensory/motor assessments.
d. When subject is in surgery, no sensory or motor function assessments will be conducted.

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4. LIST OF ACRONYMS/ABBREVIATIONS AND DEFINITIONS OF TERMS

4.1. List of Acronyms/Abbreviations

AE	Adverse event
ANCOVA	Analysis of Covariance
ASA	American Society of Anesthesiology
AUC	Area under the curve
BMI	Body mass index
CBD	Cannabidiol
C/L	Apparent clearance
C_{max}	Maximum plasma concentration
CFR	Code of Federal Regulations
CNS	Central nervous system
CRF	Case Report Form
eCRF	Electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
h	Hour(s)
HCF	Health care facility
HCl	Hydrochloride
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IPACK	Infiltration between the Popliteal Artery and Capsule of the Knee
IPO	International Pain Outcome
IRB	Institutional Review Board
IV	Intravenous
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
LAST	Local anesthetic system toxicity
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
NRS	Numeric Rating Scale
NSAIDs	Non-steroidal anti-inflammatory drugs
NVM	Nerve to Vastus Medialis
OMED	Oral morphine equivalent
OR	Operating room

PACU	Post Anesthesia Care Unit
PNS	Peripheral nerve stimulator
POD	Post-operative day
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
$t_{1/2el}$	Apparent terminal elimination half-life
TEAE	Treatment-emergent adverse event
THC	Tetrahydrocannabinol
TKA	Total knee arthroplasty
US	United States
Vd	Apparent volume of distribution

4.2. Definition of Terms

Pharmacokinetic terms are defined in Section 12.6.

5. ETHICS

5.1. Institutional Review Board/Independent ethics committee

Prior to enrolling subjects into this study, each study site will obtain the approval of an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) that complies with the International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) and/or the United States (US) Food and Drug Administration (FDA) Title 21 Code of Federal Regulations (CFR) Part 56. Attention is directed to the basic elements that are required to be incorporated into the informed consent form (ICF) under 21 CFR Part 50.25 and ICH GCP.

5.2. Ethical Conduct of the Study

This study will be conducted in accordance with the clinical research guidelines established by the FDA Title 21 CFR, Parts 50, 54, 56, and 312, and the ICH GCP. Study documents will be maintained in accordance with applicable regulations.

5.3. Subject Information, and Consent

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

The Investigator will explain to the subject that he or she is completely free to decline entry into the study and may withdraw from the study at any time, for any reason, without risking his or her medical care. Similarly, the Investigator and/or Pacira Pharmaceuticals, Inc. ("Pacira") 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 2000 [Edinburgh]).

6. INVESTIGATORS AND STUDY ADMINISTRATION STRUCTURE

Information regarding the investigators, sites, laboratories, and other service providers is available upon request to the IRBs and regulatory agencies.

7. INTRODUCTION

Postsurgical pain is one of the most common forms of acute pain (Schug 1993; Carr 1999). In contrast to chronic pain, for which no adaptive value has been demonstrated, acute pain is the normal physiological response to tissue insult or injury and has adaptive value by serving as a warning of danger or damage. Most acute pain is either treatable or avoidable, especially when it occurs in a clinical setting. However, if acute pain is poorly or inappropriately treated, it may progress to chronic pain (Perkins 2000; Petersen-Felix 2002). Thus, effectively modulating the response to acute pain may be considered a primary step in the prevention of chronic pain (Stephen 2003). The suboptimal management of acute pain has been recognized as a problem by clinicians

for more than 50 years (Papper 1952; Marks 1973) and has been formally identified as a public health concern by various societies and government institutions worldwide.

In 1992, the US Agency for Health Care Policy and Research developed guidelines for the management of postoperative pain in the hopes of increasing awareness of the consequences of poor pain control in the postoperative setting and promoting better pain management techniques (Stephen 2003). These consequences, which include delayed healing, longer hospitalization, and the development of chronic pain, are significant not only from the patient's perspective (decrease in functionality and quality of life) but also from the health economic perspective (increase in healthcare resource utilization and costs).

A multimodal approach to postoperative analgesia, using a combination of agents (e.g., opioids, local anesthetics, non-steroidal anti-inflammatory drugs [NSAIDs]), and delivery techniques (patient-controlled analgesia, epidural and regional blocks) is currently recognized as best practice for pain management (Breivik 1995a; Breivik 1995b; American Society of Anesthesiologists [ASA] Task Force 1995; Dahl 2000).

EXPAREL® was developed to extend pain relief with a single-dose administration without the use of indwelling catheters and to decrease the requirement for supplemental opioid medications. A New Drug Application (NDA) for EXPAREL was submitted as a 505(b)(2) application and subsequently approved by the US FDA on October 28, 2011 (NDA 022-496). On 2018, the FDA approved EXAPREL for interscalene brachial plexus nerve block for adults. On March 22, 2021, FDA approved EXPAREL use in patients 6 years of age and older for single-dose infiltration to produce postsurgical local analgesia.

7.1. Indication

EXPAREL was initially approved by the US 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."

The indication was further amended and approved by the US FDA in March 2021 to read: "EXPAREL is indicated:

- In patients aged 6 years and older for single-dose infiltration to produce postsurgical local analgesia
- In adults as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia."

7.2. Current Therapies/Treatments

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 (ASA Task Force 1995).

Current modalities of postsurgical analgesic treatment include infiltration and nerve block with local anesthetic agents, usually combined with the systemic administration of analgesics (multimodal therapy). Multimodal therapy usually includes opioid medications, NSAIDs, and/or

acetaminophen provided through a variety of routes including intravenous, transdermal patch, and oral administration. Opioids are widely used and considered amongst the most powerful analgesics; however, they also have considerable drawbacks, including time and resources required for monitoring opioid-related side effects. A reduction in the use of postoperative opioids is desirable to decrease the incidence and severity of opioid-induced adverse effects, such as respiratory depression, nausea, vomiting, constipation, somnolence, pruritus, and urinary retention.

Postoperative pain is a predictable component of the postoperative process, which is often poorly managed, resulting in clinical and physiological changes that increase morbidity and mortality (inability to ambulate early, etc.), diminish quality of life, and extend length of stay, thereby increasing hospital expenditures (Oderda 2007) and reducing patient satisfaction. Effective relief of acute pain with minimal opioid complications, on the other hand, may improve clinical outcomes, avoid complications (like delay in regaining bowel function or an inability to tolerate liquid and solid oral intake), and conserve healthcare resources. As such, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) requires that all healthcare facilities practice adequate pain management and monitor opioid-related adverse events (AEs) (Apfelbaum 2003).

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 less than 8 hours. EXPAREL (Pacira Pharmaceuticals, Inc., ["Pacira"]) 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.

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 hydrochloride (HCl) solution, a well-characterized anesthetic/analgesic, with more than 35 years of 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 liquid components than that used in DepoCyt.

7.4. Summary of Human Clinical Experience with EXPAREL

As of July 2021, the EXPAREL clinical development program consists of 41 premarketing clinical studies: 21 Phase 1 studies, 7 Phase 2 studies, 13 Phase 3 studies; in addition, 21 Phase 4 (postmarketing) studies have been completed. Since its approval, EXPAREL has been administered to over 9 million subjects in the US (Investigator's Brochure).

EXPAREL was well tolerated and had a favorable safety profile when administered as a field block, as an interscalene brachial plexus nerve block, and as a combined popliteal and adductor canal

block in varying degrees of vascularity in subjects undergoing various surgical procedures. The frequency and types of events are consistent with the profile of other local anaesthetics.

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

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

Study 402-C-333 was conducted to examine the magnitude and duration of the analgesic effect achieved with a single dose of EXPAREL and EXPAREL admixed with bupivacaine HCl administered as a combined popliteal and adductor canal block to subjects undergoing lower extremity surgeries. EXPAREL (133 mg) was demonstrated to be safe and well tolerated when administered as a single dose as a combined popliteal and adductor canal block. The most frequent AEs (ie, nausea, constipation, hypoaesthesia, headache) are consistent with those previously seen with EXPAREL [EXPAREL USPI], suggesting that administration as a combined block doesn't alter the known safety profile of EXPAREL.

Please see the EXPAREL Full Prescribing Information for safety information regarding the use of EXPAREL (liposome bupivacaine injectable suspension) for the treatment of postsurgical pain.

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

7.5. Rationale of the Study

Pacira is investigating the efficacy, safety, and pharmacokinetics (PK) of a single dose of EXPAREL administered via adductor canal block in subjects undergoing primary unilateral total knee arthroplasty (TKA).

A dose of EXPAREL 10 mL (133 mg) admixed with 10 mL (50 mg) 0.5% bupivacaine HCl is expected to provide prolonged pain relief and is safe after TKA compared with 10 mL (50mg) 0.5% bupivacaine HCl mixed with 10 mL normal saline when injected in 20 mL volumes as an adductor canal block. The study will also investigate the PK and PD of EXPAREL 133 mg admixed with 50 mg of 0.5% bupivacaine, and 0.5% bupivacaine 50 mg when administered as an adductor canal block.

8. OBJECTIVES

8.1. Primary Objective

The primary objective is to compare the magnitude of the postsurgical analgesic effect following a single dose of EXPAREL admixed with bupivacaine HCl vs. bupivacaine HCl when administered via an adductor canal block in subjects undergoing primary unilateral total knee arthroplasty (TKA).

8.2. Secondary Objectives

The secondary objectives are to:

1. Compare the total postsurgical opioid consumption (in oral morphine equivalents) following a single dose of EXPAREL admixed with bupivacaine HCl vs. bupivacaine HCl.
2. Compare the time to first opioid consumption post-surgery, following a single dose of EXPAREL admixed with bupivacaine HCl vs. bupivacaine HCl.
3. Characterize and compare the magnitude of the duration of sensory and motor block following a single dose of EXPAREL admixed with bupivacaine HCl and bupivacaine HCl.
4. Assess the safety, and pharmacokinetic (PK) profile of EXPAREL admixed with bupivacaine HCl and bupivacaine HCl.

9. OVERALL STUDY DESIGN AND PLAN

9.1. Study Design

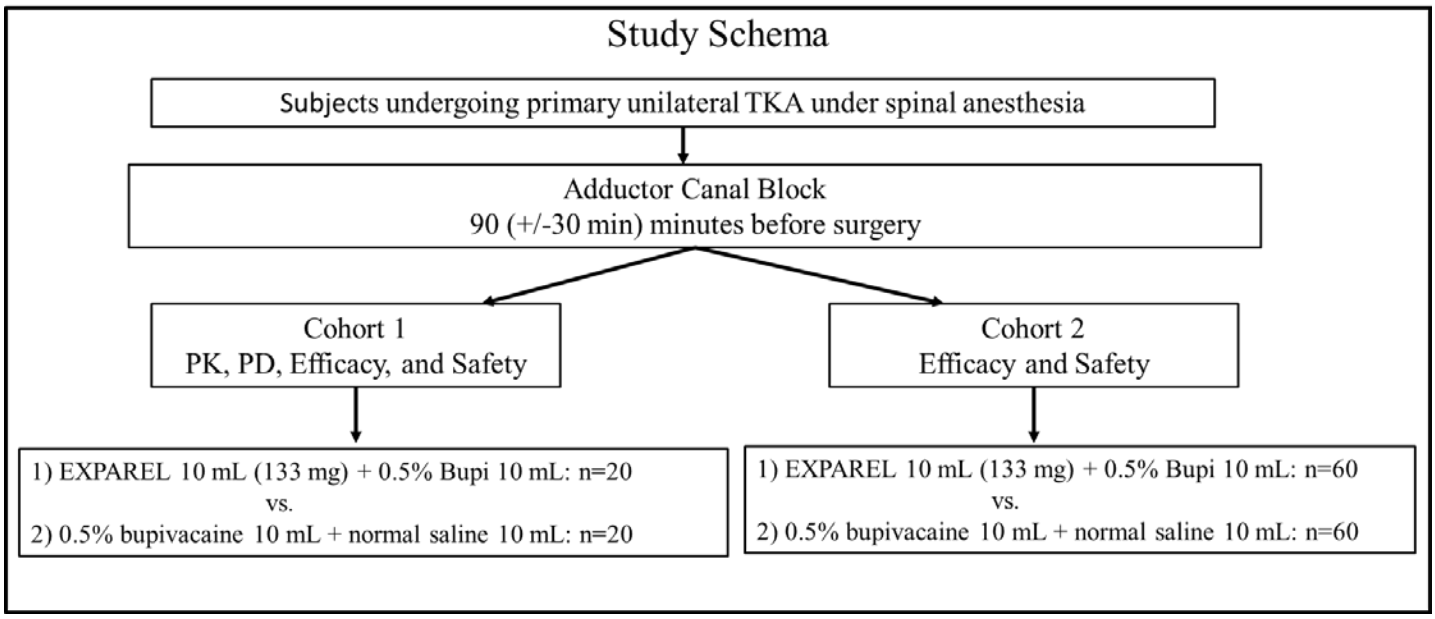
This is a Phase 3, multicenter, randomized, double-blind, active-controlled, study in approximately 160 subjects undergoing primary unilateral TKA under spinal anesthesia. The study will have 2 cohorts. Both cohorts will enroll in parallel.

Cohort 1 (PK, PD, Efficacy, and Safety):
Cohort 1 will enroll approximately 40 subjects (20 subjects per treatment arm) undergoing primary unilateral TKA under spinal anesthesia to obtain information on PK profile, PD, efficacy, and safety. Subjects in this cohort will be randomized (1:1) to receive an adductor canal block with a single dose of either EXPAREL 10 mL (133 mg) admixed with 10 mL 0.5% bupivacaine HCl (50 mg) or 10 mL 0.5% bupivacaine HCl (50 mg) mixed with 10 mL normal saline. The total dose volume will be consistent (20 mL) for all subjects.

Cohort 2 (Efficacy and Safety):
Cohort 2 will enroll approximately 120 subjects (60 subjects per treatment arm) undergoing primary unilateral TKA under spinal anesthesia to obtain information on efficacy and safety. Subjects in this cohort will be randomized (1:1) to receive an adductor canal block with a single dose of either EXPAREL 10 mL (133 mg) admixed with 10 mL 0.5% bupivacaine HCl (50 mg) or 10 mL 0.5% bupivacaine HCl (50 mg) mixed with 10 mL normal saline. The total dose volume will be consistent (20 mL) for all subjects.

An adaptive study design will be used in this study. An interim analysis to evaluate the sample size assumptions and evaluate futility will occur when a total of approximately 80 subjects (40 subjects in each arm) combined from either Cohort 1 or Cohort 2 have enrolled and provided complete assessment data for the primary efficacy outcome.

Figure 1: Study Schema



9.2. Duration of the Study and Subject Participation

Participation will begin upon signing of the ICF. No more than 45 days should pass between the time consent is obtained and the administration of study drug. Study drug administration will be on the same day of surgery. A final follow-up phone call will occur on Post-operative Day (POD) 14 (±3 days).

The time from study drug administration until the end of participation is POD 14 (±3 days). Therefore, subjects may participate in the study for up to 62 days.

9.2.1 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 will 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 pausing the study if the type, frequency, or seriousness/severity of such events suggests a potential threat to the safety of the study subjects. If such action is taken, a thorough review of all available data will be performed. Based on the results of this review and discussions with Investigators and/or regulatory authorities, the study may be restarted or permanently terminated as warranted.

In addition, any death will be thoroughly reviewed, and appropriate action taken.

The following adverse event study stopping rules will be applied:

- The study will be stopped after 1 death where a clear alternate cause is not readily apparent.

- The study will be stopped after 2 non-fatal serious adverse events where a clear alternate cause is not readily apparent.
- The study will be stopped after 2 moderate to severe symptoms deemed definitely related to local anesthetic systemic toxicity.

9.3. Discussion of Study Design

This Phase 3, multicenter, randomized, double-blind, active-controlled study will enroll approximately 160 subjects to evaluate the efficacy and safety of EXPAREL 133 mg admixed with 0.5% bupivacaine HCl and 0.5% bupivacaine HCl when administered as an adductor canal block, in subjects undergoing primary unilateral TKA.

Only Cohort 1 subjects (40 subjects) will provide blood samples for PK assessments and will be assessed for PD. Subjects in Cohort 1 will also provide information on efficacy and safety of EXPAREL 133 mg admixed with 0.5% bupivacaine HCl (50 mg) and 0.5% bupivacaine HCl (50 mg).

Cohort 2 subjects (120 subjects) will provide information on efficacy and safety of EXPAREL 133 mg admixed with 0.5% bupivacaine HCl (50 mg) and 0.5% bupivacaine HCl (50 mg).

The two treatment arms of the study for Cohort 1 and Cohort 2 are as follows:

1. **EXPAREL admix arm:** subjects randomized to this treatment arm will receive 10 mL (133 mg) EXPAREL admixed with 10 mL (50 mg) 0.5% bupivacaine HCl.
2. **Bupivacaine HCl arm:** subjects randomized to this treatment arm will receive 10 mL (50 mg) 0.5% bupivacaine HCl mixed with 10 mL normal saline.

10. STUDY POPULATION

Approximately 160 adult subjects undergoing primary unilateral TKA under spinal anesthesia will be enrolled in the study.

10.1. Inclusion Criteria

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

1. Male or female, ages 18 or older at screening.
2. Indicated to undergo primary unilateral total knee arthroplasty under spinal anesthesia.
3. Primary indication for TKA is degenerative osteoarthritis of the knee.
4. American Society of Anesthesiologists (ASA) physical status 1, 2, or 3 (see Appendix 5, Section 18.5).
5. Able to provide informed consent, adhere to the study schedule, and complete all study assessments.
6. Body Mass Index (BMI) ≥18 and <40 kg/m2.

10.2. Exclusion Criteria

A subject will not be eligible for the study if any of the following criteria are met:

1. Allergy, hypersensitivity, intolerance, or contraindication to any of the study medications for which an alternative is not named in the protocol (e.g., amide-type local anesthetics, opioids, bupivacaine HCl, NSAIDs).
2. Planned concurrent surgical procedure (e.g., bilateral TKA).
3. Undergoing unicompartmental TKA or revision TKA.
4. Concurrent painful physical condition (e.g., arthritis, fibromyalgia, cancer) that may require analgesic treatment with NSAIDs or opioids in the post dosing period for pain that is not strictly related to the knee surgery and which, in the Investigator's opinion, may confound the post dosing assessments.
5. Inadequate sensory function below the knee as assessed by the Investigator.
6. History of contralateral TKA within 1 year.
7. Previous open knee surgery on the knee being considered for TKA. Prior arthroscopy is permitted.
8. History of, suspected, or known addiction to or abuse of illicit drug(s), prescription medicine(s), or alcohol within the past 2 years.
9. Administration of an investigational drug within 30 days or 5 elimination half-lives of such investigational drug, whichever is longer, prior to study drug administration, or planned administration of another investigational product or procedure during the subject's participation in this study.
10. Previous participation in an EXPAREL study.
11. Uncontrolled anxiety, schizophrenia, or other psychiatric disorder that, in the opinion of the Investigator, could interfere with study assessments or compliance.
12. Currently pregnant, nursing, or planning to become pregnant during the study.
13. Clinically significant medical disease that, in the opinion of the Investigator, would make participation in a clinical study inappropriate. This includes diabetic neuropathy, coagulation or bleeding disorders, severe peripheral vascular disease, renal insufficiency, hepatic dysfunction or other conditions that would constitute a contraindication to participation in the study.
14. Currently on a neuromodulating agent (e.g., gabapentin, pregabalin [Lyrica], duloxetine [Cymbalta], etc.)].
15. Current use of systemic glucocorticoids within 30 days of randomization in this study.
16. Use of dexmedetomidine HCl (Precedex®) or clonidine within 3 days of study drug administration.
17. Any use of marijuana [including Tetrahydrocannabinol (THC) and Cannabidiol (CBD)] within 30 days prior to randomization, or planned use during the course of the study.
18. Chronic opioid use (average ≥30 oral morphine equivalents/day) within 30 days prior to randomization.

Given the COVID-19 pandemic, if there is a concern about a subject's recent or potential exposure to COVID-19, or if the subject is not medically fit/cleared for surgery due to suspected COVID-19 illness/symptoms, the subject must be excluded per Exclusion criterion #13.

10.3. Removal of Subjects from Therapy or Assessment

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

If any clinically significant event or condition is uncovered during the study period (e.g., excessive bleeding, acute sepsis) that might render the subject medically unstable or compromise the subject's postsurgical course, the subject should be withdrawn from the study and the event or condition should be reported as an AE or SAE.

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

10.3.1. Withdrawal Secondary to Adverse Events

If a subject experiences an AE that renders the subject incapable of continuing with the remaining assessments, the subject will be discontinued from further participation in the study. A final evaluation, including the End of Study assessments (see Section 10.3.3), should be performed so that the subject's study participation can be terminated in a safe and orderly manner.

Any subject who discontinues because of an AE should be instructed to notify the study personnel of any abnormal symptoms and to come to the study site if medical evaluation is needed and the urgency of the situation permits. Any subject exhibiting AEs will receive appropriate treatment at the discretion of the Investigator until resolution of the AE.

This study involves a single administration of the 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).

In addition, the subject may be withdrawn from the study if the subject meets the following criterion during or after the surgery:

Any clinically significant event or condition uncovered during the surgery (e.g., excessive bleeding, acute sepsis) that, in the opinion of the Investigator, renders the subject medically unstable or complicates the subject's postsurgical course.

10.3.2. Voluntary or Study Investigator Withdrawal

Subjects are free to discontinue from the study at any time, without prejudice to future treatment. A subject may be discontinued from the study if the subject refuses study treatment (i.e., the adductor canal block) or refuses to comply with study procedures. Subjects should be encouraged to complete the study safety assessments. 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 the study drug, the subject will be asked to complete a final evaluation, including the early termination assessments (see Section 10.3.3), so that the subject can be withdrawn in a safe and orderly manner.

After termination from the study, the subject may be followed for safety including monitoring of AEs/SAEs through POD 14.

10.3.3. Early Termination Assessments

In case of early termination, the following assessments shall be performed:

- Record date and time of withdrawal
- Record reason for withdrawal
- Review adverse events; any ongoing AEs/SAEs will need to be followed to resolution
- Record responses to pain assessment:
    - Pain intensity scores (using the NRS) measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, how much pain are you experiencing in your operative knee **right now**?"
    - Pain intensity scores (using the NRS) measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, what was the **worst** pain in your operative knee in the last 24 hours?"
    - Pain intensity scores (using the NRS) measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, what was the **average** pain in your operative knee in the last 24 hours?"

11. TREATMENTS

11.1. Treatments to be Administered

Treatments for Cohort 1 and Cohort 2:

On the day of surgery, subjects will receive an ultrasound-guided adductor canal block with one of the following treatments (study drug):

1. **EXPAREL admix arm:** subjects randomized to this treatment arm will receive 10 mL (133 mg) EXPAREL admixed with 10 mL (50 mg) 0.5% bupivacaine HCl
2. **Bupivacaine HCl arm:** subjects randomized to this treatment arm will receive 10 mL (50 mg) 0.5% bupivacaine HCl mixed with 10 mL normal saline.

Block Procedure:

Subjects may be lightly sedated with 1 to 2 mg of midazolam intravenously (IV) before the nerve block procedure. The study drug (EXPAREL admixed with bupivacaine HCl or bupivacaine HCl) will be administered under ultrasound guidance 90 min (±30 min) prior to surgery. A peripheral nerve stimulator will be used to confirm nerves in the adductor canal before study drug administration (see Section 13.3). A confirmatory ultrasound video will be captured during the nerve block procedure (during hydrodissection by saline injection and study drug administration), with needle in place to ensure accurate block placement. The Investigator will provide the video to the sponsor within 24 hours from the end of block procedure that will be reviewed by an independent ultrasound adjudication committee to ensure accuracy of study drug administration. Only two unblinded study drug administrators (anesthesiologist) will be assigned per site to perform the block procedures unless approved in advance in writing by the Sponsor on a case-by-case basis.

The designated study drug administrators (anesthesiologist) will not participate in any other study related assessments after randomization.

For all study arms, the total volume of 20 mL will be administered as the adductor canal block.

11.1.1. Study Drug Administration Considerations

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

EXPAREL may not be administered to a subject if the vial has been open for more than 4 hours. In order to prevent EXPAREL from settling, gently invert and re invert the vials of EXPAREL multiple times to re-suspend the particles immediately prior to withdrawal from the vial. Similarly, inverting and re-inverting the syringe prior to administration is required.

As recommended in the EXPAREL Full Prescribing Information, no other drugs (e.g., epinephrine, dexamethasone, clonidine) are to be admixed with EXPAREL other than bupivacaine HCl. Lidocaine and other local anesthetics are not permitted to be locally administered during the surgery because they are known to interact with EXPAREL, resulting in the displacement of bupivacaine and elevated plasma levels. When a topical antiseptic is applied to the surgical site, the solutions should not be allowed to come in contact with each other (e.g., the area must be dry before EXPAREL is administered). 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

11.1.2. Bupivacaine HCl Administration Considerations

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

Bupivacaine HCl is contraindicated in subjects with known hypersensitivity to amide-like local anesthetics. Caution must be exercised to prevent incidental intravenous administration of bupivacaine during block placement.

11.2. Identity of Investigational Products

11.2.1. 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 liposomes (DepoFoam drug delivery system). Bupivacaine is present at a nominal concentration of 13.3 mg/mL. For this study, EXPAREL will be provided in 20 mL, 1.3% (13.3 mg/mL) single-use, clear glass vials. EXPAREL vials should be stored refrigerated at 2°C to 8°C (36°F to 46°F).

11.2.2. Description of Reference Product

The reference product will be 0.5% bupivacaine HCl to be administered via adductor canal block.

11.2.3. Description of Volume Expansion Agent

Normal saline (0.9% sodium chloride solution) for injection will be used for the expansion of study drug volume for the 0.5% bupivacaine HCl arm.

11.3. Method of Assigning Subjects to Treatment

11.3.1. Randomization Scheme

This is a randomized study. Cohort 1 will enroll approximately 40 total subjects undergoing primary unilateral TKA randomized 1:1 in the EXPAREL admix arm and bupivacaine HCl arm.

Cohort 2 will enroll approximately 120 total subjects undergoing primary unilateral TKA, 60 subjects in each treatment arm; EXPAREL admix arm and bupivacaine HCl arm. Subjects will be randomized 1:1 to treatment arms.

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

11.3.2. Randomization Procedures for Treatment Assignment

Once a subject is identified as being qualified to participate in the study (see Section 10), and is at the study site for surgery, the Investigator or designee will obtain a randomization assignment. The subject will be considered randomized into the study once the study treatment is assigned.

11.3.3. Replacement of Subjects

Subjects who are withdrawn from the study before receiving study drug may be replaced. Once assigned, subject numbers will not be reused; subjects enrolled to replace those who withdraw will be assigned a unique subject number and randomized to treatment according to the procedures outlined above. Subjects who are randomized but are withdrawn from the study before receiving study drug or do not undergo the surgical procedure may be replaced. Additionally, subjects may be replaced if insufficient and/or incomplete data are noted on PK profiles or efficacy endpoints.

11.4. Selection of Doses in the Study

During the clinical development of EXPAREL, single doses ranging from 2 mg to 665 mg have been safely administered via various routes. Pharmacokinetic studies have shown that because EXPAREL releases bupivacaine gradually as the lipid structure breaks down, administration of EXPAREL 266 mg results in a maximum plasma concentration equivalent to that seen with standard bupivacaine HCl 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.

As a part of the clinical development program, a Phase 3 study (402-C-333) evaluating the PK, PD, efficacy, and safety of EXPAREL as a combined sciatic nerve (in popliteal fossa) and saphenous nerve (in adductor canal) block in subjects undergoing lower extremity surgeries was conducted. Both EXPAREL (266 mg) and EXPAREL admix arms were safe, compared to bupivacaine HCl arm. Pacira would like to evaluate and compare efficacy and safety along with PK concentrations of EXPAREL 133 mg admixed with bupivacaine HCl 50 mg vs. bupivacaine HCl 50 mg for the adductor canal block when used for the more painful procedures like TKA.

11.5. Blinding

11.5.1. Blinding Procedures

EXPAREL admixed with 0.5% bupivacaine HCl, and 0.5% bupivacaine HCl are visually distinguishable; therefore, to maintain the double-blind study design, the individuals preparing and administering study drug, or transporting unblinded drug will not be allowed to perform any of the study assessments after randomization (with the possible logistical exception of drawing blood in the operating room (OR) to be processed by blinded staff for the PK assessments) or reveal the assigned study treatment to any other members of the study team at any time. Additionally, efforts will be made to prevent the subject from observing the study drug syringe. Syringes containing study drug will need to be gently inverted several times to re-suspend any settling of the study drug that may have occurred prior to administration. The administration of study drug will be recorded using the minimal amount of information necessary to avoid unblinding staff who will be participating in blinded procedures.

Staff members conducting study-specific, postsurgical assessments and the subjects will remain blinded to the assigned treatment throughout the study in part by not being present during the administration of the nerve blocks. The site PI must be blinded to the study drug and will not be involved in and/or present during study drug administration procedure.

If a subject experiences an SAE, Pacira will not automatically unblind the subject's treatment, unless it is necessary to manage treatment of the SAE. Expedited SAEs will be unblinded by Pacira for regulatory reporting purposes.

At each site, only the designated unblinded study staff will receive unblinded randomization assignments; the designated unblinded pharmacist or administrator will be responsible for preparing the study drug. Only the two designated unblinded study drug administrators (anesthesiologist) at each site will be permitted to administer study drug.

No crossover will be permitted between the blinded and unblinded study site personnel throughout the study. The assignment of site monitors will also be segregated. Blinded monitors will review CRFs, clinic charts, and all other study-related documents that do not disclose the allocation of study treatment. Care should be taken in recording and review of operating room (OR) records to not record information in an unblinded fashion. Pharmacy or any other clinic records providing unblinded information (e.g., randomization, study drug preparation, study drug accountability, study drug administration) will be reviewed by specialized unblinded monitors who will notify Pacira of treatment noncompliance.

The independent review committee conducting the interim analyses will not be blinded to the study drug.

Additional details are outlined in the study-specific Blinding Plan.

11.5.2. Unblinding Procedure

Blinded study personnel should not be unblinded to the subject treatment assignments during the study. The Investigator will have the ability to unblind a subject through the randomization system if it is felt that subject safety warrants such unblinding. However, if possible, the Investigator should

discuss the safety issues with the Pacira Medical Monitor before attempting such unblinding. Any unblinding will be documented through immediate notification of the Pacira study team and the Investigator within the interactive response technology system used for randomization. The reason for unblinding will be documented. Any accidental unblinding events (i.e., through mishaps in the operating room or miscommunication among study staff) must be reported to Pacira immediately.

Any unblinding performed through the randomization system will be recorded as a transaction, and the appropriate study personnel will be notified that such a transaction occurred. Any incidence(s) of unblinding will be noted in the clinical study report with a full discussion of the events leading to the decision to unblind.

11.6. Prior and Concomitant Therapy and Medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary. The number and percent of subjects taking concomitant medications will be tabulated for each treatment group by Anatomic Therapeutic Chemical class and preferred terms.

11.6.1. Before Study Drug Administration

All subjects must receive the following medication within 4 hours prior to surgery:

- Celecoxib 200 mg, orally (PO)

Other Permitted Prior Medications and Therapy:

- 1-2 mg of midazolam (Versed)
- Ondansetron

Restricted Prior Medications and Therapy:

- Systemic glucocorticosteroids and neuromodulating agents (e.g., gabapentin, pregabalin [Lyrica], duloxetine [Cymbalta], etc.).
- Long-acting or sustained release opioid medications and NSAIDs (except for low-dose aspirin used for cardio protection) are not permitted within 3 days of study drug administration.
- Dexmedetomidine HCl (Precedex) and clonidine use is not permitted within 3 days of study drug administration.
- Scopolamine Patch is not permitted.
- No opioid medications are permitted within 24 hours of study drug administration.
- 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.
- No drugs (other than the described bupivacaine HCl admixture) are to be admixed with study drug (e.g., epinephrine, dexamethasone, clonidine).

- Lidocaine (except, if used as a local anesthetic at the site of IV placement) and other local anesthetics will not be permitted to be locally administered in the area of the nerve block administration other than use in a superficial cutaneous wheal for needle insertion.

11.6.2. Perioperative

- All subjects will receive an infiltration between the popliteal artery and capsule of the knee (IPACK) under ultrasound guidance with 15 mL of 0.25% bupivacaine HCl (37.5 mg) immediately following study drug administration (should be done with the same set-up for the nerve block).
- All subjects will receive spinal anesthesia immediately prior to surgery with 0.5% bupivacaine HCl (up to 15 mg). If the spinal fails or cannot be completed, the subject may receive total intravenous anesthesia (TIVA).
- All subjects will receive a dose of 1000 mg of intravenous (IV) acetaminophen at the time of surgical incision
- Propofol is permitted for induction and intra-operative sedation.

Other Permitted medications:

- Tranexamic acid (TXA) is permitted.

Restricted Medications:

- No other medication (including opioids) should be mixed with the bupivacaine for spinal anesthesia
- The use of dexamethasone, acetaminophen/paracetamol, ketorolac, or other NSAIDs will not be permitted preemptively or intraoperatively except for emergency use to treat an AE.
- Intraoperative use of opioids (except IV fentanyl, not to exceed 1 ug/kg unless deemed medically necessary) and ketamine will not be permitted.

11.6.3. Post-Surgery

- All subjects will receive one post-operative dose of 1000 mg of IV acetaminophen, administered approximately 8 hours after the first dose (approximately 8 hours after incision). The maximum total dose will not exceed 2000 mg. No additional acetaminophen is permitted after the second IV acetaminophen dose.

Other Permitted Medications:

- Ondansetron or metoclopramide may be used for postoperative nausea and vomiting.
- Postsurgical pain medications for breakthrough pain as outlined in Section 11.7.

Restricted Medications:

- No other analgesics, including fentanyl, are permitted within 96 hours after surgery.
- Scopolamine patch is not permitted.
- Dexmedetomidine HCl (Precedex) use is not permitted.

- Lidocaine (except, if used as a local anesthetic at the site of IV placement) and other local anesthetics will not be permitted to be locally administered in the area of the nerve block administration through POD 7.
- Patient control analgesia (PCA) is not permitted.
- Systemic glucocorticosteroids and neuromodulating agents (e.g., gabapentin, pregabalin [Lyrica], duloxetine [Cymbalta], etc.).

11.7. Postsurgical Pain Medication for Breakthrough Pain

An unscheduled pain intensity assessment using the NRS (measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, how much pain are you experiencing in your operative knee **right now**?") must be completed immediately prior to administration of any breakthrough pain medication up to 96 hours post-surgery.

Oxycodone will be administered on an as needed (PRN) basis for breakthrough pain through 96 hours post-surgery; opioids should not be given on a pre-determined schedule. Immediate release oral (PO) oxycodone will be administered in a stepwise approach:

- Initial dose of 5 mg oxycodone may be offered.
- If the initial opioid dose is insufficient for pain relief, an additional 5 mg oxycodone may be offered up to a maximum of 10 mg (total dose)
- If a subject is unable to tolerate PO medication (or the PO oxycodone pain relief is insufficient), IV morphine (initiated at 2 mg) or hydromorphone (initiated at 0.2 mg) may be administered.

No NSAIDs or other opioids including Tramadol are allowed for the breakthrough pain management per protocol. No Acetaminophen (other than the scheduled IV acetaminophen) should be used for breakthrough pain.

For study purposes, it is important to standardize pain management modalities during the first 96 hours post-surgery. Therefore, the study staff must adhere closely to the treatment options and requirements noted in the protocol. After 96 hours, the analgesic regimen may be adjusted for each subject individually as deemed appropriate by the physician responsible for the postsurgical care.

All postsurgical analgesics administered (opioids and other analgesics), must be recorded through hospital discharge.

11.8. Treatment Compliance

Study drug (EXPAREL admix, or bupivacaine HCl) administration will be performed by an unblinded study Investigator (anesthesiologist) qualified by experience and training.

All details of study drug administration, including dose volume and start and stop time, will be recorded in a blinded fashion in the source and eCRF.

11.9. Accountability of Study Drug

The Investigator or designee (e.g., pharmacist) is responsible for 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 an unblinded study monitor. A record of drug return or destruction will be maintained and provided to Pacira. Inventory records must be readily available for inspection by the unblinded study monitor and appropriate regulatory authorities at any time. A copy of the inventory records, drug accountability information, and notice of return or destruction will be returned to Pacira at the end of the study. Only authorized personnel identified by the Investigator will have the ability to access and administer the drug.

12. STUDY ENDPOINTS AND MEASUREMENTS

12.1. Efficacy Assessments

- Pain intensity measured using the NRS as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, how much pain are you experiencing in your operative knee **right now**?" will be assessed:
    - Upon arrival in the Post-anesthesia Care Unit (PACU) (±5 min)
    - Every 15 minutes in the PACU (±5 min)
    - At PACU discharge (±5 min)
    - Every 6 hours from the end of surgery until 96 hours post-surgery: 6 h (±2 h), 12 h (±2 h), 18 h (±2 h), 24 h (±2 h), 30 h (±2 h), 36 h (±2 h), 42 h (±2 h), 48 h (±2 h), 54 h (±2 h), 60 h (±2 h), 66 h (±2 h), 72 h (±2 h), 78 h (±3 h), 84 h (±3 h), 90 h (±3 h), and 96 h (±3 h)
- An unscheduled pain intensity assessment using NRS as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, how much pain are you experiencing in your operative knee **right now**?" will be obtained immediately prior to administration of any breakthrough pain medication until 96 hours post-surgery.
- Pain intensity using the NRS at 24 (±2 h), 48 (±2 h), 72 (±2 h), and 96 (±3 h) post-surgery, measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, what was the **worst** pain in your operative knee in the last 24 hours?"
- Pain intensity using the NRS at 24 (±2 h), 48 (±2 h), 72 (±2 h), and 96 (±3 h) post-surgery, measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, what was the **average** pain in your operative knee in the last 24 hours?"

Subjects will be instructed to focus all NRS pain intensity ratings on the operative knee, and no other locations where they may be experiencing pain.

In addition, subject's satisfaction with pain management using 1 question from the International Pain Outcome (IPO) questionnaire will be recorded at 96 hours (±3 h) post-surgery.

12.2. Efficacy Endpoints

Primary Efficacy Endpoint:

- The area under the curve (AUC) of NRS pain intensity scores from 0-96 hours post-surgery.

Secondary Efficacy Endpoints:

- Total postsurgical opioid consumption in oral morphine equivalents (OMED) from 0 to 96 hours post-surgery.
- Time to first opioid consumption post-surgery.
- Worst and average NRS pain intensity scores through 24h, 48h, 72h, and 96h from the end of surgery.

12.3. Safety Assessments

The following safety assessments will be conducted by blinded study staff at the time points specified:

- SAEs will be recorded from the time of informed consent and AEs will be recorded from the time of randomization through POD 14.

12.4. Safety Endpoints

- Incidence of treatment-emergent AEs (TEAEs) and SAEs from start of the nerve block procedure through POD 14.

12.5. Pharmacokinetic Assessments (Cohort 1 only)

The blood samples for PK assessment will be obtained from the Cohort 1 subjects. A total of 17 PK samples will be collected for each subject in Cohort 1. These samples will be obtained at Predose (up to 15 min before block), 30 min (±5 min), 45 min (±5 min), and 1 h (±15 min), 2 h (±30 min), 8 h (±30 min), 12 h (±30 min), 24 h (±1 h), 30 h (±1 h), 48 h (±1 h), 60 h (±2 h), 72 h (±2 h), 84 h (±2 h), 96 h (±3 h), 120 h (±3 h), 144 h (±3 h), and 168 h (±3 h) hours from end of block procedure (See Table 2).

12.6. Pharmacokinetic Endpoints (Cohort 1 only)

The following PK endpoints will be determined:

- Area under the plasma concentration-versus-time curve (AUC)
- Maximum plasma concentration (C_{max}) and time of C_{max} (T_{max})
- The apparent terminal elimination half-life ($t_{1/2el}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution (Vd)

12.7. Pharmacodynamic Assessments (Cohort 1 only)

Pharmacodynamic assessments must be performed by blinded, trained, licensed medical staff (e.g., Physician, Registered Nurse, Physician Assistant) and documented on the Investigator's study Delegation Log. A limited number of study staff (blinded to the study drug assignment) should perform the sensory/motor assessments.

Assessment of sensory functions (Light Touch Assessment):

- Sensory assessment for light touch will be performed at pre-dose (up to 15 min before block), 15 min (±5 min), 30 min (±5 min), 45 min (±5 min), 1 h (±15 min), 2 h (±30 min), 8 h (±30 min), 12 h (±30 min), 24 h (±1 h), 30 h (±1 h), 48 h (±1 h), 60 h (±2 h), 72 h (±2 h), 84 h (±2 h), 96 h (±3 h), 120 h (±3 h), 144 h (±3 h), and 168 h (±3 h) from the end of the nerve block

procedures, or until full sensory function has returned to baseline (pre-dose) levels (see Appendix 3, Section 18.3). Each light touch area of assessment will be rated independently. Additional unscheduled assessments may be performed, particularly around the surgery, if no onset of block is noted on the last scheduled assessment prior to surgery.

For each sensory assessment performed, both locations mentioned below will be assessed for light touch. If at the 168-h assessment there is a sensory deficit, the incident will be recorded as an AE. The physician will assess the subject for other etiologies that may explain the persistent sensory deficit. If the sensory deficit persists at the 168-h assessment, the subject is to return for unscheduled visit(s) at the Investigator's discretion until the sensory function has returned.

Sensory function assessment will include the following two locations:

1. Proximal - Medial aspect of the lower leg (3-4 cm below the knee)
2. Distal - Medial aspect of the lower leg (3-4 cm above ankle)

Onset of sensory block will be defined as the earliest timepoint with loss of light touch sensation along the distribution of the target nerve distal to the site of the block.

Offset of sensory block will be defined as the first timepoint of return of light touch sensation along the distribution of the target nerve distal to the site of the block. After offset of sensory assessments are noted (light touch sensation in both test areas in a single assessment), no subsequent assessments will be required.

Duration of sensory block will be defined as the time between onset and offset of light touch sensation.

Assessment of motor function:

Motor function (onset and offset of motor block) will be assessed by active movement of the knee (knee extension). This will be used to determine the duration of the motor blockade.

- The motor function test will be performed at pre-dose (up to 15 min before block), 15 min (±5 min), 30 min (±5 min), 45 min (±5 min), 1 h (±15 min), 2 h (±30 min), 8 h (±30 min), 12 h (±30 min), 24 h (±1 h), 30 h (±1 h), 48 h (±1 h), 60 h (±2 h), 72 h (±2 h), 84 h (±2 h), 96 h (±3 h), 120 h (±3 h), 144 h (±3 h), and 168 h (±3 h) from the end of the block procedures, or until motor function has returned to baseline (pre-dose) level (see Appendix 4, Section 18.4). Once the offset of motor block is recorded and documented, no further scheduled motor assessments are required. Additional unscheduled assessments may be performed, particularly around the surgery, if no onset of block is noted on the last scheduled assessment prior to surgery.

  If at the 168-h assessment there is a motor function deficit, the incident will be recorded as an AE. The physician will assess the subject for other etiologies that may explain the persistent motor deficit. If the motor deficit persists at 168 h, the subject is to return for unscheduled visit(s) at the Investigator's discretion until the motor function has returned.

Onset of motor block will be defined as the earliest timepoint with no knee extension.

Offset of motor block will be defined as resolution of the motor block with knee extension. After offset of motor block is noted, no subsequent assessments will be conducted.

Duration of motor block will be defined as time between onset and offset of motor block.

12.8. Pharmacodynamic Endpoints (Cohort 1 only)

The following pharmacodynamics endpoints will be determined:

- Median time to onset of sensory block and motor block
- Median duration of sensory block and motor block

12.9. Appropriateness of Measures

The endpoints selected for this study were based on validated methodologies and other well-established clinical measurements used in the peer reviewed literature. Measurements were further refined in this study based on previous nerve block experience with EXPAREL and other Phase 3 or 4 studies.

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

All PK, sensory/motor function assessments, and safety assessments conducted after baseline (pre-dose) will be timed from the end of the block. End of block procedure is defined as the time of completion of study drug administration via adductor canal block.

All NRS scores, vital signs, and EKG to be collected after surgery will be timed from the end of surgery.

At timepoints when multiple assessments coincide, assessments will be performed in the following sequence: pain intensity assessment, sensory assessments, motor assessment, blood draw for PK assessment, vital signs, 12-lead EKG, as applicable.

The start of surgery is defined as the time of the first incision. The end of surgery is defined as the time recorded in the surgical record. Postsurgical is defined as after the end of surgery.

Postsurgical analgesia and collection of study data will take place under the supervision of study staff at the site.

13.1.1. Pain Intensity Assessment

Pain intensity will be assessed using an 11-point NRS (0-10) as follows:

- Pain intensity scores (using the NRS) measured as “On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, what was the **worst** pain in your operative knee in the last 30 days?” and “On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, what was the **average** pain in your operative knee in the last 30 days?” will be assessed on the day of surgery prior to study drug administration.

- Pain intensity scores (using the NRS) measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, how much pain are you experiencing in your operative knee **right now**?" will be assessed:
    - Upon arrival in the Post-anesthesia Care Unit (PACU) (±5 min)
    - Every 15 minutes in the PACU (±5 min)
    - At PACU discharge (±5 min)
    - Every 6 hours from the end of surgery until 96 hours post-surgery: 6 h (±2 h), 12 h (±2 h), 18 h (±2 h), 24 h (±2 h), 30 h (±2 h), 36 h (±2 h), 42 h (±2 h), 48 h (±2 h), 54 h (±2 h), 60 h (±2 h), 66 h (±2 h), 72 h (±2 h), 78 h (±3 h), 84 h (±3 h), 90 h (±3 h), and 96 h (±3 h)
    - If a subject is asleep, the subject will not be awakened to assess pain. If the subject awakens within the assessment window, a pain score will be collected then.
    - Study staff will be instructed not to complete the NRS pain intensity score after any physical activity, including the motor block assessment (for Cohort 1 subjects). If that is not possible, to assess pain intensity at rest, the subject should rest quietly in a supine or seated position that does not exacerbate subject's postsurgical pain for 5-10 minutes before assessing the pain score using the NRS.

- An unscheduled pain intensity scores (using the NRS) measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, how much pain are you experiencing in your operative knee **right now**?" will be obtained immediately prior to administration of any breakthrough pain medication until 96 hours post-surgery
- Pain intensity using the NRS at 24 (±2 h), 48 (±2 h), 72 (±2 h), and 96 (±3 h) post-surgery, measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, what was the **worst** pain in your operative knee in the last 24 hours?"
- Pain intensity using the NRS at 24 (±2 h), 48 (±2 h), 72 (±2 h), and 96 (±3 h) post-surgery, measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, what was the **average** pain in your operative knee in the last 24 hours?"

Subjects will be instructed to focus all NRS pain intensity ratings on the operative knee, and no other locations where they may be experiencing pain.

13.1.2. Subject Satisfaction with Postsurgical Pain Control

Study staff will record subject's satisfaction with pain management using 1 question from the International Pain Outcome (IPO) questionnaire at 96 hours (±3 h) post-surgery. (see Appendix 2, Section 18.2).

13.1.3. Pharmacokinetic Assessments (Cohort 1 only)

The blood samples for PK assessment will be obtained from the Cohort 1 subjects. A total of 17 PK samples will be collected for each subject in Cohort 1. These samples will be obtained at Predose (up to 15 min before block), 30 min (±5 min), 45 min (±5 min), and 1 h (±15 min), 2 h (±30 min), 8 h (±30 min), 12 h (±30 min), 24 h (±1 h), 30 h (±1 h), 48 h (±1 h), 60 h (±2 h), 72 h (±2 h), 84 h

(±2 h), 96 h (±3 h), 120 h (±3 h), 144 h (±3 h), and 168 h (±3 h) hours from end of block procedure (See Table 2).

13.1.4. Pharmacodynamic Assessments (Cohort 1 only)

Pharmacodynamic assessments must be performed by blinded, trained, licensed medical staff (e.g., Physician, Registered Nurse, Physician Assistant) and documented on the Investigator's study Delegation Log. A limited number of study staff (blinded to study drug assignment) should perform the sensory/motor assessments.

Onset and duration of sensory block will be assessed using the light touch assessment sensation to characterize the sensory block (see Appendix 3, Section 18.3).

Onset and duration of motor block will be assessed by active movement of the knee (knee extension) to characterize the motor block (see Appendix 4, Section 18.4)

13.2. Study Procedures

13.2.1. Obtaining Informed Consent

Potential subjects undergoing primary unilateral TKA under spinal anesthesia will be approached by the Investigator and/or the study staff for informed consent up to 45 days before the surgery. Subjects may be consented on the day of the surgery, if the consent process is started early with ample time for the subject to review the informed consent form (ICF) and have all questions answered by the Investigator/study staff prior to providing informed consent.

13.2.2. Screening

Subjects may be screened up to 45 days prior to day of surgery but eligibility must be re-confirmed on the day of surgery prior to randomization. Screening procedures that are standard of care at the institution may be completed prior to written informed consent and documented within the 45-day time window.

The following screening procedures will be performed after the ICF is signed (if not standard of care):

- Assess eligibility
- Record medical/surgical history
    - As a general guidance, relevant medical/surgical history within the last 5 years (including all ongoing history, regardless of start date) should be recorded in the electronic CRF (eCRF), with the exception of history that is relevant to the TKA surgery, in which case all years should be recorded.
    - If a site's standard process includes detailed collection of all history (regardless of relevance/age), only the relevant items should be recorded in the eCRF as outlined above; an asterisk or similar indicator can be used in the source documentation to indicate the relevant items that should be included in the eCRF for source data verification purposes.
- Record prior medications (in relationship to medical history)
    - Prior medications taken within 30 days of randomization (including all ongoing medications, regardless of start date) will be recorded in the eCRF.

- Record demographics and baseline characteristics
- Record subject height and weight for BMI calculation
- Assess chronic opioid use in the past 30 days (average ≥30 oral morphine equivalents/day) and any use of marijuana (including THC and CBD) in the past 30 days.
- Conduct urine pregnancy test for women of childbearing potential
- Perform 12-lead EKG
- Record SAEs from the time the ICF is signed
- Record medications for treatment of SAEs

13.2.3. Baseline Procedures (Prior to Study Drug Administration)

- On the day of surgery, before performing any pain assessments, study staff will review the study Pain Rating Guide with the subject.
- On the day of surgery, before administration of the block, the study staff must record responses to the following pain assessments:
    - Pain intensity scores (using the NRS) measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, what was the **worst** pain in your operative knee in the last 30 days?"
    - Pain intensity scores (using the NRS) measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, what was the **average** pain in your operative knee in the last 30 days?"
- Conduct urine pregnancy test for women of childbearing potential
- Conduct urine drug screen
- Vital signs will be measured and recorded after the subject has rested in a supine position for at least 5 minutes
- Record changes to concomitant medications since screening
- Confirm eligibility and randomize subject
- Record AEs/ SAEs
- For Cohort 1 only:
    - Perform sensory function assessments within 15 minutes before block
    - Perform motor function assessment within 15 minutes before block
    - Obtain blood sample for PK assessment within 15 minutes before block

13.3. Nerve Block Procedure

Note: Specific supplies listed below provided by the Sponsor in the study drug administration kits are subject to change based on availability.

13.3.1 Procedures for Adductor Canal Block

A: Placement of ultrasound probe:

- Ensure that the "notch" is positioned on the top left of the ultrasound screen prior to scanning. When scanning, have the notched side of the ultrasound probe facing the anterior side of the thigh (toward the operator).
- With the patient in the supine position, have the subject bend the operative knee slightly and externally rotate the hip.
- Place the ultrasound transducer at the midpoint between the inguinal crease and the superior pole of the patella, and at the midpoint between the anterior point and posterior point of the thigh. Adjust ultrasound depth as needed. The superficial femoral artery should be visible directly beneath the Sartorius muscle (this scanning and probe placement technique will make the top of the ultrasound screen be anatomically "medial" and the bottom of the screen be anatomically "lateral").
- The entry point will be confirmed by locating the point at which the superficial femoral artery is in the middle of the sartorius muscle.
- The sartorius muscle, the superficial femoral artery and the vastus medialis muscle are the primary ultrasound landmarks for the injection.
- The Saphenous nerve is frequently visible as a hyperechoic structure immediately anterior to the superficial femoral artery.
- Both the nerve to vastus medialis (NVM) and the saphenous nerve will be blocked as both provide innervation to the knee joint. The nerves usually lie between the sartorius muscle and the vastus medialis muscle in this scan. The NVM will usually lie more anterior (closer to the needle insertion site and away from the superficial femoral artery and will be encountered first with this needle approach. The NVM is not as readily visible, at times, and is separated from the saphenous nerve by a vasto-adductor membrane.

B: Insertion of needle into adductor canal:

- A 100 mm insulated needle will be used connected to a peripheral nerve stimulator (PNS).
- From an anterior/medial in plane approach, insert the insulated needle within the fascial plane between the vastus medialis muscle and the sartorius muscle (the needle tip will be going toward the superficial femoral artery).
- This approach will first identify and block the NVM with ultrasound and PNS guidance and subsequently approach and block the saphenous nerve after penetrating the vasto-adductor membrane.
- The PNS will be used to help identify both the NVM and the saphenous nerve.
- Before entering the needle insertion site, the PNS should be turned to 2 hertz and 0.5-1,0 mA. With a tone change, ensure a circuit has been created. An acceptable evoked response for the NVM will occur on the medial knee with either potential patellar twitch or distal vastus medialis tendon response. Do not accept direct muscle stimulation if the vastus muscle has been penetrated.

- Once this is accomplished as described, the approach to the saphenous nerve will continue.
- Advance the needle through the vasto-adductor membrane until the tip is just anterior to the superficial femoral artery.
- Use the same nerve stimulator approach as before to elicit saphenous response. This can be paresthesia in the distal medial malleolus or potentially the distal medial knee (infra-patellar branch). Subjects should be asked to report a "tapping" or similar sensation on the medial leg/medial malleolus.
- The injection will occur immediately anterior to the superficial femoral artery, below the sartorius muscle.

C: Saline hydrodissection for fascial plane confirmation:

- Once the NVM or saphenous nerve is identified and after careful aspiration, slowly start the saline injection to visualize the NVM or saphenous nerve so as not to injure it.
- The goal is to confirm needle tip position, and no more than 1-2 mL of saline should be required.
- After saline injection and visual confirmation of the nerve, follow study drug administration as described below (D).

D: Study drug administration:

- Each identified nerve (NVM and saphenous nerve) will receive 10 mL of the study drug.
- Slowly start injecting the 10 mL of study drug around each nerve as visualized during saline injection. This will be a step wise approach as the NVM will be identified first and then the saphenous nerve subsequently.
- Ultrasound video must be captured from the beginning of hydrodissection until the end of study drug administration. The video will be provided to the sponsor within 24 hours from the end of block procedure.
- Record the start and end time of the adductor canal block.

13.4. IPACK Infiltration Procedure

All subjects will receive an IPACK infiltration with 15 mL of 0.25% bupivacaine HCl (37.5 mg) immediately following study drug administration (should be done with the same set-up for the nerve block, prior to surgery). This technique infiltrates local anesthetic in the inter-space between the popliteal artery and the posterior capsule of the knee (IPACK).

- With the patient in the supine position, have the subject bend the operative knee slightly and externally rotate the hip (as done in adductor canal).
- This will be a medial to lateral technique.
- A new 100 mm insulated needle will need to be used.
- A liner ultrasound probe can be used (many use a curvilinear probe) and positioned in the posterior popliteal fossa. Scanning will occur from caudal to cephalad within the fossa.

- An adequate depth will be needed to visual the femur anteriorly to the popliteal artery and popliteal vein.
- From the popliteal fossa, scan cephalad to the popliteal crease where visualization of the femoral condyles can be appreciated anteriorly (or bottom of the ultrasound screen) and the popliteal artery posteriorly (top of ultrasound screen).
- The tibial and peroneal nerves may be appreciated posteriorly (top of the screen) to the popliteal artery and vein (may be compressed).
- Scanning can go slightly more cephalic to the evolution of the femoral shaft (change in bony contour under ultrasound).
- Needle insertion will occur on the medial side of the distal thigh and traverse from medial to lateral along the posterior border of the bony landmark under ultrasound guidance. The insertion position can be measured using the cm markings on the ultrasound screen to make the insertion site more accurate, this in-plane 90-degree approach will optimize needle visualization.
- Infiltration will occur anterior to the popliteal artery posterior to the femur.
- Record date and start/end time of IPACK infiltration.

13.5. Post-Block Assessments and Procedures

The following assessments will be conducted in Cohort 1 subjects only:

- Assess sensory and motor function.
    - Perform sensory/motor function assessments at 15 min (±5 min), 30 min (±5 min), 45 min (±5 min), 1 h (±15 min), 2 h (±30 min), 8 h (±30 min), 12 h (±30 min), 24 h (±1 h), 30 h (±1 h), 48 h (±1 h), 60 h (±2 h), 72 h (±2 h), 84 h (±2 h), 96 h (±3 h), 120 h (±3 h), 144 h (±3 h), and 168 h (±3 h) from the end of the block procedure, or until the sensory/motor function has returned to baseline (pre-dose) levels. The light touch and motor function tests will be rated independently from each other.
- Collect scheduled PK blood samples. These samples will be obtained at 30 min (±5 min), 45 min (±5 min), and 1 h (±15 min), 2 h (±30 min), 8 h (±30 min), 12 h (±30 min), 24 h (±1 h), 30 h (±1 h), 48 h (±1 h), 60 h (±2 h), 72 h (±2 h), 84 h (±2 h), 96 h (±3 h), 120 h (±3 h), 144 h (±3 h), and 168 h (±3 h) hours from end of block procedure (See Table 2).

In both Cohort 1 and Cohort 2 subjects:

- Record AEs/SAEs.
- Record concomitant medications.

13.6. Intraoperative Procedures

- Record date and start/end time of spinal anesthesia.
- Record intraoperative drugs administered and doses.
- Record date and start/end times of surgery.
- Record AEs/ SAEs.

- Record concomitant medications

13.7. Post-Anesthesia Care Unit (PACU) Procedures

- Record date/time of admission to and discharge from the PACU.
- Record AEs/ SAEs.
- Record concomitant medications.
- Record pain intensity scores (using the NRS) measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, how much pain are you experiencing in your operative knee **right now**?" will be assessed:
    - Upon arrival in the Post-anesthesia Care Unit (PACU) (±5 min)
    - Every 15 minutes in the PACU (±5 min)
    - At PACU discharge (±5 min)
- Record an unscheduled pain intensity score (using the NRS) measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, how much pain are you experiencing in your operative knee **right now**?" immediately prior to administration of any breakthrough pain medication.
- Record date, time, and dosage of any breakthrough pain medication.
- Measure and record vital signs as follows:
    - Upon arrival in the PACU (±5 min)
    - At PACU discharge (±5 min)
- For Cohort 1 subjects only (See Table 2):
    - Collect scheduled PK blood sample(s).
    - Perform sensory and motor function assessments.

13.8. Postsurgical Assessments from End of Surgery through Discharge

- Record pain intensity scores (using the NRS) measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, how much pain are you experiencing in your operative knee **right now**?" will be assessed:
    - Every 6 hours from the end of surgery until 96 hours post-surgery: 6 h (±2 h), 12 h (±2 h), 18 h (±2 h), 24 h (±2 h), 30 h (±2 h), 36 h (±2 h), 42 h (±2 h), 48 h (±2 h), 54 h (±2 h), 60 h (±2 h), 66 h (±2 h), 72 h (±2 h), 78 h (±3 h), 84 h (±3 h), 90 h (±3 h), and 96 h (±3 h).
    - If a subject is asleep, the subject will not be awakened to assess pain. If the subject awakens within the assessment window, a pain score will be collected then.
    - Study staff will be instructed not to complete the NRS pain intensity score after any physical activity, including the motor block assessment (for Cohort 1 subjects). If that is not possible, to assess pain intensity at rest, the subject should rest quietly in

a supine or seated position that does not exacerbate subject's postsurgical pain for 5-10 minutes before assessing the pain score using the NRS.

- Record an unscheduled pain intensity score (using the NRS) measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, how much pain are you experiencing in your operative knee **right now**?" immediately prior to administration of any breakthrough pain medication until 96 hours post-surgery.
- Record pain intensity scores (using the NRS) at 24 (±2 h), 48 (±2 h), 72 (±2 h), and 96 (±3 h) post-surgery, measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, what was the **worst** pain in your operative knee in the last 24 hours?"
- Record pain intensity scores (using the NRS) at 24 (±2 h), 48 (±2 h), 72 (±2 h), and 96 (±3 h) post-surgery, measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, what was the **average** pain in your operative knee in the last 24 hours?"
- Record subject's satisfaction with pain management using 1 question from the International Pain Outcome (IPO) questionnaire at 96 hours (±3 h) post-surgery.
- Record AEs/ SAEs.
- Record concomitant medications.
- Record vital signs (i.e., blood pressure, pulse, respiratory rate, oxygen saturation, and body temperature) after the subject has rested in a supine position for at least 5 minutes. See Table 1
- Perform 12-lead EKG. See Table 1
- For Cohort 1 subjects only: (See Table 2):
    - Collect scheduled PK blood sample(s).
    - Perform sensory and motor function assessments.

Postoperatively the subject will progress to full weight bearing as tolerated per the surgeon's standard of care. A walker is recommended for physical therapy until the fall risk is minimized and the subject can transfer and ambulate safely.

13.9. Health Care Facility Discharge

- Subjects in Cohort 1 and Cohort 2 will be discharged after the completion of the 168 h and 96 h assessments, respectively.
- Record date and time of health care facility discharge.

13.10. Unscheduled Visits

- If a sensory or motor function deficit persists on POD 7 (168 h post-surgery), the subject is to return for unscheduled visit(s) at the Investigator's discretion through POD 14 or until the sensory or motor function has returned to baseline, whichever occurs first.
- Record concomitant medications including all analgesic medication.
- Record AEs/SAEs.

13.11. Postsurgical Day 14 Follow-up Phone Call

- Ask the subject about any new AE(s) and the resolution of any ongoing adverse event(s) since discharge. Record any adverse event information.
- Ask the subject about any medication(s) taken since discharge from the health care facility.

14. ADVERSE EVENT REPORTING

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

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

14.1. Adverse Events

14.1.1. Definitions

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 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 administration of the study treatment is considered a treatment-emergent adverse event (TEAE).

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.

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

14.1.2. Recording Adverse Events

It is the responsibility of the Investigator to document all AEs with an onset after the subject is randomized and SAEs with an onset after the subject signs the ICF. For the purpose of this study, all AEs that occur through POD 14 must be recorded regardless of whether or not they are

considered related to study drug. Any AEs occurring after POD 14 only need to be reported if considered related to study drug by Investigator. Whenever feasible, AE terms must be documented as medical diagnoses (highest possible level of integration); otherwise, the AEs must be reported separately as individual signs or symptoms. Only one AE per record should be recorded in the AE CRF; for example, an AE of nausea and vomiting would be listed as two separate events: the event of nausea and the event of vomiting. If a diagnosis is established after symptoms are recorded on the AE CRF, the diagnosis must be recorded, and the symptoms removed. Whenever possible, abnormal laboratory results must be reported as their clinical corollary (e.g., low potassium should be recorded as hypokalemia).

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

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

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

14.1.3. Severity of Adverse Events

In general, the severity of an AE should be categorized using the following guidelines:

Mild: An AE that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

Moderate: An AE that is discomforting and interferes with normal everyday activities.

Severe: An AE that prevents normal everyday activities.

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

14.1.4. Relationship of Adverse Events to Study Drug

The Investigator will assess the relationship of the AE to study drug after careful medical consideration on a case-by-case basis. General guidelines for determining the causality of an AE 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).

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 the 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 the 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).

14.1.7. Adverse Events of Special Interest

Based on review of all peripheral nerve blocks, the following conditions will be considered to be adverse events of special interest upon review of the AEs:

- Fall
- Persistent[1] tingling
- Persistent[1] numbness
- Persistent[1] weakness
- Hypersensitivity
- Seizures
- Tremors
- Dizziness
- Hematoma formation
- Cardiovascular depression
- Dyspnea
- Cardiovascular arrest
- Altered sensorium
- Visual disturbances
- Local anesthetic systemic toxicity (LAST)

[1] **Persistent**: Any conditions (e.g., tingling, numbness, or sensory/motor weakness affecting the nerve block region, after the study drug administration) that persists for greater than 168 hours from the time of onset.

In case an AE of special interest (AESI) or serious AE (SAE) occurs during the study, if the investigator or medical monitor considers that the event may be related to study treatment or suggests the possible occurrence of local anesthetic systemic toxicity (LAST; with or without the need for treatment [e.g., intralipids]), an unscheduled PK blood sample, 12-lead EKG, and vital signs must be collected. Neurological assessments will be conducted according to the study site's standard of care at least once daily until resolution of symptoms.

Investigators, study coordinators, and patient study assessors will be trained on adverse event ascertainment in general, with a special focus directed to signs and symptoms that may represent evidence of systemic toxicity. All AEs of special interest will be managed per standard of care and should be reported to the Medical Monitor and recorded in the database.

14.2. Serious Adverse Events

14.2.1. Definition of a Serious Adverse Event

Serious Adverse Event (SAE): An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death[1]
- A life-threatening adverse event[2]
- Inpatient hospitalization or prolongation of existing hospitalization[3]
- A persistent or significant incapacity[4]
- Congenital anomaly/birth defect[5]
- Medically significant[6]

[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]**Congenital anomaly/birth defect**: Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

[6]**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 Department 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 14, whether or not related to EXPAREL, must be reported by the Investigator or designee to Pacira Drug Safety within 24 hours of discovery by either email (CCI [redacted] and

CCI) or fax (CCI). In addition, the Investigator or designee is encouraged to contact the Medical Monitor to discuss the case, as needed.

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

If the Investigator is made aware of any SAEs after Day 14, 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 and signed off for this study prior to the database lock/unblinding.

15.1. Study Hypothesis

The primary null and alternative hypothesis is:

- H_0: EXPAREL admix arm is not different from bupivacaine HCl arm with respect to the AUC of the NRS pain intensity scores from 0 to 96 hours post-surgery.
- Ha: EXPAREL admix arm is less than bupivacaine HCl arm with respect to the AUC of the NRS pain intensity scores from 0 to 96 hours post-surgery.

15.2. Study Endpoints

The endpoints to be assessed in this study are listed in Section 12.2 (Efficacy Endpoints), Section 12.4 (Safety Endpoints), Section 12.6 (Pharmacokinetic Endpoints), and Section 12.8 (Pharmacodynamic Endpoints).

15.3. Determination of Sample Size

The total sample size for Cohort 1 and Cohort 2 was calculated based on the primary outcome measure of NRS pain intensity scores. A total sample size of 160 subjects (1:1 randomization, 80 EXPAREL admix : 80 Bupivacaine HCl) provides at least 80% power to detect a treatment difference of 80 units in the AUCs (SD=180) comparing EXPAREL admix arm with Bupivacaine HCl arm at one-sided 0.025 significance level.

15.4. Analysis Populations

The following study populations are planned:

- Efficacy population will consist of all randomized subjects who receive the study drug, undergo the planned surgery, and have at least one post-study drug administration NRS pain assessment. All analyses will be based on randomized treatment regardless of actual treatment received.

- Safety population will consist of all randomized subjects who received study drug. All analyses will be based on actual treatment received.
- PK population will consist of all randomized subjects in Cohort 1 who receive study drug and provide sufficient samples to enable calculation of PK parameters.
- PD population will consist of randomized subjects in Cohort 1 who receive study drug and provide sufficient data to allow for calculation of PD parameters required for analysis.

15.5. Handling Subject Dropouts and Discontinuations

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

15.6. Statistical Analyses

Continuous variables will be summarized using descriptive statistics (n [number of subjects contributing data], mean, SD, median, minimum, and maximum). Categorical variables will be tabulated (n and percentage) by category.

15.6.1. Baseline Characteristics

Baseline characteristics will be summarized or tabulated as appropriate.

15.6.2. Efficacy Analyses

All efficacy endpoint analyses will be conducted using the efficacy population.

The primary efficacy analysis endpoint is AUC of NRS pain intensity scores from 0-96 hours post-surgery, and it will be analyzed using ANCOVA model with treatment as a main effect. Additional covariates may be included. EXPAREL admix arm will be compared to Bupivacaine HCl arm. Based on the model, the least squared mean (LSM) difference between EXPAREL admix arm and Bupivacaine HCl arm will be estimated with 95% confidence interval.

Total postsurgical opioid consumption in oral morphine equivalents (OMED) from 0 to 96 hours will be summarized by treatment arm and overall. To test the difference between the EXPAREL admix arm and Bupivacaine HCl arm, an ANCOVA model will be used. Time to first postsurgical opioid medication will be analyzed using the Kaplan-Meier survival method. Worst and average NRS pain intensity scores through 24h, 48h, 72h, and 96h from the end of surgery will be summarized by treatment arm and overall.

Summary statistics (n, mean, median, standard deviation, minimum, maximum) will be shown for each continuous measure of efficacy by treatment arm and overall. Number and percentage of subjects in each category will be shown for each categorical measure of efficacy by treatment arm and overall.

All assessments will be listed in by-subject data listing.

15.6.3. Safety Analyses

All safety analyses will be based on the safety population.

Adverse event verbatim terms will be mapped to preferred terms and related system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). Events that start prior to the start of study drug administration will be identified in a by-subject listing. Incidence rates of TEAEs and the proportion of subjects prematurely withdrawn from the study due to a TEAE will be shown for each treatment arm. Incidence rates will also be displayed for each treatment arm for TEAEs by severity and separately by relationship. If severity of an AE is not reported, then for tables of AEs by severity, the event will be classified as 'Severe' and will be footnoted for the table to indicate this imputation. If relationship to study drug is not reported for an AE, then for tables of study-drug related AEs, the event will be assigned the relationship of 'definite.' Incidence rates of SAEs will also be shown for each treatment arm. All incidence rates will be categorized and displayed by system organ class and preferred term.

15.6.4. Pharmacokinetic Analysis

Pharmacokinetic parameters will be estimated from the PK analysis set, using plasma drug concentration-time profiles, where appropriate, by non-compartmental analysis.

Actual sampling time will be used for all calculations of the PK parameters. If there is any doubt in the actual time a sample was taken, then the scheduled time will be used.

Descriptive statistics will be used to summarize the PK parameters.

15.7. Significance Testing

Unless specified otherwise, all statistical tests will be 1-sided at alpha=0.025 level.

15.8. Interim Analysis

An unblinded interim analysis will occur when a total of approximately 80 subjects (40 in each arm) combined from Cohort 1 and Cohort 2 have enrolled with complete assessment data for the primary efficacy outcome. The efficacy will be evaluated and compared between study arms. Primary purpose of this interim analysis is to evaluate the sample size assumptions and evaluate futility. Full details on the planned or additional interim analysis will be covered in a prospective interim analysis plan.

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17. INVESTIGATOR AGREEMENT

Printed Name of Investigator: _____

Printed Title/Position: _____

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

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

_____ _____

Signature of Investigator Date

18. APPENDICES

18.1. Appendix 1: Pain Intensity Scores using the Numeric Rating Scale (NRS)

Pain intensity will be measured using the 11-point NRS. The study staff will record the subject's pain on a scale of 0 (no pain) to 10 (worst possible pain). Subjects will be instructed to focus all NRS pain intensity ratings on the operative knee, and not other locations where they may be experiencing pain.

- Pain intensity scores (using the NRS) measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, what was the **worst** pain in your operative knee in the last 30 days?" and "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, what was the **average** pain in your operative knee in the last 30 days?" will be assessed at Day of surgery (prior to surgery).
- Pain intensity scores (using the NRS) measured as "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, how much pain are you experiencing in your operative knee **right now**?" will be assessed:
  - Upon arrival in the PACU (±5 min)
  - Every 15 minutes in the PACU (±5 min)
  - At PACU discharge (±5 min)
  - Every 6 hours from the end of surgery until 96 hours post-surgery: 6 h (±2 h), 12 h (±2 h), 18 h (±2 h), 24 h (±2 h), 30 h (±2 h), 36 h (±2 h), 42 h (±2 h), 48 h (±2 h), 54 h (±2 h), 60 h (±2 h), 66 h (±2 h), 72 h (±2 h), 78 h (±3 h), 84 h (±3 h), 90 h (±3 h), and 96 h (±3 h)
  - If a subject is asleep, the subject will not be awakened to assess pain. If the subject awakens within the assessment window, a pain score will be collected then
  - Study staff will be instructed not to complete the NRS pain intensity score after any physical activity, including the motor block assessment (for Cohort 1 subjects). If that is not possible, to assess pain intensity at rest, the subject should rest quietly in a supine or seated position that does not exacerbate his or her postsurgical pain for 5-10 minutes before entering the pain score using the NRS. Subjects will also be required to provide unscheduled pain assessments prior to consumption of any breakthrough pain medication
  - An unscheduled NRS assessment will be obtained immediately prior to administration of any breakthrough pain medication until 96 hours post-surgery
- Pain intensity scores (using the NRS) measured as,

  "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, what was the **worst** pain in your operative knee in the last 24 hours?" and

  "On a scale from 0 to 10, where 0 equals no pain and 10 equals the worst possible pain, what was the **average** pain in your operative knee in the last 24 hours?" will be assessed:

  At 24 (±2 h), 48 (±2 h), 72 (±2 h), and 96 (±3 h) post-surgery.

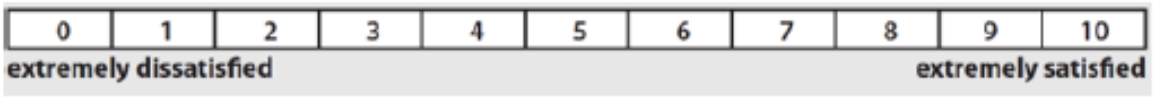
18.2. Appendix 2: Subject's Satisfaction with Pain Management Questionnaire

For the purposes of this study, only 1 question from the International Pain Outcome (IPO) Questionnaire (Rothaug 2013) shall be used. Subject satisfaction will be recorded once 96 hours (±3 h) post-surgery.

Dear Sir/Madam,

Please answer the following questions about your pain control after surgery

Circle the one number that best shows how satisfied you are with the results of your pain treatment since your surgery:



18.3. Appendix 3: Sensory Function Assessment (Light Touch assessment) (Cohort 1 Subjects)

Pharmacodynamic assessments must be performed by blinded, trained, licensed medical staff (e.g., Physician, Registered Nurse, Physician Assistant) and documented on the Investigator's study Delegation Log. A limited number of study staff (blinded to study drug assignment) should perform the sensory/motor assessments.

Sensory assessment for light touch will be performed at pre-dose (up to 15 min before block), 15 min (±5 min), 30 min (±5 min), 45 min (±5 min), 1 h (±15 min), 2 h (±30 min), 8 h (±30 min), 12 h (±30 min), 24 h (±1 h), 30 h (±1 h), 48 h (±1 h), 60 h (±2 h), 72 h (±2 h), 84 h (±2 h), 96 h (±3 h), 120 h (±3 h), 144 h (±3 h), and 168 h (±3 h) from the end of the nerve block procedures, or until full sensory function has returned to baseline (pre-dose) levels. Each light touch area of assessment will be rated independently. Additional unscheduled assessments may be performed, particularly around the surgery, if no onset of block is noted on the last scheduled assessment prior to surgery.

For each sensory assessment performed, both locations mentioned below will be assessed for light touch. If on 168 h assessment there is a sensory deficit, the incident will be recorded as an AE. The physician will assess the subject for other etiologies that may explain the persistent sensory deficit. If the sensory deficit persists on 168 h, the subject is to return for unscheduled visit(s) at the Investigator's discretion until the sensory function has returned.

Sensory function assessment will include the following two locations:

1. Proximal - Medial aspect of the lower leg (3-4 cm below the knee)
2. Distal - Medial aspect of the lower leg (3-4 cm above ankle)

The intent of applying the tongue depressor to the contralateral leg is to establish a reference sensation to compare to the test area. The subject is to determine if the sensation on the contralateral leg is the same as the test area ("Yes" = the same) or if there is a decreased sensation or not the same sensation ("NO" = not the same).

The test may be repeated in case of ambiguous or inconsistent responses until the examiner is satisfied with the accuracy of the assessment. The assessments will be conducted single-blinded (i.e., the subject will be instructed to close their eyes).

After offset of sensory assessments are noted (return of light touch sensation in both test areas in a single assessment), no subsequent assessments will be required.

Tongue Depressor Assessment

The tongue depressor assessment procedures are as follows:

- The subject will be instructed to close their eyes before the application of the wooden tongue depressor.
- Instruct the subject you will be touching the subject on both legs and they will be asked if the touch sensation is the same (YES) or not the same (NO) when comparing each side.

- For the subject's reference, the end of the tongue depressor is dragged over the contralateral assessment area with consistent light touch.
- The end of the tongue depressor is then dragged over the corresponding test assessment area with consistent light touch.
- The subject will be asked if the touch sensation of the tongue depressor is the same (YES) or not the same (NO) when comparing each side.
- Record the subject's response (YES or NO) to the touch sensation in the assessment area.
- Proceed to test the other area as above.

18.4. Appendix 4: Motor Function Assessment (Cohort 1 Subjects)

Pharmacodynamic assessments must be performed by blinded, trained, licensed medical staff (e.g., Physician, Registered Nurse, Physician Assistant) and documented on the Investigator's study Delegation Log. A limited number of study staff (blinded to study drug assignment) should perform the sensory/motor assessments.

Motor function (onset and offset of motor block) will be assessed by active movement of the knee (knee extension). This will be used to determine the duration of the motor blockade.

The motor function test will be performed at pre-dose (up to 15 min before block), 15 min (±5 min), 30 min (±5 min), 45 min (±5 min), 1 h (±15 min), 2 h (±30 min), 8 h (±30 min), 12 h (±30 min), 24 h (±1 h), 30 h (±1 h), 48 h (±1 h), 60 h (±2 h), 72 h (±2 h), 84 h (±2 h), 96 h (±3 h), 120 h (±3 h), 144 h (±3 h), and 168 h (±3 h) from the end of the block procedures, or until motor function has returned to baseline (pre-dose) level. Once the offset of motor block is recorded and documented, no further scheduled motor assessments are required.

Additional unscheduled assessments may be performed, particularly around the surgery, if no onset of block is noted on the last scheduled assessment prior to surgery.

If on 168 h assessment there is a motor function deficit, the incident will be recorded as an AE. The physician will assess the subject for other etiologies that may explain the persistent motor deficit. If the motor deficit persists on 168 h, the subject is to return for unscheduled visit(s) at the Investigator's discretion until the motor function has returned.

The motor block will be evaluated by performing Knee Extension. The following steps should be followed:

1. Position the subject by sitting upright.
2. Instruct the subject to straighten (extend) the knee. Avoid knee hyperextension.

During post-operative period when the subject is unable to sit, knee extension will be tested with the bed in the chair position, or the head of the bed elevated as far as possible. Pillows will be placed under the knee to flex the hip to 90 degrees. The examiner assures that the foot is lifted off the bed when asking the patient to extend the knee.

<u>The level of knee extension will be noted as either:</u>

Knee extension

No knee extension

18.5. Appendix 5: ASA Physical Status Classification System

Last approved by the ASA House of Delegates on October 15, 2014

ASA PS Classification	Definition	Examples, including, but not limited to:
ASA I	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use
ASA II	A patient with mild systemic disease	Mild diseases only without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity (30 < BMI < 40), well-controlled DM/HTN, mild lung disease
ASA III	A patient with severe systemic disease	Substantive functional limitations; One or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant PCA < 60 weeks, history (>3 months) of MI, CVA, TIA, or CAD/stents.
ASA IV	A patient with severe systemic disease that is a constant threat to life	Examples include (but not limited to): recent (< 3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
ASA V	A moribund patient who is not expected to survive without the operation	Examples include (but not limited to): ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	

ARD=acute respiratory distress; ASA=American Society of Anesthesiologists; BMI=body mass index; CAD=coronary artery disease; COPD=chronic obstructive pulmonary disease; CVA=cerebrovascular accident; DIC=disseminated intravascular coagulation; DM=diabetes mellitus; ESRD=end-stage renal disease; HTN=hypertension; MI=myocardial infarction; PCA=postconceptional age; PS=physical status; TIA=transient ischemic attack