Pacira Pharmaceuticals, Inc.

DISCLOSURE: REDACTED CLINICAL STUDY PROTOCOL AMENDMENT 2

Title: A Phase 3, Randomized, Double-Blind, Active-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of EXPAREL vs. Bupivacaine HCl Administered as a Sciatic (in the Popliteal Fossa) Nerve Block for Postsurgical Analgesia in Subjects Undergoing Bunionectomy
NCT Number: NCT05157841
Protocol Number: 402-C-334

Clinical Study Protocol Amendment 2, Approval Date: 24-Feb-2022

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Clinical Study Protocol

Amendment 2

A Phase 3, Randomized, Double-Blind, Active-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of EXPAREL vs. Bupivacaine HCl Administered as a Sciatic (in the Popliteal Fossa) Nerve Block for Postsurgical Analgesia in Subjects Undergoing Bunionectomy

Protocol No.:	402-C-334
EudraCT No.:	Not applicable
IND No.:	069,198
Study Phase:	3
Study Drug:	EXPAREL® (bupivacaine liposome injectable suspension)
Original Protocol Date:	23-Sep-2021
Amendment 1 Date:	22-Oct-2021
Amendment 2 Date:	24-Feb-2022
Study Sites:	Multicenter study in the United States
Sponsor:	Pacira Pharmaceuticals, Inc.

5 Sylvan Way
Parsippany, NJ 07054
Tel: CCI

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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 CCI [redacted]	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 Ingredients: Bupivacaine, 1.3%, 13.3 mg/mL		

Title of Study: A Phase 3, Randomized, Double-Blind, Active-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of EXPAREL vs. Bupivacaine HCl Administered as a Sciatic (in the Popliteal Fossa) Nerve Block for Postsurgical Analgesia in Subjects Undergoing Bunionectomy

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: The study objectives following the administration of study drug as a sciatic (in the popliteal fossa) nerve block in subjects undergoing bunionectomy are listed below.

Primary Objective:

- To compare the magnitude of the postsurgical analgesic effect following a single dose of EXPAREL vs. 0.25% bupivacaine hydrochloride (HCl)

Secondary Objectives:

- To compare the total postsurgical opioid consumption (in oral morphine equivalents) from 0 to 96 hours following a single dose of EXPAREL vs. 0.25% bupivacaine HCl
- To compare the percentage of opioid-free subjects post-surgery through 96 hours following a single dose of EXPAREL vs. 0.25% bupivacaine HCl
- To compare the time to first opioid consumption post-surgery, following a single dose of EXPAREL vs. 0.25% bupivacaine HCl
- To characterize and compare the magnitude of the duration of motor and sensory block following a single dose of EXPAREL vs. 0.25% bupivacaine HCl
- To assess the safety and pharmacokinetic (PK) profile of EXPAREL or 0.25% bupivacaine HCl

Methodology:

This is a Phase 3, multicenter, randomized, double-blind, active controlled study in approximately 180 subjects undergoing bunionectomy. The study will be conducted in two parts (Part A and Part B). Part A will be completed and analyzed before enrollment in Part B is initiated.

Part A (PK, PD, Efficacy, and Safety):

Part A is a 3-arm study: Part A will enroll approximately 60 subjects undergoing bunionectomy to obtain information on PK profile, pharmacodynamics (PD), efficacy, and safety. Subjects will be randomized (1:1:1) to receive a combined sciatic (in the popliteal fossa) nerve block with a single dose of either EXPAREL 266 mg, EXPAREL 133 mg, or 0.25% bupivacaine HCl (50 mg).

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Part B (Efficacy and Safety):
Part B is a 2-arm study: Part B will enroll approximately 120 subjects undergoing bunionectomy to evaluate the efficacy and safety of EXPAREL compared with bupivacaine HCl. Based on the findings of the interim analysis after completion of Part A, the study may stop for futility or proceed to Part B. Part B will continue enrolling with one of the EXPAREL arms (EXPAREL 266 mg arm or EXPAREL 133 mg arm) and the bupivacaine HCl arm. Therefore, the EXPAREL study arm that fails to show efficacy (conditional power less than 30% in the Part A analysis) will be dropped and the study will continue with two study arms. The final analysis will include subjects from both Part A and Part B.

An adaptive study design will be used in this study. An unblinded interim analysis will be conducted by an independent party after completion of Part A enrollment with completed assessment data for the primary efficacy outcome. The conditional power of success for the primary efficacy outcomes comparing each of the two EXPAREL arms (EXPAREL 266 arm and EXPAREL 133 arm) to the bupivacaine HCl arm will be calculated:

1. If the conditional power of one EXPAREL arm is less than 30% and the other EXPAREL arm is greater than or equal to 30%:
   - The EXPAREL arm with conditional power less than 30% will be dropped in Part B.

2. If both EXPAREL arms have a conditional power greater than or equal to 30%:
   - If the conditional power of the 266 mg EXPAREL arm is more than 10% greater than the conditional power of the 133 mg EXPAREL arm, then the 266 mg EXPAREL arm will be kept and the 133 mg EXPAREL arm will be dropped. Otherwise, the 133 mg EXPAREL arm will be kept and the 266 mg EXPAREL arm will be dropped in Part B.

3. If the conditional power of both treatment arms is less than 30%:
   - The study will stop for futility.

Obtaining Informed Consent
Potential subjects undergoing bunionectomy 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 the 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.

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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, 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, 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:

- Pain intensity scores on the numeric rating scale (NRS) 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 foot in the last 30 days?"
- Pain intensity scores on the NRS 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 foot in the last 30 days?"

In addition, the following procedures will be conducted: conduct urine pregnancy test for women of childbearing potential, conduct urine drug screen, 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 Part A only: subjects will also be asked to perform sensory function assessments, perform motor function assessments and obtain PK samples. Sensory and motor function assessments will be conducted by trained blinded study staff.

Treatment Arms for Part A:

On the day of surgery, subjects will receive an ultrasound-guided sciatic (in the popliteal fossa) nerve block with one of the following treatments:

- **EXPAREL 266 arm:** subjects randomized to this treatment arm will receive 20 mL (266 mg) EXPAREL mixed with 10 mL saline
- **EXPAREL 133 arm:** subjects randomized to this treatment arm will receive 10 mL (133 mg) EXPAREL mixed with 20 mL saline
- **Bupivacaine HCl arm:** subjects randomized to this treatment arm will receive 20 mL (50 mg) 0.25% bupivacaine HCl mixed with 10 mL saline

Treatment Arms for Part B:

On the day of surgery, subjects will receive an ultrasound-guided sciatic (in the popliteal fossa) nerve block with one of the following treatments:

- **EXPAREL 266 arm:** subjects randomized to this treatment arm will receive 20 mL (266 mg) EXPAREL mixed with 10 mL saline

  OR

  EXPAREL 133 arm: subjects randomized to this treatment arm will receive 10 mL (133 mg) EXPAREL mixed with 20 mL saline

- **Bupivacaine HCl arm:** subjects randomized to this treatment arm will receive 20 mL (50 mg) 0.25% bupivacaine HCl mixed with 10 mL saline

Block Procedure:

Subjects may be lightly sedated with 1 to 2 mg of midazolam intravenously (IV) before the block procedure. The study drug (EXPAREL 266 mg, EXPAREL 133 mg, or bupivacaine HCl) will be administered under ultrasound guidance 90 min (±30 min) prior to surgery. A confirmatory ultrasound video will be taken during hydrodissection and infiltration of the study drug, with the needle in place to ensure accurate block placement. The Investigator will provide the videos to the sponsor within 24 hours from end of the block procedure that will be reviewed by an independent ultrasound adjudication committee to evaluate the 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.

A peripheral nerve stimulator will be used before infiltrating the study drug to obtain a response (i.e., muscle twitch).

For all study arms, a total volume of 30 mL will be administered as a sciatic nerve block (in the popliteal fossa).

Pre-operative Medication and Anesthesia:
All eligible subjects will also receive the following medication within four hours prior to surgery:

- Celecoxib 200 mg, orally (PO).

Gabapentinoids will not be allowed.

Anesthesia and Intra-operative Medication:
All subjects in Part A and Part B will receive a Mayo field block with 20mL 0.5% bupivacaine HCl after study drug administration (i.e., in the operating room immediately prior to surgical incision). The Mayo field block should be performed by the surgeon.

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. 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 allowed/restricted perioperative medications are included in protocol Section 11.6.1 and Section 11.6.2.

Study Schema:

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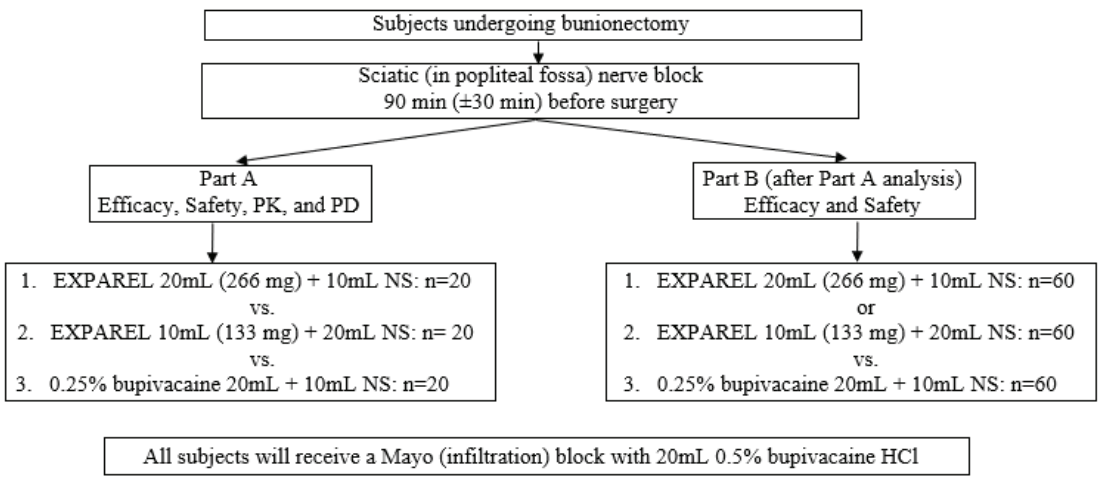
Study Schema



Breakthrough Pain Medication:

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

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.

Medications will be administered on an as needed (PRN) basis; opioids should not be given on a pre-determined schedule.

- Immediate release oral (PO) oxycodone may 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.

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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 postsurgical care.

Post-surgical Assessments:

The post-surgical assessments are as follows: record pain intensity scores (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 foot **right now**?" from the end of surgery to 96 hours post-surgery at the designated timepoints. Additional assessments include: record pain intensity scores on the NRS 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 foot 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 foot in the last 24 hours?" and subject to report satisfaction with pain management questionnaire at 96h. 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 Part A subjects at: 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).
- Additionally, for Part A subjects at: 120 h (±3 h), 144 h (±3 h), and 168 h (±3 h)

For subjects in Part A, assessments will include collection of scheduled PK blood samples. Subjects in Part A will also undergo sensory and motor function assessments. AEs, SAEs, and concomitant medications will be recorded for all subjects.

To mitigate the risk from falls, subjects will be required to be non-weight bearing for at least 2 weeks post-surgery, unless the Investigator determines a limited touch down or partial weight bearing for balance with a walker assist device is more appropriate to reduce the risk of fall.

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.

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Health Care Facility Discharge:
Subjects in Part A and Part B will be discharged after the completion of the 168h and 96h assessments, respectively.

Postoperative Day (POD) 14:
For the assessment of AEs, SAEs, and concomitant medication use, a follow-up phone call will be made on POD 14 (±3 days).

Number of Subjects (Planned): Approximately 180 adult subjects undergoing bunionectomy will be enrolled in the study. Approximately 60 subjects are planned for Part A and will be randomized 1:1:1 to the EXPAREL 266 arm, EXPAREL 133 arm, or bupivacaine HCI arm.

Approximately120 subjects are planned for Part B and will be randomized 1:1 to an EXPAREL arm (either the EXPAREL 266 arm or EXPAREL 133 arm, to be selected based on Part A analysis), or bupivacaine HCI arm.

Eligibility Criteria:

Inclusion Criteria:

1. Male or female, ages 18 or older at screening
2. American Society of Anesthesiologists (ASA) physical status 1, 2, or 3 (see Appendix 5, Section 18.5)
3. Able to provide informed consent, adhere to the study schedule, and complete all study assessments
4. Primary surgical indication is related to a bunion deformity (i.e., hallux valgus) and subject is scheduled to undergo a distal metaphyseal osteotomy procedure (e.g., Austin procedure as opposed to Lapiplasty, Lapidus bunionectomies or base wedge bunionectomies)
5. Indicated to undergo elective (i.e., not emergency) bunionectomy
6. Body Mass Index (BMI) ≥18 and <40 kg/m^2

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. 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 foot surgery and which, in the Investigator's opinion, may confound the post dosing assessments
3. Inadequate sensory function of the foot/ankle as assessed by the Investigator
4. History of, suspected, or known addiction to or abuse of illicit drug(s), prescription medicine(s), or alcohol within the past 2 years

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

5. 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
6. Previous participation in an EXPAREL study
7. Uncontrolled anxiety, schizophrenia, or other psychiatric disorder that, in the opinion of the Investigator, could interfere with study assessments or compliance
8. Currently pregnant, nursing, or planning to become pregnant during the study
9. 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
10. Currently on a neuromodulating agent (e.g., gabapentin, pregabalin [Lyrica], duloxetine [Cymbalta], etc.)
11. Current use of systemic glucocorticoids within 30 days of randomization in this study
12. Use of dexmedetomidine HCl (Precedex®) or clonidine within 3 days of study drug administration
13. 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
14. Chronic opioid use within 30 days prior to randomization (average ≥30 oral morphine equivalents/day)

Given the COVID-19 pandemic, the subject must be medically fit/cleared for surgery by the Investigator. 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 (or other serious illness), the subject must be excluded per *Exclusion criterion #9.*

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 266 arm:** single administration of 20 mL (266 mg) EXPAREL mixed with 10 mL saline
- **EXPAREL 133 arm:** single administration of 10 mL (133 mg) EXPAREL mixed with 20 mL saline

Lot number: To be determined.
Mode of administration: Sciatic (in the popliteal fossa) nerve block

Reference Product, Dose, Mode of Administration, and Lot Number:
Name: 0.25% bupivacaine HCl
Active ingredient: Bupivacaine
Dosage: Single administration of 20 mL (50 mg) 0.25% bupivacaine HCl mixed with 10 mL saline

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

Lot number: To be determined
Mode of administration: Sciatic (in the popliteal fossa) nerve 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 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 foot **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 NRS assessment will be obtained immediately prior to administration of any breakthrough pain medication until 96 hours post-surgery
- Pain intensity using the NRS once daily at 24 (±2 h), 48 (±2 h), 72 (±2 h), and 96 (±3 h) from the end of 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 foot in the last 24 hours?"
- Pain intensity using the NRS once daily at 24 (±2 h), 48 (±2 h), 72 (±2 h), and 96 (±3 h) from the end of 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 foot in the last 24 hours?"

Subjects will be instructed to focus all NRS pain intensity ratings on the operative foot, and not 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 Endpoint:

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

Secondary Endpoints:

- Total postsurgical opioid consumption in oral morphine equivalents (OMED) from 0 to 96 hours post-surgery
- Percentage of opioid-free subjects through 96 hours
- 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.

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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 (Part A Subjects Only):

Blood samples for PK assessment and the sensory/motor function assessments will be assessed at scheduled timepoints (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)
- Apparent volume of distribution (Vd)

Pharmacodynamic Endpoints:

The following pharmacodynamic 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 for Part A and B was calculated based on the primary outcome measure of NRS pain intensity scores. A sample size of 80 subjects per study arm [1:1 randomization, 80 EXPAREL (EXPAREL 266 or EXPAREL 133), 80 Bupivacaine HCl] provides at least 85% power to detect a treatment difference of 110 units in the AUCs (SD=230) comparing the EXPAREL arm with the Bupivacaine HCl arm at a 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.

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.

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

An adaptive study design will be used in this study. An unblinded interim analysis will occur after completion of Part A enrollment with completed assessment data for the primary efficacy outcome. The conditional power of success for the primary efficacy outcome comparing each of the two EXPAREL arms (EXPAREL 266 arm and EXPAREL 133 arm) to the bupivacaine HCl arm will be calculated:

1. If the conditional power of one EXPAREL arm is less than 30% and the other EXPAREL arm is greater than or equal to 30%:
   - The EXPAREL arm with conditional power less than 30% will be dropped in Part B.

2. If both EXPAREL arms have a conditional power greater than or equal to 30%:
   - If the conditional power of the 266 mg EXPAREL arm is more than 10% greater than the conditional power of the 133 mg EXPAREL arm, then the 266 mg EXPAREL arm will be kept and the 133 mg EXPAREL arm will be dropped. Otherwise, the 133 mg EXPAREL arm will be kept and the 266 mg EXPAREL arm will be dropped in Part B.

3. If the conditional power of both treatment arms is less than 30%:
   - The study will stop for futility.

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

	Screening Visit[1]	Day of Surgery (Prior to Surgery)	OR	PACU	Time from End of Surgery (h)																	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	120-168 ±3[2]		
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 pre-op and post-op scheduled medications[7]		X	◄	- - -	- - -	►																	
Capture ultrasound video for nerve block and send to sponsor		X																					
Administer Mayo field block			X																				
Record block start/end times[8]		X	X																				
Record surgery start and end times			X																				
Record intra-op medication administered			X																				
Record PACU time in and out				X																			

					Time from End of Surgery (h)																		
	Screen-ing Visit[1]	**Day of Surgery (Prior to Surgery)**	**OR**	**PACU**	**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 **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	X	
Record scheduled ***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]		◄- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - - ►
Subject 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; PO=by mouth/orally administered; 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 day the 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 Part A subjects only: A 12-lead EKG will be performed, and Vital sign will be measured and recorded at additional time points 120 (±3h), 144 (±3h), and at 168 (±3h).
3. Subjects in Part A and Part B will be discharged after 168 h and 96 h assessments, respectively.
4. Eligibility, prior medications, 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 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. Record all pre-operative and post-operative scheduled analgesic medication (celecoxib and acetaminophen).
8. Block to be administered 90 min (±30 min) prior to surgery.
9. The NRS pain intensity assessment should not be completed after any physical activity, including the motor block assessment. 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 h 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 Part A 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 (Part A 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

AE	Adverse event
ANOVA	Analysis of variance
ASA	American Society of Anesthesiologists
AUC	Area Under the Curve
BMI	Body mass index
C_{max}	Maximum plasma concentration
CBD	Cannabidiol
CFR	Code of Federal Regulations
CL/F	Apparent clearance
CRF	Case report form
d	Day
eCRF	Electronic case report form
ED	Emergency Department
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCF	Health care facility
HCl	Hydrochloride
h	Hour(s)
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IPO	International Pain Outcome
IRB	Institutional Review Board
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numeric rating scale
NSAIDs	Nonsteroidal anti-inflammatory drugs
OMED	Oral morphine equivalent
OR	Operating room
PACU	Post-anesthesia care unit
PD	Pharmacodynamic
PK	Pharmacokinetic
PO	Oral
POD	Post-operative day
PRN	As needed
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard Deviation
$t_{1/2el}$	Apparent terminal elimination half-life
T_{max}	Time to maximum plasma concentration
TEAE	Treatment-emergent adverse event

THC	Tetrahydrocannabinol
US	United States
Vd	Apparent volume of distribution

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 Council for Harmonisation (ICH) Good Clinical Practice (GCP) and/or the United States (US) Food and Drug Administration (FDA) Title 21 Code of Federal Regulations (CFR) Part 56. 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, study sites, laboratories, and other service providers is available upon request to the IRB/IECs 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 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 for the Study

Pacira is investigating the pharmacokinetics (PK), efficacy, and safety of EXPAREL administered as a sciatic (in the popliteal fossa) nerve block in adult subjects undergoing bunionectomy.

A dose of 20 mL (266 mg) EXPAREL with 10 mL of saline or a dose of 10 mL (133 mg) EXPAREL with 20 mL saline is expected to provide prolonged pain relief after this painful procedure compared with 20 mL (50mg) 0.25% bupivacaine HCl with 10 mL saline when injected in the sciatic nerve (in the popliteal fossa).

8. OBJECTIVES

The study objectives following the administration of study drug as a sciatic (in the popliteal fossa) nerve block in subjects undergoing bunionectomy are listed below.

8.1. Primary Objective

To compare the magnitude of the postsurgical analgesic effect following a single dose of EXPAREL vs. 0.25% bupivacaine HCl.

8.2. Secondary Objectives

- To compare the total postsurgical opioid consumption (in oral morphine equivalents) from 0 to 96 hours following a single dose of EXPAREL vs. 0.25% bupivacaine HCl
- To compare the percentage of opioid-free subjects post-surgery through 96 hours following a single dose of EXPAREL vs. 0.25% bupivacaine HCl
- To compare the time to first opioid consumption post-surgery, following a single dose of EXPAREL vs. 0.25% bupivacaine HCl
- To characterize and compare the magnitude of the duration of motor and sensory block following a single dose of EXPAREL vs. 0.25% bupivacaine HCl
- To assess the safety and pharmacokinetic (PK) profile of EXPAREL or 0.25% 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 180 subjects undergoing bunionectomy. The study will be conducted in two parts (i.e., Part A and Part B). All subjects in Part A and Part B will receive a Mayo field block with 20mL 0.5% bupivacaine HCl after study drug administration (i.e., in the operating room immediately prior to surgical incision).

Part A (Efficacy, Safety, PK, and PD):

Part A will enroll approximately 60 subjects undergoing bunionectomy to obtain information on PK profile, pharmacodynamics (PD), efficacy, and safety. Subjects will be randomized (1:1:1) to receive a combined sciatic (in the popliteal fossa) nerve block with EXPAREL 266 mg, EXPAREL 133 mg, or 0.25% bupivacaine HCl.

Part B (Efficacy and Safety):

Part B will enroll approximately 120 subjects undergoing bunionectomy to evaluate the efficacy and safety of EXPAREL compared with bupivacaine HCl. Based on the findings of the interim analysis after completion of Part A, the study may stop for futility or proceed to Part B. Part B will continue enrolling with one of the EXPAREL study arms and the bupivacaine HCl study arm.

Therefore, the EXPAREL study arm that fails to show efficacy (conditional power less than 30%) will be dropped and the study will continue with two study arms. The final analysis will include subjects from both Part A and Part B.

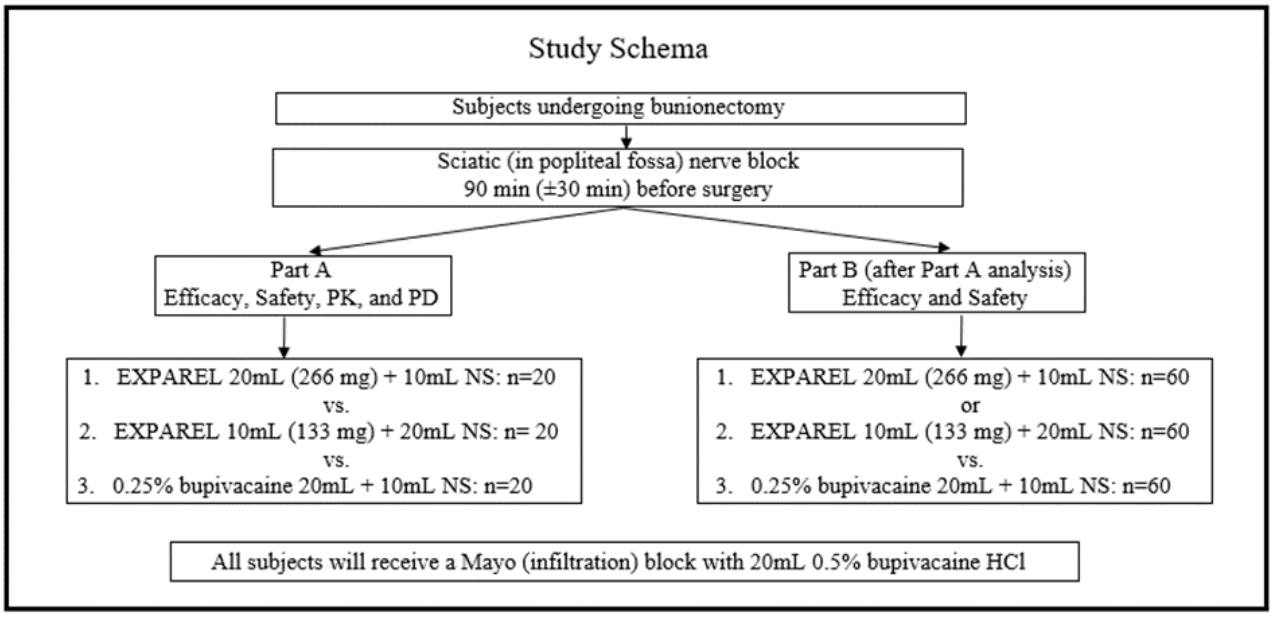
An adaptive study design will be used in this study. An unblinded interim analysis will be conducted by an independent party after completion of Part A enrollment with completed assessment data for the primary efficacy outcome. The conditional power of success for the primary efficacy outcomes comparing each of the two EXPAREL arms (EXPAREL 266 arm and EXPAREL 133 arm) to the bupivacaine HCl arm will be calculated:

1. If the conditional power of one EXPAREL arm is less than 30% and the other EXPAREL arm is greater than or equal to 30%:
   - The EXPAREL arm with conditional power less than 30% will be dropped in Part B.

2. If both EXPAREL arms have a conditional power greater than or equal to 30%:
   - If the conditional power of the 266 mg EXPAREL arm is more than 10% greater than the conditional power of the 133 mg EXPAREL arm, then the 266 mg EXPAREL arm will be kept and the 133 mg EXPAREL arm will be dropped. Otherwise, the 133 mg EXPAREL arm will be kept and the 266 mg EXPAREL arm will be dropped in Part B.

3. If the conditional power of both treatment arms is less than 30%:
   - The study will stop for futility.

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 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 Post-operative Day (POD) 14 (±3 days). Therefore, each subject may participate in the study for up to a maximum of 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 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.

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.

This trial design also includes efficacy stopping rules using group sequential design stopping rules as described in Section 15.8.

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

9.3. Discussion of Study Design

This Phase 3, multicenter, randomized, double-blind, active-controlled study will enroll approximately 180 subjects to evaluate the efficacy and safety of EXPAREL and 0.25% bupivacaine HCl when administered as a sciatic (in the popliteal fossa) nerve block in subjects undergoing bunionectomy. The study will be conducted in two parts (i.e., Part A and Part B).

Only Part A subjects (60 subjects) will provide blood samples for PK assessments and will be assessed for PD. Subjects will provide information on efficacy and safety of 20 mL EXPAREL (266 mg) mixed with 10 mL saline, 10 mL (133 mg) EXPAREL mixed with 20 mL saline, and 20 mL (50 mg) 0.25% bupivacaine HCl mixed with 10 mL saline.

Part B will assess the efficacy and safety of 20 mL EXPAREL (266 mg) mixed with 10 mL saline or 10 mL (133 mg) EXPAREL mixed with 20 mL saline, and 20 mL (50 mg) 0.25% bupivacaine HCl mixed with 10 mL saline in 120 subjects undergoing bunionectomy.

The three treatment arms of the study for Part A are as follows:

- **EXPAREL 266 arm:** subjects randomized to this treatment arm will receive 20 mL (266 mg) EXPAREL mixed with 10 mL saline.

- **EXPAREL 133 arm:** subjects randomized to this treatment arm will receive 10 mL (133 mg) EXPAREL mixed with 20 mL saline.
- **Bupivacaine HCl arm:** subjects randomized to this treatment arm will receive 20 mL (50 mg) 0.25% bupivacaine HCl mixed with 10mL saline.

The two treatment arms of the study for Part B are as follows:

- **EXPAREL 266 arm:** subjects randomized to this treatment arm will receive 20 mL (266 mg) EXPAREL mixed with 10 mL saline.

  OR

  EXPAREL 133 arm: subjects randomized to this treatment arm will receive 10 mL (133 mg) EXPAREL mixed with 20 mL saline.
- **Bupivacaine HCl arm:** subjects randomized to this treatment arm will receive 20 mL (50 mg) 0.25% bupivacaine HCl mixed with 10mL saline.

For all arms, a total volume of 30 mL will be administered as a sciatic nerve block (in the popliteal fossa).

10. STUDY POPULATION

Approximately 180 adult subjects undergoing bunionectomy 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. American Society of Anesthesiologists (ASA) physical status 1, 2, or 3 (see Appendix 5, Section 18.5)
3. Able to provide informed consent, adhere to the study schedule, and complete all study assessments
4. Primary surgical indication is related to a bunion deformity (i.e., hallux valgus) and subject is scheduled to undergo a distal metaphyseal osteotomy procedure (e.g., Austin procedure as opposed to Lapiplasty, Lapidus bunionectomies or base wedge bunionectomies)
5. Indicated to undergo elective (i.e., not emergency) bunionectomy
6. Body Mass Index (BMI) ≥18 and <40 kg/m^2

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. 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 foot surgery and which, in the Investigator's opinion, may confound the post dosing assessments
3. Inadequate sensory function of the foot/ankle as assessed by the Investigator.
4. History of, suspected, or known addiction to or abuse of illicit drug(s), prescription medicine(s), or alcohol within the past 2 years
5. 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
6. Previous participation in an EXPAREL study
7. Uncontrolled anxiety, schizophrenia, or other psychiatric disorder that, in the opinion of the Investigator, could interfere with study assessments or compliance
8. Currently pregnant, nursing, or planning to become pregnant during the study
9. 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
10. Currently on a neuromodulating agent (e.g., gabapentin, pregabalin [Lyrica], duloxetine [Cymbalta], etc.)
11. Current use of systemic glucocorticoids within 30 days of randomization in this study
12. Use of dexmedetomidine HCl (Precedex®) or clonidine within 3 days of study drug administration
13. 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
14. Chronic opioid use within 30 days prior to randomization (average ≥30 oral morphine equivalents/day)

Given the COVID-19 pandemic, the subject must be medically fit/cleared for surgery by the Investigator. 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 (or other serious illness), the subject must be excluded per *Exclusion criterion #9.*

10.3. Removal of Subjects from Therapy or Assessment

Every reasonable effort will 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 withdraws from the study and has an ongoing AE, every effort must be made to follow up on 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 early termination 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., sciatic [in the popliteal fossa] nerve 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 through POD 14.

10.3.3. Early Termination Assessments

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

- Record date, time, and reason of withdrawal
- Review adverse events; any ongoing AEs/SAEs will need to be followed to resolution
- Record responses to pain assessment:
  - Pain intensity scores on 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 foot **right now**?"
  - Pain intensity scores on the NRS 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 foot in the last 24 hours?"
  - Pain intensity scores on the NRS 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 foot in the last 24 hours?"

11. TREATMENTS

11.1. Treatments to be Administered

Treatment Arms for Part A:

Part A is a 3-arm study. On the day of surgery, subjects will receive an ultrasound-guided sciatic (in the popliteal fossa) nerve block with one of the following treatments:

- **EXPAREL 266 arm:** subjects randomized to this treatment arm will receive 20 mL (266 mg) EXPAREL mixed with 10 mL saline
- **EXPAREL 133 arm:** subjects randomized to this treatment arm will receive 10 mL (133 mg) EXPAREL mixed with 20 mL saline
- **Bupivacaine HCl arm:** subjects randomized to this treatment arm will receive 20 mL (50 mg) 0.25% bupivacaine HCl mixed with 10 mL saline

Treatment Arms for Part B:

Part B is a 2-arm study. On the day of surgery, subjects will receive an ultrasound-guided sciatic (in the popliteal fossa) nerve block with one of the following treatments:

- **EXPAREL 266 arm:** subjects randomized to this treatment arm will receive 20 mL (266 mg) EXPAREL mixed with 10 mL saline

  OR

  EXPAREL 133 arm: subjects randomized to this treatment arm will receive 10 mL (133 mg) EXPAREL mixed with 20 mL saline
- **Bupivacaine HCl arm:** subjects randomized to this treatment arm will receive 20 mL (50 mg) 0.25% bupivacaine HCl mixed with 10 mL saline

Block Procedure:

Subjects may be lightly sedated with 1 to 2 mg of midazolam IV before the block procedure. The study drug (EXPAREL or 0.25% bupivacaine HCl) will be administered under ultrasound guidance 90 min (±30 min) prior to surgery. A confirmatory ultrasound video will be taken during hydrodissection and infiltration of the study drug, with the needle in place to ensure accurate block placement. The Investigator will provide the videos to the sponsor within 24 hours from end of the block procedure that will be reviewed by an independent ultrasound adjudication committee to evaluate the 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.

A peripheral nerve stimulator will be used before infiltrating the study drug to obtain a response (i.e., muscle twitch).

For all arms, the total volume (30 mL) will be administered as the sciatic (in the popliteal fossa) nerve block.

11.1.1. Study Drug Administration Considerations

As described in the EXPAREL Full Prescribing Information (March 2021), no agents are to be admixed with EXPAREL (e.g., epinephrine, dexamethasone, clonidine) 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.

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, invert and re-invert vials of EXPAREL multiple times to re-suspend the particles immediately prior to withdrawal from the vial. Similarly, gently inverting and re-inverting the syringe prior to administration is recommended.

The maximum dosage of EXPAREL should not exceed 266 mg.

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 a 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 the 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 is 0.25% bupivacaine HCl administered via a sciatic (in the popliteal fossa) nerve block.

11.2.3. Description of Volume Expansion Agent

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

11.3. Method of Assigning Subjects to Treatment

11.3.1. Randomization Scheme

This is a randomized study. Subjects in Part A will enroll approximately 60 total subjects undergoing bunionectomy randomized 1:1:1 in the EXPAREL 266 arm, EXPAREL 133 arm and bupivacaine HCl arm.

Part B will enroll approximately 120 total subjects undergoing bunionectomy, 60 subjects in each treatment arm; EXPAREL 266 or EXPAREL 133 arm, and the bupivacaine HCl arm. 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

Once a subject is identified as being qualified for the study in accordance with the eligibility criteria (see Section 10.1 and Section 10.2), the Investigator or designee will obtain a randomization assignment on the day of surgery. The subject will be considered randomized into the study once the study treatment is assigned.

11.3.3. Replacement of Subjects

Subjects who withdraw from the study before receiving study drug may be replaced. Once a subject number is 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 the 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 the bupivacaine HCl arm. Pacira would like to evaluate and compare efficacy and safety along with PK concentrations of EXPAREL 266 mg, EXPAREL 133 mg, and bupivacaine HCl 50 mg to determine the most appropriate (efficacious and safe) dose for the current study population.

11.5. Blinding

11.5.1. Unblinding Procedures

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.

11.5.2. Blinding Procedure

EXPAREL and 0.25% 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 block. The site PI must be blinded to the study drug and will not be involved in and/or present during study drug administration.

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 member will receive unblinded randomization assignments; the designated unblinded pharmacist or administrator will be responsible for preparing 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 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.

11.6. 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 arm by Anatomic Therapeutic Chemical class and preferred terms.

11.6.1. Prior to Study Drug Administration

<u>All subjects will receive the following medications within 4 hours prior to surgery:</u>

- Celecoxib 200 mg (PO)

<u>Other permitted Prior Medications and Therapy:</u>

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

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

- 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) or 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 product within 30 days or 5 elimination half-lives of such investigational drug, whichever is longer, prior to study drug administration, or planned administration of another investigational product or procedure during the subject's participation in this study is not permitted.
- No drugs (other than the described bupivacaine HCl admixture) are to be admixed with study drug (e.g., epinephrine, dexamethasone, clonidine).
- Lidocaine and other local anesthetics will not be permitted to be locally administered 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 a Mayo field block with 20 mL 0.5% bupivacaine HCl after study drug administration (i.e., in the operating room immediately prior to surgical incision). The Mayo field block should be performed by the surgeon.

All subjects will receive a dose of 1000 mg of intravenous (IV) acetaminophen at the time of surgical incision.

Other Permitted Medications:

- Single-dose administration of ondansetron or metoclopramide may be used intra-operatively for nausea/vomiting prevention.
- Propofol is permitted for induction and intra-operative sedation.

Restricted Medications:

- General anesthesia and opioid sedation are not permitted. Neuraxial or regional anesthesia technique (except the investigational related blocks) are not permitted.
- Intraoperative use of opioids (except fentanyl, not to exceed 1 ug/kg unless deemed medically necessary) and ketamine will not be permitted.
- 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.

- Lidocaine and other local anesthetics will not be permitted to be locally administered in the area of the nerve block administration.

11.6.3. Post-surgery

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.

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.
- Patient Controlled Analgesia is not permitted.
- Dexmedetomidine HCl (Precedex) use is prohibited.
- 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.
- 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 foot **right now**?") must be completed immediately prior to administration of any breakthrough pain medication up to 96 hours post-surgery.

Medications will be administered on an as needed basis; opioids should not be given on a pre-determined schedule.

- Immediate release PO oxycodone may 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, must be recorded through hospital discharge.

11.8. Treatment Compliance

Study drug (EXPAREL 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 study drug 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 study 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 foot **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: 6h (±2h), 12h (±2h), 18h (±2h), 24h (±2h), 30h (±2h), 36h (±2h), 42h (±2h), 48h (±2h), 54h (±2h), 60h (±2h), 66h (±2h), 72h (±2h), 78h (±3h), 84h (±3h), 90h (±3h), and 96h (±3h)

- An unscheduled NRS assessment will be obtained immediately prior to administration of any breakthrough pain medication until 96 hours post-surgery.
- Pain intensity using the NRS once daily at 24h, 48h, 72h, and 96h 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 foot in the last 24 hours?"
- Pain intensity using the NRS once daily at 24h, 48h, 72h, and 96h 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 foot in the last 24 hours?"

  Subjects will be instructed to focus all NRS pain intensity ratings on the operative foot, 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 (±3h) post-surgery.

12.2. Efficacy Endpoints

Primary Endpoint:

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

Secondary Endpoints:

- Total postsurgical opioid consumption in oral morphine equivalents (OMED) from 0 to 96 hours post-surgery
- Percentage of opioid-free subjects through 96 hours
- 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.

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 and SAEs from the start of block procedure through POD 14

12.5. Pharmacokinetic Assessments (Part A Subjects)

Blood samples for PK assessment will be obtained from Part A subjects. A total of 17 PK samples will be collected for each subject. These samples will be obtained at pre-dose (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), 12h (±30 min), 24h (±1h), 30h (±1h), 48h (±1h), 60h (±2h), 72h (±2h), 84h (±2h), 96h (±3h), 120h (±3h), 144h (±3h), and 168h (±3h) hours from end of block procedure. (See Table 2).

12.6. Pharmacokinetic Endpoints (Part A Subjects)

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 (Part A 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 should perform the sensory/motor assessments.

Assessment of sensory function (Light Touch Assessment):

Sensory function will be assessed using a tongue depressor to evaluate light touch. Sensory function will assessed 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 procedure, or until full sensory function has returned to baseline (pre-block) levels (see Appendix 3, Section 18.4). 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 sensory assessment, both locations identified below will be assessed for light touch. If on the 168h 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 168h, 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 - Lateral aspect of the lower leg (3-4 cm above ankle)
2. Distal - Sole of the foot

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 voluntary active movement of the foot. This will be used to determine the onset and duration of 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), 1h (±15 min), 2h (±30 min), 8h (±30 min), 12h (±30 min), 24h (±1h), 30h (±1h), 48h (±1h), 60h (±2h), 72 h (±2h), 84h (±2h), 96h (±3h), 120h (±3h), 144h (±3h), and 168h (±3h) from end of block procedure, or until full motor function has returned to pre-dose levels (see Appendix 4, Section 18.3). 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.

Onset of motor block will be defined as the earliest timepoint with partial or no foot movement.

Offset of motor block will be defined as resolution of the motor block with complete foot movement. 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 (see Appendix 4, Section 18.3).

12.8. Pharmacodynamic Endpoints (Part A Subjects)

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

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 after the sciatic (in the popliteal fossa) nerve 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 as applicable, vital signs, 12-lead EKG.

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 on 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 foot **right now**?" will be assessed:
  - Upon arrival in the PACU (±5 min)
  - Every 15 mins in the PACU (±5 min)
  - Prior to PACU discharge (±5 min)
  - Every 6 hours from the end of surgery until 96 hours: 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. 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 using the NRS at 24 (±2h), 48 (±2h), 72 (±2h), and 96 (±3h) 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 foot in the last 24 hours?"
- Pain intensity using the NRS at 24 (±2h), 48 (±2h), 72 (±2h), and 96 (±3h) 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 foot in the last 24 hours?"

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

13.1.2. Subject Satisfaction with Postsurgical Pain Control

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. (see Appendix 2, Section 18.2).

13.1.3. Pharmacokinetic Assessments (Part A Subjects)

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

13.1.4. Pharmacodynamic assessment (Part A Subjects)

Onset and duration of sensory block will be assessed using the light touch assessment to characterize the sensory block (see Appendix 4, Section 18.3).

Onset and duration of motor block will be assessed using the movement of the foot to characterize the motor block (see Appendix 3, Section 18.4).

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.

13.2. Study Procedures

13.2.1. Obtaining Informed Consent

Potential subjects undergoing bunionectomy 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 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 the day of surgery but eligibility should be re-confirmed on the day of surgery. 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. Any screening procedures that are not standard of care must be completed after written informed consent is provided and prior to randomization.

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 bunionectomy, 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
    - 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)
- Assess marijuana (including THC or CBD) use 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 Investigator/study staff must record responses to the following pain assessments:
  - Pain intensity scores on the NRS 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 foot in the last 30 days?"
  - Pain intensity scores on the NRS 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 foot 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
- Instruct the subjects on duties and responsibilities for assessment completion
- Part A subjects:
  - Perform sensory function assessment (pre-dose (up to 15 min before block))
  - Perform motor function assessment pre-dose (up to 15 min before block))
  - Obtain blood sample for PK assessment within 15 minutes before block

13.3. Nerve Block Procedure

- Subjects may be lightly sedated with 1 to 2 mg of IV midazolam before the block procedure.
- Disinfect the area where the block will be administered
- Administer study drug as a sciatic (in the popliteal fossa) nerve block using ultrasound and nerve stimulator 90 min (±30 min) prior to surgery (unblinded staff only with shielding of the subject's vision of the study drug syringe)
- Record start and end times of study drug administration
- Record concomitant medications
- Record AEs/ SAEs
- Ultrasound video must be captured from the beginning of hydrodissection until the end of study drug administration. Send ultrasound video to study sponsor within 24 hours from the end of 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 Sciatic (in the Popliteal Fossa) Nerve Block

A: Placement of ultrasound probe:

- Position the patient supine with the leg placed on an elevated footrest or lateral (operative side up). Using a linear probe, place the ultrasound probe in the popliteal fossa, 3 to 5 cm above the popliteal crease in the transverse orientation.
- Start scanning within the popliteal fossa to identify the popliteal artery and vein. The tibial nerve will lie posterior to the vascular structures (i.e., popliteal artery and vein).
- Start scanning where the sciatic nerve splits into the peroneal and tibial nerves but still enclosed in the connective tissue sheath (perineural sheath).

B: Insertion of needle into perineural sheath:

- Use a 100 mm, insulated needle connected to a nerve stimulator, initially set at 0.8-1.0 mA.
- Needle insertion will occur on the lateral thigh using an in-plane needle approach from lateral to medial.
- The needle should be advanced in plane until the needle tip has pierced the sciatic nerve sheath (perineural sheath).
- Once the needle has pierced the surrounding sheath, an appropriate motor response with peripheral nerve stimulation at 0.8- 1.0 mA should be obtained (Dorsiflexion or eversion for the peroneal nerve and plantar flexion or inversion for the tibial nerve is expected).

Note: The goal is to split the injectate equally between the two nerves using motor stimulation as a guide.

C: Saline hydrodissection for fascial plane confirmation:

Once the perineural sheath has been penetrated by the needle, use saline (1-2 mL) to confirm needle placement.

D: Study drug administration:

Inject 30 mL of the study drug admixture in the sheath, between the peroneal and tibial nerves.

13.4. Post-Block Assessments

The following assessments will be conducted in Part A subjects only:

- Assess sensory and motor function (onset and offset of block)
  - Perform sensory/motor function assessments at 15 min (±5 min), 30 min (±5 min), 45 min (±5 min), 1h (±15 min), 2h (±30 min), 8h (±30 min), 12h (±30

min), 24h (±1h), 30 h (±1h), 48h (±1h), 60h (±2h), 72h (±2h), 84h (±2h), 96h (±3h), 120h (±3h), 144h (±3h), and 168h (±3h) from the end of the block procedure, or until full sensory/motor function has returned to pre-dose levels after one evaluation. 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), 1h (±15 min), 2h (±30 min), 8h (±30 min), 12 h (±30 min), 24h (±1h), 30h (±1h), 48h (±1h), 60h (±2h), 72h (±2h), 84h (±2h), 96h (±3h), 120h (±3h), 144h (±3h), and 168h (±3h) from end of block procedure. (See Table 2).

For all study subjects:

- Record AEs/ SAEs
- Record concomitant medications

13.5. Mayo Field Block Procedure

- Position the patient supine (the leg may be placed on an elevated footrest)
- Disinfect the area where the block will be administered as is standard for the facility
- Administer Mayo field block prior to surgery in the operating room
- Record start and end times of administration
- Record AEs/ SAEs

13.5.1. Procedures for Mayo Field Block

- Raise a skin wheal proximally and dorsally in the first intermetatarsal space
- Advance the needle in the dorsomedial to plantar-medial direction injecting 3-5 mL of 0.5% bupivacaine HCl
- Advance the needle in the dorsomedial to dorso-lateral direction injecting 3-5 mL of 0.5% bupivacaine HCl
- Advance the needle in the dorsolateral to plantar-lateral direction injecting 3-5 mL of 0.5% bupivacaine HCl
- Advance the needle in the plantar-medial to plantar-lateral direction injecting 3-5 mL of 0.5% bupivacaine HCl
- The block should encircle the entire metatarsal bone

13.6. Intraoperative Procedures

- Record type of sedation
- 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 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 foot **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 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 foot **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 Part A subjects only:
  - 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 (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 foot **right now**?" from the end of surgery to 96 hours post-surgery as follows:
  - Every 6 hours from the end of surgery to 96-hour post-surgery, i.e., 6h (±2h), 12h (±2h), 18h (±2h), 24h (±2h), 30h (±2h), 36h (±2h), 42h (±2h), 48h (±2h), 54h (±2h), 60h (±2h), 66h (±2h), 72h (±2h), 78h (±3h), 84h (±3h), 90h (±3h), and 96h (±3h).
  - 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. 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.

- 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 foot **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 foot 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 foot 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 Part A subjects only:
  - Collect scheduled PK blood sample(s).
  - Perform sensory and motor function assessments.

To mitigate the risk from falls, subjects will be required to be non-weight bearing for at least 2 weeks post-surgery, unless the Investigator determines a limited touch down or partial weight bearing for balance with a walker assist device is more appropriate to reduce the risk of fall.

13.9. Health Care Facility Discharge

- Subjects in Part A who undergo PK analysis, sensory and motor function assessments will be discharged after the completion of the 168h assessments. Subjects in Part B will be discharged after the completion of the 96h assessments.
- Record date and time of health care facility discharge.

13.10. Unscheduled Visits

- If a sensory or motor function deficit persists on POD 7 (168h 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 Phone Call

- Ask the subject about any new AEs, SAEs and the resolution of any ongoing adverse event(s) since discharge. Record any adverse event information.
- Ask the subject about any concomitant 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, AEs and SAEs are defined in Section 14.1.1 and Section 14.2.1, respectively.

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

14.1. Adverse Events

14.1.1. Definitions

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

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

An AE that occurs after the administration of the study treatment is considered a treatment-emergent adverse event (TEAE).

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

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

14.1.2. Recording Adverse Events

It is the responsibility of the Investigator to document all AEs 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); however, the event itself, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based

on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

14.1.4. Relationship of Adverse Events to Study Drug

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

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

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

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

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

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)

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:

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

[1]**Persistent**: Any condition (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

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

- Death[1]
- A life-threatening AE[2]
- Inpatient hospitalization or prolongation of existing hospitalization[3]
- A persistent or significant incapacity[4]
- Congenital anomaly/birth defect[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 must make every effort to obtain and document the cause of death for all subjects who die during the study. If, despite all efforts, the cause of death remains unknown, the AE must be documented as an "unspecified fatal event."

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

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

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

[5]**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 room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

14.2.2. Reporting Serious Adverse Events

Any SAE or death that occurs at any time after the subject signs the ICF through POD 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 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 must be followed by a full written summary using the SAE Form detailing relevant aspects of the SAE in question. Where applicable, information from relevant hospital records and autopsy reports must be obtained and all 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 Postsurgical Day 14, these must also be reported to Pacira Drug Safety or designee provided the SAE is considered related to EXPAREL. The site would then provide a completed SAE form within 1 business day and the event would be followed until resolution, or until adequate stabilization is met.

15. STATISTICAL METHODS

A comprehensive statistical analysis plan (SAP) will be finalized for this study prior to database lock.

15.1. Study Hypothesis

The primary null hypothesis is:

H0: The AUC of the NRS pain intensity scores from 0 to 96 hours post-surgery in the EXPAREL arm is equal or higher compared to that of the bupivacaine HCl arm.

The alternative hypothesis is:

HA: The AUC of the NRS pain intensity scores from 0 to 96 hours post-surgery for the EXPAREL arm is less than that of the bupivacaine HCl arm.

EXPAREL arm denotes either EXPAREL 266 arm or EXPAREL 133 arm, to be selected based on Part A analysis.

15.2. Study Endpoints

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

15.3. Determination of Sample Size

The total sample size for Part A and B was calculated based on the primary outcome measure of NRS pain intensity scores. A sample size of 80 subjects per study arm (1:1 randomization, 80 EXPAREL, 80 Bupivacaine HCl) provides at least 85% power to detect a treatment difference of 110 units in the AUCs (SD=230) comparing EXPAREL arm with Bupivacaine HCl arm at one-sided 0.025 significance level.

An adaptive study design will be used in this study. An unblinded interim analysis will occur after completion of Part A enrollment with completed assessment data for the primary efficacy outcome. The conditional power of success for the primary efficacy outcomes comparing each of the two EXPAREL arms (EXPAREL 266 arm and EXPAREL 133 arm) to the bupivacaine HCl arm will be calculated:

1. If the conditional power of one EXPAREL arm is less than 30% and the other EXPAREL arm is greater than or equal to 30%:
   - The EXPAREL arm with conditional power less than 30% will be dropped in Part B.
2. If both EXPAREL arms have a conditional power greater than or equal to 30%:
   - If the conditional power of the 266 mg EXPAREL arm is more than 10% greater than the conditional power of the 133 mg EXPAREL arm, then the 266 mg EXPAREL arm will be kept and the 133 mg EXPAREL arm will be dropped. Otherwise, the 133 mg EXPAREL arm will be kept and the 266 mg EXPAREL arm will be dropped in Part B.
3. If the conditional power of both treatment arms is less than 30%:
   - The study will stop for futility.

15.4. Analysis Populations

The following analysis sets are planned:

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

Efficacy: The efficacy analysis set will include 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.

Pharmacokinetic: The pharmacokinetic analysis set will include all subjects in Part A who receive study drug and who provide sufficient samples to allow for calculation of PK parameters required for analysis.

Pharmacodynamic: The pharmacodynamics analysis set will include all subjects in Part A who receive study drug and who 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

15.6.1. Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment arm.

Baseline is defined as the last non-missing assessment of a given assessment prior to the first dose of the trial drug unless otherwise specified.

15.6.2. Study Procedure Compliance

In each analysis set, the percentage and number of subjects who were screened and the percentage and number of subjects who failed to complete the study, including reasons for discontinuation, will be displayed by treatment arm.

15.6.3. Efficacy Analyses

All efficacy analyses will be based on the efficacy analysis set and will be analyzed according to the randomized treatment.

The primary efficacy analysis endpoints are AUC of NRS pain intensity scores from 0-96 hours post-surgery, and they will be analyzed using ANCOVA model with treatment as a main effect. Additional covariates may be included. Each of the EXPAREL group will be compared to Bupivacaine HCl group. Based on the model, the least squared mean (LSM) difference between each of the EXPAREL groups and bupivacaine HCl group will be estimated with two-sided 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 each of the EXPAREL group and Bupivacaine HCl group, 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 presented in by-subject data listings.

15.6.4. Safety Analyses

All safety analyses will be based on actual treatment received.

15.6.4.1. Pharmacokinetic Analyses

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.

15.6.4.2. Adverse Events

Adverse event verbatim terms will be mapped to preferred terms and related system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). Events that start prior to the start of study drug administration will be identified in a by-subject listings. Incidence rates of TEAEs and the proportion of subject 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.

15.7. Significance Testing

All tests will be either one-sided on a significance level of 0.025 or two-sided on a significance level of 0.05.

15.8. Interim Analyses

An unblinded interim analysis will occur after completion of Part A enrollment with completed assessment data for the primary efficacy outcome. Efficacy will be evaluated and compared between study arms. Based on the findings of the interim analysis, the study may stop for futility or proceed to Part B.

The conditional power of success for the primary efficacy outcomes comparing each of the two EXPAREL arms (EXPAREL 266 arm and EXPAREL 133 arm) to the bupivacaine HCl arm will be calculated:

1. If the conditional power of one EXPAREL arm is less than 30% and the other EXPAREL arm is greater than or equal to 30%:
    - The EXPAREL arm with conditional power less than 30% will be dropped in Part B.

2. If both EXPAREL arms have a conditional power greater than or equal to 30%:
    - If the conditional power of the 266 mg EXPAREL arm is more than 10% greater than the conditional power of the 133 mg EXPAREL arm, then the 266 mg EXPAREL arm will be kept and the 133 mg EXPAREL arm will be dropped. Otherwise, the 133 mg EXPAREL arm will be kept and the 266 mg EXPAREL arm will be dropped in Part B.
3. If the conditional power of both treatment arms is less than 30%:
    - The study will stop for futility.

Full details on the interim analysis will be covered in a prospective interim analysis plan.

16. REFERENCES

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

_____ _____

Signature of Investigator Date

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 subject will be asked to rate their worst or average pain on a scale of 0 (no pain) - 10 (worst possible pain).

- Pain intensity 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 foot 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 foot in the last 30 days?" will be assessed at Baseline/Day of surgery
- Pain intensity 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 foot **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: 6h (±2h), 12h (±2h), 18h (±2h), 24h (±2h), 30h (±2h), 36h (±2h), 42h (±2h), 48h (±2h), 54h (±2h), 60h (±2h), 66h (±2h), 72h (±2h), 78h (±3h), 84h (±3h), 90h (±3h), and 96h (±3h)
  - 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 the subject has completed any physical activity, including the motor block assessment. 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.
  - An unscheduled NRS assessment will be obtained immediately prior to administration of any breakthrough pain medication until 96 hours post-surgery
- Pain intensity 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 foot 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 foot in the last 24 hours?" will be assessed on the Day of surgery (prior to surgery):
  - At 24h (±2h), 48h (±2h), 72h (±2h), and 96h (±3h) post-surgery.

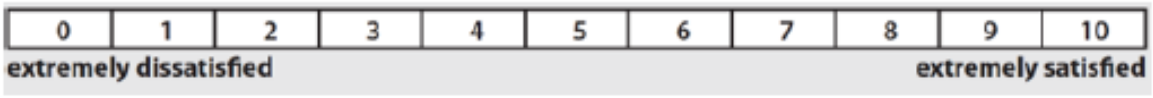
18.2. Appendix 2: Subject Satisfaction Questionnaire

For the purposes of this study, only 1 question from the International Pain Outcome (IPO) Questionnaire (Rothaug 2013) will 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 Test) (Part A 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.

For the sensory function assessment, the subject's sensitivity to light touch in the distal part of innervated dermatomes of the sciatic nerve will be assessed with their eyes closed using a tongue depressor. Sensory function will assessed at pre-dose (up to 15 min before block), 15 min (±5 min), 30 min (±5 min), 45 min (±5 min), 1h (±15 min), 2h (±30 min), 8h (±30 min), 12h (±30 min), 24h (±1h), 30h (±1h), 48h (±1h), 60h (±2h), 72h (±2h), 84h (±2h), 96h (±3h), 120h (±3h), 144h (±3h), and 168h (±3h) from the end of the nerve block procedure, or until full sensory function has returned to baseline (pre-block) 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 sensory assessment, both locations identified below will be assessed for light touch. If on the 168h 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 168h, 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 - Lateral aspect of the lower leg (3-4 cm above ankle)
2. Distal - Sole of the foot

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 Test (Part A 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 foot. 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), 1h (±15 min), 2h (±30 min), 8h (±30 min), 12h (±30 min), 24h (±1h), 30h (±1h), 48h (±1h), 60h (±2h), 72h (±2h), 84h (±2h), 96h (±3h), 120h (±3h), 144h (±3h), and 168h (±3h) from the end of the block procedures, or until full motor function has returned to pre-dose levels after one evaluation.

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.

Motor Function Test

The motor function test procedures are as follows:

- The subject will be supine and asked to flex and extend the foot of the study leg.
- The level of foot movement will be noted as either:
  - partial or no foot movement
  - complete foot movement

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