Clinical Study Protocol

A Phase 3, Randomized, Double Blinded, Active Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of EXPAREL, EXPAREL admixed with Bupivacaine HCl vs. Bupivacaine HCl Administered as Combined Sciatic (in popliteal fossa) and Saphenous (in adductor canal) Nerve Blocks for Postsurgical Analgesia in Subjects Undergoing Lower Extremity Surgeries

Protocol No.: 402-C-333
EudraCT No.: Not applicable
IND No.: 069,198
Study Phase: 3
Study Drug: EXPAREL® (bupivacaine liposome injectable suspension)

Original Protocol Date: July 28, 2020
Amendment 1: November 06, 2020

Study Sites: Multicenter study in USA
Sponsor: Pacira Pharmaceuticals, Inc.
5 Sylvan Way
Parsippany, NJ 07054
Tel: (973) 254-3560

1. SIGNATURE PAGE

DocuSigned by:
Donald Manning
Signer Name: Donald Manning
Signing Reason: I approve this document
Signing Time: 06-Nov-2020 | 12:05:45 PM EST
E092D856DC394A9B80AB96BC2794DF0F

06-Nov-2020

Donald C. Manning, MD, PhD
Chief Medical Officer

Date

DocuSigned by:
Gary Nevins
Signer Name: Gary Nevins
Signing Reason: I approve this document
Signing Time: 06-Nov-2020 | 11:05:56 AM EST
558D44F13780486C86D569374F58CB46

06-Nov-2020

Gary Nevins, DC
Executive Medical Director, Clinical Research

Date

DocuSigned by:
Kimberly Hebert
Signer Name: Kimberly Hebert
Signing Reason: I approve this document
Signing Time: 06-Nov-2020 | 11:11:18 AM EST
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06-Nov-2020

Kimberly Hebert
Executive Director, Clinical Operations

Date

DocuSigned by:
Vincent Yu
Signer Name: Vincent Yu
Signing Reason: I approve this document
Signing Time: 06-Nov-2020 | 7:20:21 AM PST
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06-Nov-2020

Vincent Yu, PhD
Vice President, Biometrics

Date

DocuSigned by:
Michael Rozycki
Signer Name: Michael Rozycki
Signing Reason: I approve this document
Signing Time: 06-Nov-2020 | 8:58:06 AM PST
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06-Nov-2020

Michael Rozycki, PhD
Senior Vice President, Regulatory Affairs

Date

2. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Pacira Pharmaceuticals, Inc.
5 Sylvan Way
Parsippany, NJ 07054
(973) 254-3560</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
Volume:
Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Products:
EXPAREL® (bupivacaine liposome injectable suspension)</td></tr>
<tr><td>Name of Active Ingredients:
Bupivacaine, 1.3%, 13.3 mg/mL</td></tr>
<tr><td colspan="3">Title of Study: A Phase 3, Randomized, Double Blinded, Active Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of EXPAREL, EXPAREL admixed with Bupivacaine HCl vs. Bupivacaine HCl Administered as Combined Sciatic (in popliteal fossa) and Saphenous (in adductor canal) Nerve Blocks for Postsurgical Analgesia in Subjects Undergoing Lower Extremity Surgeries</td></tr>
<tr><td colspan="3">Principal investigators: TBD</td></tr>
<tr><td colspan="3">Study Center(s): Multicenter study in the United States (US)</td></tr>
<tr><td colspan="3">Publications (Reference): None</td></tr>
<tr><td colspan="3">Objectives: The study objectives following the administration of study drug as a combined sciatic (in the popliteal fossa) and saphenous (in the adductor canal) nerve blocks in subjects undergoing lower extremity surgeries are listed below.
<u>Primary Objective</u>:
• To compare the magnitude of the analgesic effect following a single dose injection of EXPAREL vs. 0.25% bupivacaine hydrochloride (HCl)
<u>Secondary Objectives</u>:
• To compare the total opioid consumption (in oral morphine equivalents) from 0 to 96 hours following a single dose injection of EXPAREL vs. 0.25% bupivacaine HCl
• To compare the time to first opioid consumption following a single dose injection of EXPAREL vs. 0.25% bupivacaine HCl
• To characterize and compare the magnitude of the analgesic effect following a single dose injection of EXPAREL vs. EXPAREL admixed with 0.25% bupivacaine HCl
• To characterize and compare the magnitude of the duration of motor block following a single dose injection of EXPAREL vs. EXPAREL admixed with 0.25% bupivacaine HCl
• To assess the efficacy, safety, and pharmacokinetic (PK) profile of EXPAREL; EXPAREL admixed with 0.25% bupivacaine HCl and/or 0.25% bupivacaine HCl</td></tr>
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Methodology:
This is a Phase 3, multicenter, randomized, double-blind, active controlled, 3-arm study in approximately 120 subjects undergoing lower extremity surgeries. The study will have 2 cohorts. Both cohorts will enroll in parallel.

Cohort 1 will enroll about 60 subjects undergoing bunionectomy to obtain information on PK profile, pharmacodynamics (PD), efficacy, and safety. Subjects in this cohort will be randomized (1:1:1) to receive combined sciatic (in the popliteal fossa) and saphenous (in the adductor canal) nerve blocks with EXPAREL, EXPAREL admixed with 0.25% bupivacaine HCl, or 0.25% bupivacaine HCl. Only select sites will enroll subjects for Cohort 1.

Cohort 2 will enroll about 60 subjects to obtain information on efficacy and safety. Subjects in this cohort will receive combined sciatic (in the popliteal fossa) and saphenous (in the adductor canal) nerve blocks. Subjects will be randomized (1:1:1) to receive EXPAREL, EXPAREL admixed with 0.25% bupivacaine HCl, or 0.25% bupivacaine HCl, and will be stratified by each surgery grouping.

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

An adaptive study design will be used in this study. For efficacy, an interim analysis will occur when a total of approximately 60 subjects combined from either Cohort 1 or Cohort 2 have enrolled and provided complete assessment data for their primary efficacy outcome.

Obtaining Informed Consent
Potential subjects undergoing one of the eligible surgeries will be approached by the investigator and/or the study staff for informed consent up to 30 days before the surgery. Subject 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 the questions answered by the investigator/study staff prior to providing informed consent.

Screening
Subjects may be screened up to 30 days prior to day of surgery but eligibility should be re-confirmed on 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 30-day time window. Any screening procedures that are not standard of care, must be completed after written informed consent is provided and prior to surgery.

The following screening procedures should be performed after the ICF is signed: explain study purpose and procedures, assess eligibility, record medical/surgical history, record prior and concomitant medications, record demographics and baseline characteristics including Pain Catastrophizing Scale (PCS), 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, record adverse events (AEs)/serious adverse events (SAEs) starting when the ICF is signed and record concomitant medications for treatment of AEs.

Day of Surgery
On the day of surgery, before administration of the block, the subject must record responses to the following pain assessments:

- Pain intensity scores on the numeric rating scale (NRS) as "What was your worst pain in the last 30 days?"
- Pain intensity scores (using the NRS) "What was your average pain in the last 30 days?"

In addition, the following procedures will be conducted: conduct urine pregnancy test for women of childbearing potential, record changes to concomitant medications since screening, confirm eligibility and

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randomize subject, record AEs/ SAEs and any treatment(s) for the events, and provide e-diary and instruct the subjects on duties and responsibilities for assessment completion. For Cohort 1 only, the following procedures are conducted: perform sensory function assessment, perform motor function assessment and obtain PK samples.

Cohort 1: PK, PD, Efficacy, and Safety

The participants enrolled in Cohort 1 will provide blood samples for PK and measures for efficacy and safety. About 60 subjects undergoing bunionectomy will be enrolled in this cohort. On the day of surgery, eligible subjects will be randomized (1:1:1) to receive EXPAREL (n=20), EXPAREL admixed with 0.25% bupivacaine HCl (n=20), or bupivacaine HCl (n=20) as a combined sciatic (in the popliteal fossa) and saphenous (in the adductor canal) nerve blocks.

Cohort 2: Efficacy and Safety

The participants enrolled in Cohort 2 will provide measures for efficacy and safety. About 60 subjects will be enrolled in this cohort. On day of surgery, eligible subjects will be randomized 1:1:1 to receive EXPAREL (n=20), EXPAREL admixed with 0.25% bupivacaine HCl (n=20), or bupivacaine HCl (n=20). All subjects will receive combined sciatic (in the popliteal fossa) and saphenous (in the adductor canal) nerve blocks, by stratifying by each surgery grouping.

Treatments for Cohort 1 and Cohort 2

On the day of surgery, Cohort 1 and 2 subjects will receive ultrasound-guided combined sciatic (in popliteal fossa) and adductor canal nerve block with one of the following treatments:

- **EXPAREL arm:** subjects randomized to this treatment arm will receive 20 mL (266 mg) EXPAREL mixed with 20 mL saline
- **EXPAREL admix arm:** subjects randomized to this treatment arm will receive 20 mL (266 mg) EXPAREL admixed with 20 mL (50 mg) 0.25% bupivacaine HCl
- **Bupivacaine HCl arm:** subjects randomized to this treatment arm will receive 40 mL (100 mg) 0.25% bupivacaine HCl

Block procedure:

Subjects may be lightly sedated with 1 to 2 mg of midazolam intravenously (IV) before the block procedure. The study drug (EXPAREL, EXPAREL admixed with 0.25% bupivacaine HCl, or bupivacaine HCl) will be administered under ultrasound guidance 90 min (±30 min) prior to surgery.

For all arms, the total volume (40 mL) will be split such that 20 mL will be administered as the sciatic nerve block (in popliteal fossa) and 20 mL will be administered as the saphenous nerve block (in the adductor canal).

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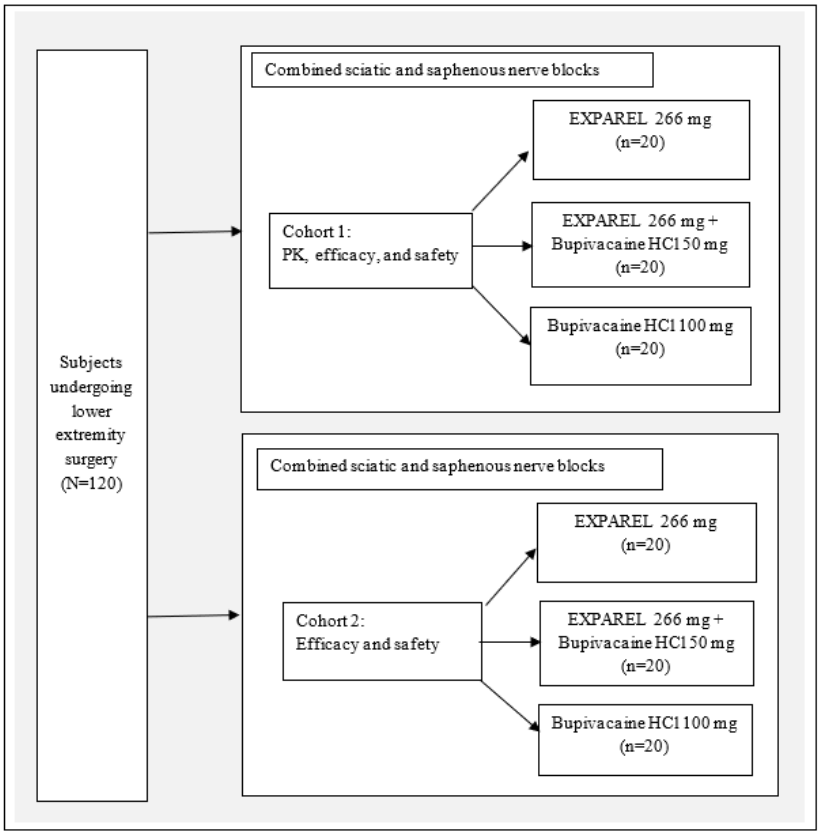
Study Schema:



Note: Cohort 1 will enroll bunionectomy subjects only.

Breakthrough Pain Medication:

All opioid and other analgesics (pain medications) administered post-surgery through Post-operative Day (POD) 14 should be recorded.

Medications will be provided on an as needed (PRN) basis in relation to the breakthrough pain intensity. The intent is to use the guide below in a step-wise approach; acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) should be used for the initial treatment of post-surgical pain and escalation to opioids (and subsequent increased dose of opioids) should be implemented if the initial pain treatment (and initial opioid dose) is insufficient for pain relief. Opioids should not be the first choice for pain relief unless clinically indicated in the opinion of the investigator and should not be given on a schedule.

- For the initial treatment of post-surgical pain, subjects may receive either acetaminophen or NSAIDs without exceeding the maximum daily dose.

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- If the initial pain treatment (acetaminophen or NSAIDs) is insufficient for pain relief, 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, 10 mg oxycodone may be offered.
- 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.

Post discharge, the subject may be provided with a prescription for oxycodone 5 mg. The subject may take acetaminophen, NSAIDs, or the prescribed oxycodone and will be given instructions on which medication to take PRN based on their pain intensity.

Post-surgical Assessments:

The post-surgical assessments are as follows: record pain intensity scores (NRS) (see Appendix 1, Section 18.1) measured as "How much pain are you experiencing right now?" from the end of surgery to 96 hours post-surgery at the designated timepoints. Additional assessments include: record pain intensity scores (NRS) measured as "What was your worst pain in the last 24 hours?" and "What was your average pain in the last 24 hours?" and subject to record satisfaction with pain management questionnaire. For Cohort 1 only, assessments include: collect scheduled PK blood samples, perform sensory and motor function assessments, record AEs/ SAEs and record concomitant medications.

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.

Health Care Facility Discharge:

Subjects in Cohort 1 and Cohort 2 will be discharged after the completion of the 168 h and 96 h assessments, respectively. Record date and time of health care facility discharge. Re-instruct on duties and responsibilities with the e-diary and for breakthrough medications.

Number of Subjects (Planned): Approximately 120 adult subjects undergoing lower extremity surgeries will be enrolled for the study. The surgeries that can be included in the study are: bunionectomy, 1st metatarsophalangeal fusion, specific forefoot surgeries (Weil osteotomy, Clayton-Hoffman procedures only), midfoot fusion, hindfoot fusion, and total ankle arthroplasty.

Eligibility Criteria:

At screening, the subject should satisfy the following inclusion and exclusion criteria:

Inclusion Criteria:

1. Healthy adult male or female volunteers ages 18 or older
2. American Society of Anesthesiologists (ASA) physical status 1, 2, or 3 (see Appendix 6, Section 18.6)
3. Able to provide informed consent, adhere to the study schedule, and complete all study assessments
4. Body Mass Index (BMI) ≥18 and ≤40 kg/m^2

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Exclusion Criteria:

1. Allergy, hypersensitivity, intolerance, or contraindication to any of the study medications for which an alternative is not named in the protocol (e.g., amide-type local anesthetics, opioids, bupivacaine HCl, NSAIDs)
2. Concurrent painful physical condition that may require analgesic treatment (such as long-term, consistent use of opioids) in the post dosing period for pain and which, in the investigator's opinion, may confound the post dosing assessments
3. History of, suspected, or known addiction to or abuse of illicit drug(s), prescription medicine(s), or alcohol within the past 2 years
4. 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
5. Previous participation in an EXPAREL study
6. Uncontrolled anxiety, schizophrenia, or other psychiatric disorder that, in the opinion of the investigator, could interfere with study assessments or compliance
7. Currently pregnant, nursing, or planning to become pregnant during the study
8. 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
9. Currently on a neuromodulating agent (e.g., gabapentin, pregabalin [Lyrica], duloxetine [Cymbalta], etc.)]
10. Inadequate sensory function on the foot (monofilament test)
11. Chronic opioid use within 30 days prior to randomization (average ≥30 oral morphine equivalents/day)

Test Product, Dose, Mode of Administration, and Lot Number: Name: EXPAREL (bupivacaine liposome injectable suspension)
Active ingredient: Bupivacaine
Dosage:

- **EXPAREL arm:** single administration of 20 mL (266 mg) EXPAREL mixed with 20 mL saline
- **EXPAREL admix arm:** single administration of 20 mL (266 mg) EXPAREL admixed with 20 mL (50 mg) 0.25% bupivacaine HCl

Lot number: To be determined.
Mode of administration: Combined sciatic (in popliteal fossa) and saphenous (adductor canal) nerve blocks

Reference Product, Dose, Mode of Administration, and Lot Number:
Name: 0.25% bupivacaine HCl
Active ingredient: Bupivacaine
Dosage: Single administration of 40 mL (100 mg) 0.25% bupivacaine HCl
Lot number: To be determined
Mode of administration: Combined sciatic (in popliteal fossa) and saphenous (in adductor canal) nerve blocks

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Duration of Subject Participation in Study:

Participation will begin upon signing of the ICF. No more than 30 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 47 days.

Efficacy Assessments:

- Pain intensity measured using the NRS as "How much pain are you experiencing 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 21:00 (±3 h) from POD 1 to POD 14 measured as "What was your **worst** pain in the last 24 hours?"
- Pain intensity using the NRS once daily at 21:00 (±3 h) from POD 1 to POD 14 measured as "What was your **average** pain in the last 24 hours?"

Subjects will be instructed to focus all NRS pain intensity ratings on the operative ankle/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 comparing EXPAREL to 0.25% bupivacaine HCl

Secondary Endpoints:

- Total postsurgical opioid consumption in oral morphine equivalents (OMED) from 0 to 96 hours post-surgery comparing EXPAREL to 0.25% bupivacaine HCl
- Time to first opioid consumption comparing EXPAREL to 0.25% bupivacaine HCl
- The AUC of the NRS pain intensity scores from 0 to 96 hours post-surgery comparing EXPAREL to EXPAREL admixed with 0.25% bupivacaine HCl
- The duration of the motor block EXPAREL to EXPAREL admixed with 0.25% bupivacaine HCl

Safety Assessments:

- Adverse events (AEs) and SAEs will be recorded from the time of informed consent through POD 14

Safety Endpoint:

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

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Pharmacokinetic and Pharmacodynamic Assessments (Cohort 1 bunionectomy subjects only):

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

Pharmacokinetic Endpoint:

The following model-predicted 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 Endpoint:

The following pharmacodynamics endpoints will be determined:

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

Statistical Methods:

A comprehensive statistical analysis plan (SAP) will be finalized for this study prior to database lock. Demographic and baseline characteristics will be summarized descriptively by treatment group for all subjects who receive study drug. Efficacy and safety endpoint analyses will be described in the SAP.

Efficacy data will be analyzed by randomized treatment group. Superiority of treatment with EXPAREL compared with bupivacaine HCl will be determined using analysis of variance (ANOVA) with treatment as main effect for the primary efficacy endpoint of AUC of the NRS pain intensity scores from 0 to 96 hours post-surgery. Additional factors such as site or surgery type may be included to adjust the model if deemed necessary. Other efficacy endpoints will be analyzed using ANOVA, logistic regression model, chi-square tests, and Kaplan-Meier and log-rank tests, as appropriate.

Safety and pharmacokinetic endpoints will be summarized descriptively by actual treatment received

Determination of Sample Size:

The sample size was calculated based on the primary efficacy endpoint of the AUC of the NRS pain intensity scores from 0 through 96 hours post-surgery comparing EXPAREL to bupivacaine HCl.

The sample size for Cohort 1 was based on the number of subjects necessary to characterize the PK following administration.

Cohort 1 and Cohort 2 subjects will be combined within treatment groups for the efficacy and safety analyses; therefore, the overall sample size was based on the primary efficacy endpoint of the AUC of the NRS pain intensity scores from 0 through 96 hours post-surgery. Assuming a 2-sided 0.05 alpha, common standard deviation (SD) of 170 a sample size of 40 subjects for EXPAREL and 40 subjects for bupivacaine HCl should

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have at least 90% power to detect a true difference of 150-units in the AUCs. Therefore, since Cohort 1 will have 60 subjects (20 EXAPREL, 20 EXPAREL admixed with bupivacaine HCl and 20 bupivacaine HCl), Cohort 2 will need to enroll 60 subjects (20 EXAPREL, 20 EXPAREL admixed with bupivacaine HCl and 20 bupivacaine HCl) to meet the total requirements.

An efficacy interim analysis will occur when approximately 60 subjects have enrolled and provided complete data for the primary efficacy outcome.

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

	Screen-ing Visit[1]	Day of Surgery Prior to Nerve Block	OR	PACU	Time from End of Surgery (h)																Health Care Facility Dis-charge[2]	PO D 14 Call ±3 days
					6 ±2	12 ±2	18 ±2	24 ±2	30 ±2	36 ±2	42 ±2	48 ±2	54 ±2	60 ±2	66 ±2	72 ±2	78 ±3	84 ±3	90 ±3	96 ±3		
Obtain ICF*	X																					
Assess/confirm eligibility *	X	X																				
Record medical/ surgical history*	X																					
Collect height/weight for BMI calculation*	X																					
Demographics and baseline characteristics*	X																					
Administer Pain Catastrophizing Scale	X																					
Record prior and concomitant medications	X	X	◄																			►
Provide e-diary and explain expectations		X[3]																				
Urine pregnancy test for WOCBP[4]	X	X[3]																				
Record *worst* and *average* pain (NRS) in the last 30 days		X[3]																				
Randomize subject; prepare study drug.		X																				
Record block start/end times[5]		X																				
Record surgery start and end times			X																			
Record intra-op medication administered			X																			
Record PACU time in and out				X																		
Record **scheduled** NRS scores[6,7]				X[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

	Screen-ing Visit[1]	Day of Surgery Prior to Nerve Block	OR	PACU	Time from End of Surgery (h)																Health Care Facility Dis-charge[2]	PO D 14 Call ±3 days
					6 ±2	12 ±2	18 ±2	24 ±2	30 ±2	36 ±2	42 ±2	48 ±2	54 ±2	60 ±2	66 ±2	72 ±2	78 ±3	84 ±3	90 ±3	96 ±3		
Subject records ***worst*** and ***average*** NRS scores daily at 21:00 (±3 h) POD 1-14[6,7]								◄	-	-	-	-	-	-	-	-	-	-	-	-	-	►
Record **unscheduled** NRS immediately prior to breakthrough pain medication[7,8,9]				◄	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	►		
Record date, time, dose of breakthrough pain medication[8,9]				◄	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	►
Record day and time of HCF admission and discharge[1]		X																			X	
Record AEs/SAEs	◄	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	►
Remind subject to return e-diary																						X
Subject to record subject satisfaction questionnaire																				X		

Abbreviations: AE=adverse event; BMI=Body Mass Index; D=day; ED=Emergency Department; 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 30 days before scheduled surgery day

1. Subjects may be screened on the same day as health care facility admission/surgery or up to 30 days prior to surgery but eligibility should be re-confirmed on day of surgery and ample time must be allowed for the informed consent process. 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. Subjects in Cohort 1 and Cohort 2 will be discharged after 168 h and 96 h assessments, respectively. At discharge, subject should be re-instructed on duties with the e-diary.
3. Provision of e-diary to subject, urine pregnancy test, and score of worst and average pain score over the previous 30 days to be assessed prior to study drug administration. The diary may be activated during the screening period in order to perform set-up and training, but no data entry may occur in the e-diary before the day of surgery.
4. Pregnancy test should be re-confirmed on the day of surgery prior to study drug administration.
5. Block to be administered 90 min (±30 min) prior to surgery.
6. 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. This assessment should not be completed immediately following physical activity.

7. Pain scores (24 h recall) once daily (i.e., worst/average pain) will be collected at 21:00 (±3 hours) from POD 1 to POD 14. Pain scores (current pain) will be collected 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.
8. Breakthrough pain medication will be provided on a PRN basis in relation to the breakthrough pain intensity. Opioids should not be the first choice for pain relief, unless clinically indicated in the opinion of the Investigator, and should not be given on a schedule.
9. For the initial treatment of post-surgical pain, subjects may receive acetaminophen or NSAIDs without exceeding the maximum daily dose. If the initial pain treatment (acetaminophen or NSAIDs) is insufficient for pain relief, immediate release PO oxycodone may be offered in a stepwise approach: initial dose of 5 mg oxycodone will be offered; if the initial opioid dose is insufficient for pain relief, 10 mg oxycodone may be offered. 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.

Table 2: Pharmacokinetic and Pharmacodynamic Assessments (Cohort 1 bunionectomy 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	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess and record sensory and motor function[b,c]	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. Once offset of sensory and motor block are determined (in two consecutive evaluations), no subsequent assessments will be conducted. Sensory and motor are assessed independently.
c. When subject is in surgery, no sensory or motor block assessments 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
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
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
PCS	Pain catastrophizing scale
PD	Pharmacodynamic
PK	Pharmacokinetic
PO	Oral
POD	Post-operative day
PRN	As needed
PTAE	Pretreatment Adverse Event
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
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, and other service providers is available upon request to the IRB/IECs and regulatory agencies.

7. INTRODUCTION

7.1. Indication

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.

EXPAREL is indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia.

Effective postsurgical pain control is a critical element in subject recovery following surgery, as the majority of subjects may experience significant pain, particularly in the first few days. Improved postsurgical pain management contributes to better healing, faster subject mobilization, shortened hospital stays, and reduced healthcare costs (American Society of Anesthesiologists Task Force on Pain Management 1995).

7.2. Current Therapies/Treatments

Current modalities of postsurgical analgesia include wound infiltration with local anesthetics combined with the systemic administration of analgesics (multimodal therapy). Multimodal therapy usually includes opioid medications, which have considerable drawbacks, including time and resources required for monitoring opioid-related side effects. A reduction in the use of postsurgical opioids is desirable to decrease the incidence and severity of opioid induced adverse events (AEs), such as respiratory depression, nausea, vomiting, constipation, somnolence, pruritus, and urinary retention.

With over 70 million surgeries performed annually in the US, postsurgical pain is a ubiquitous condition among the US population. While it is a predictable component of the postsurgical process, such pain is often poorly managed, resulting in clinical and physiological changes that increase morbidity and mortality (inability to ambulate early, etc.), diminish quality of life, and extend length of stay, thereby increasing hospital expenditures (Oderda 2007) and reducing subject 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 [PO] intake, etc.), and conserve healthcare resources. As such, the Joint Commission on Accreditation of Healthcare Organizations requires that all healthcare facilities practice adequate pain management and monitor opioid-related AEs (Apfelbaum 2003).

Opioid analgesics have long been established to be the most effective agents used for the management of moderate to severe postsurgical pain and are currently considered the mainstay of treatment. Opioid-only regimens are common and intravenous (IV) subject-controlled analgesia is a widely used delivery system for morphine sulfate. However, AEs related to opioid administration (e.g., nausea, vomiting, ileus, confusion) represent one important reason that there is a need to develop opioid-sparing strategies. Indeed, fear of gastrointestinal AEs, such as nausea and vomiting, as well as respiratory depression, present major limitations for the widespread use of opioid analgesics (Chernin 2001, Viscusi 2009). Furthermore, management of opioid-related AEs often requires medical attention (e.g., opioid antagonists, antiemetic agents) and increased pharmacy/nursing time, which may raise healthcare expenses (Carroll 1994).

7.3. EXPAREL (Bupivacaine Liposome Injectable Suspension)

Bupivacaine is one of the longer-acting local anesthetics, but even so it has a limited duration of action after local administration, usually 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

Pacira has conducted more than 36 clinical studies and one observational follow-up study to investigate EXPAREL. Across these studies, over 1800 human subjects received EXPAREL at doses ranging from 2 mg to 665 mg (equivalent to 2 mg to 750 mg bupivacaine HCl) administered by various routes: local infiltration into the surgical site, subcutaneous, perineural (or nerve block), and epidural. EXPAREL has been generally well tolerated and, in active comparator studies, AEs occurred at a similar rate as the corresponding bupivacaine HCl controls.

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." Since its approval, EXPAREL has been administered to approximately 5 million subjects in the US (January 2019).

Following the initial approval of EXPAREL, numerous clinical studies were conducted in which EXPAREL was administered via various routes of administration, including interscalene nerve block (Sternlicht 2014, Feierman 2014).

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

7.5. Rationale for the Study

Pacira is investigating the pharmacokinetics (PK), efficacy, and safety of EXPAREL administered as combined sciatic (in the popliteal fossa) and saphenous (in the adductor canal) nerve block in healthy adult subjects undergoing lower extremity surgeries.

A dose of 20 mL (266 mg) EXPAREL with 20 mL of saline or EXPAREL admixed with 20 mL (50 mg) 0.25% bupivacaine HCl is expected to provide prolonged pain relief after these painful procedures compared with 40 mL (100mg) 0.25% bupivacaine HCl when injected in 20 mL volumes in sciatic nerve (in the popliteal fossa) and the saphenous nerve (in the adductor canal).

8. OBJECTIVES

The study objectives following the administration of study drug as a combined sciatic (in the popliteal fossa) and saphenous (in the adductor canal) nerve blocks in subjects undergoing lower extremity surgeries are listed below.

8.1. Primary Objective

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

8.2. Secondary Objectives

- To compare the total opioid consumption (in oral morphine equivalents) from 0 to 96 hours following a single dose injection of EXPAREL vs. 0.25% bupivacaine HCl
- To compare the time to first opioid consumption following a single dose injection of EXPAREL vs. 0.25% bupivacaine HCl
- To characterize and compare the magnitude of the analgesic effect following a single dose injection of EXPAREL vs. EXPAREL admixed with 0.25% bupivacaine HCl
- To characterize and compare the magnitude of the duration of motor block following a single dose injection of EXPAREL vs. EXPAREL admixed with 0.25% bupivacaine HCl
- To assess the efficacy, safety, and pharmacokinetic (PK) profile of EXPAREL; EXPAREL admixed with 0.25% bupivacaine HCl and/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, 3-arm study in approximately 120 subjects undergoing lower extremity surgeries. The study will have 2 cohorts. Both cohorts will enroll in parallel.

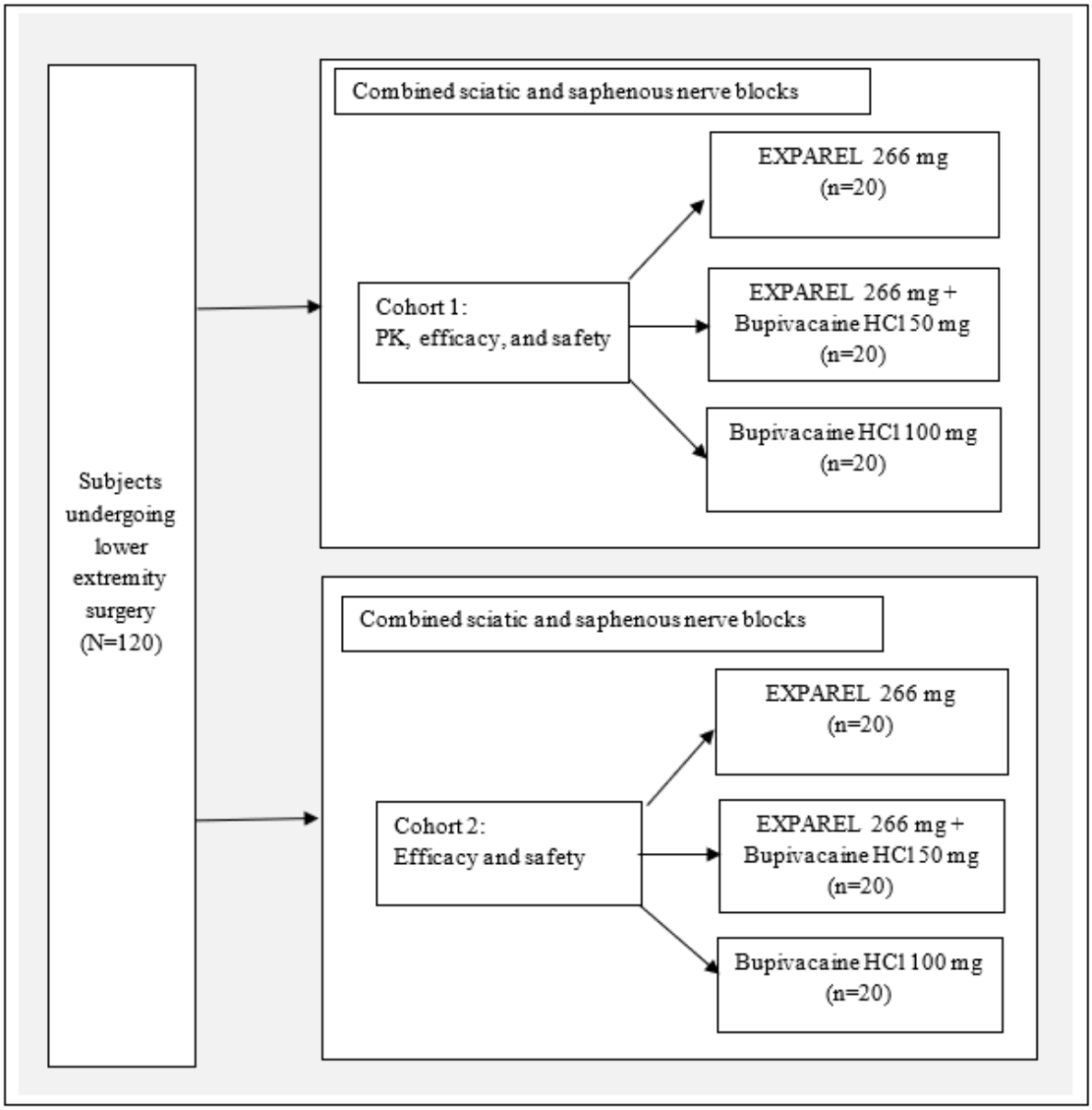
Cohort 1 will enroll about 60 subjects undergoing bunionectomy to obtain information on PK profile, pharmacodynamics (PD), efficacy, and safety. Subjects in this cohort will be randomized (1:1:1) to receive combined sciatic (in the popliteal fossa) and saphenous (in the adductor canal) nerve blocks with EXPAREL, EXPAREL admixed with 0.25% bupivacaine HCl, or 0.25% bupivacaine HCl. Only select sites will enroll subjects for Cohort 1.

Cohort 2 will enroll about 60 subjects to obtain information on efficacy and safety. Subjects in this cohort will receive combined sciatic (in the popliteal fossa) and saphenous (in the adductor canal) nerve blocks. Subjects will be randomized (1:1:1) to receive EXPAREL, EXPAREL admixed with 0.25% bupivacaine HCl, or 0.25% bupivacaine HCl, and will be stratified by each surgery grouping.

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

An adaptive study design will be used in this study. For efficacy, an interim analysis will occur when a total of approximately 60 subjects combined from either Cohort 1 or Cohort 2 have enrolled and provided complete assessment data for their primary efficacy outcome.

Figure 1: Study Schema



Note: Cohort 1 will enroll bunionectomy subjects only.

9.2. Duration of the Study and Subject Participation

Participation will begin upon signing of the ICF. No more than 30 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 47 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 review all serious adverse events (SAEs) reported from Pacira clinical studies on an ongoing basis and in real time (i.e., as the events are reported). The Medical Monitor is responsible for temporarily pausing the study if the type, frequency, or seriousness/severity of such events suggests a potential threat to the safety of the study subjects. If such action is taken, a thorough review of all available data will be performed. Based on the results of this review and discussions with investigators and/or regulatory authorities, the study may be restarted or permanently terminated as warranted.

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, double-blinded, randomized, active controlled study will enroll approximately 120 subjects to evaluate the efficacy and safety of EXPAREL, EXPAREL admixed with 0.25% bupivacaine HCl and 0.25% bupivacaine HCl when administered as a combined sciatic (in the popliteal fossa) and saphenous (in the adductor canal) nerve blocks, in subjects undergoing lower extremity surgeries.

Only Cohort 1 subjects, 60 subjects all undergoing bunionectomy surgery, will provide blood samples for PK assessments. Subjects in this cohort will provide information on efficacy and safety of EXPAREL, EXPAREL admixed with 0.25% bupivacaine HCl, and 0.25% bupivacaine HCl.

Cohort 2 will assess the efficacy and safety of EXPAREL, EXPAREL admixed with 0.25% bupivacaine HCl, and 0.25% bupivacaine HCl in 60 subjects undergoing lower extremity surgery.

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

- **EXPAREL arm:** subjects randomized to this treatment arm will receive 20 mL (266 mg) EXPAREL mixed with 20 mL saline.
- **EXPAREL admix arm:** subjects randomized to this treatment arm will receive 20 mL (266 mg) EXPAREL admixed with 20 mL (50 mg) 0.25% bupivacaine HCl.
- **Bupivacaine HCl arm:** subjects randomized to this treatment arm will receive 40 mL (100 mg) 0.25% bupivacaine HCl.

For all arms, the total volume (40 mL) will be split such that 20 mL will be administered as the sciatic nerve block (in popliteal fossa) and 20 mL will be administered as the saphenous nerve block (in the adductor canal).

10. STUDY POPULATION

Approximately 120 adult subjects undergoing lower extremity surgeries will be enrolled for the study. The surgeries that can be included in the study are:

1. Bunionectomy
2. 1st metatarsophalangeal fusion
3. Specific forefoot surgeries (Weil osteotomy, Clayton-Hoffman procedures only)
4. Midfoot fusion
5. Hindfoot fusion
6. Total ankle arthroplasty

10.1. Inclusion Criteria

At screening, the subject should satisfy the following criteria:

1. Healthy adult male or female volunteers ages 18 or older
2. American Society of Anesthesiologists (ASA) physical status 1, 2, or 3 (see Appendix 6, Section 18.6)
3. Able to provide informed consent, adhere to the study schedule, and complete all study assessments
4. Body Mass Index (BMI) ≥18 and ≤40 kg/m^2

10.2. Exclusion Criteria

At screening, the subject must not meet any of the following 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, nonsteroidal anti-inflammatory drugs [NSAIDs])
2. Concurrent painful physical condition that may require analgesic treatment (such as long-term, consistent use of opioids) in the post dosing period for pain and which, in the investigator's opinion, may confound the post dosing assessments
3. History of, suspected, or known addiction to or abuse of illicit drug(s), prescription medicine(s), or alcohol within the past 2 years
4. 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

5. Previous participation in an EXPAREL study
6. Uncontrolled anxiety, schizophrenia, or other psychiatric disorder that, in the opinion of the investigator, could interfere with study assessments or compliance
7. Currently pregnant, nursing, or planning to become pregnant during the study
8. 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
9. Currently on a neuromodulating agent (e.g., gabapentin, pregabalin [Lyrica], duloxetine [Cymbalta], etc.)
10. Inadequate sensory function on the foot (monofilament test)
11. Chronic opioid use within 30 days prior to randomization (average ≥30 oral morphine equivalents/day)

Given the COVID-19 pandemic, if there is a concern about a subject's recent or potential exposure to COVID-19, or if the subject is not medically fit/cleared for surgery due to suspected COVID-19 illness/symptoms, the subject must be excluded per Exclusion criterion #8.

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 End of Study assessments (see Section 10.3.3), should be performed so that the subject's study participation can be terminated in a safe and orderly manner.

Any subject who discontinues because of an AE should be instructed to notify the study personnel of any abnormal symptoms and to come to the study site if medical evaluation is needed and the

urgency of the situation permits. Any subject exhibiting AEs will receive appropriate treatment at the discretion of the investigator until resolution of the AE.

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., combined sciatic [in the popliteal fossa] and saphenous [in the adductor canal] nerve blocks) 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 and time of withdrawal
- Record responses to pain assessment:
  - Pain intensity scores on the Numeric Rating Scale (NRS) measured as "How much pain are you experiencing right now?"
  - Pain intensity scores (using the NRS) measured as "What was your worst pain in the last 24 hours?"
  - Pain intensity scores (using the NRS) measured as "What was your average pain in the last 24 hours?"
- Remind to return the e-diary (if applicable)
- Final phone call for safety

11. TREATMENTS

11.1. Treatments to be Administered

Cohort 1: PK, PD, Efficacy, and Safety

The participants enrolled in Cohort 1 will provide blood samples for PK and measures for efficacy and safety. About 60 subjects undergoing bunionectomy will be enrolled in this cohort. On the day of surgery, eligible subjects will be randomized (1:1:1) to receive EXPAREL (n=20), EXPAREL admixed with 0.25% bupivacaine HCl (n=20), or 0.25% bupivacaine HCl (n=20) as a combined sciatic (in the popliteal fossa) and saphenous (in the adductor canal) nerve blocks.

Cohort 2: Efficacy and Safety

The participants enrolled in Cohort 2 will provide measures for efficacy and safety. About 60 subjects will be enrolled in this cohort. On day of surgery, eligible subjects will be randomized 1:1:1 to receive EXPAREL (n=20), EXPAREL admixed with 0.25% bupivacaine HCl (n=20), or bupivacaine HCl (n=20). All subjects will receive combined sciatic (in the popliteal fossa) and saphenous (in the adductor canal) nerve blocks, by stratifying by each surgery grouping.

Treatments for Cohort 1 and Cohort 2

On the day of surgery, Cohort 1 and 2 subjects will receive ultrasound-guided combined sciatic (in popliteal fossa) and adductor canal nerve block with one of the following treatments:

- **EXPAREL arm:** subjects randomized to this treatment arm will receive 20 mL (266 mg) EXPAREL mixed with 20 mL saline
- **EXPAREL admix arm:** subjects randomized to this treatment arm will receive 20 mL (266 mg) EXPAREL admixed with 20 mL (50 mg) 0.25% bupivacaine HCl
- **Bupivacaine HCl arm:** subjects randomized to this treatment arm will receive 40 mL (100 mg) 0.25% bupivacaine HCl

Block Procedure:

Subjects may be lightly sedated with 1 to 2 mg of midazolam IV before the block procedure. The study drug (EXPAREL, EXPAREL admixed with 0.25% bupivacaine HCl, or 0.25% bupivacaine HCl) will be administered under ultrasound guidance 90 min (±30 min) prior to surgery.

For all arms, the total volume (40 mL) will be split such that 20 mL will be administered as the sciatic nerve block (in popliteal fossa) and 20 mL will be administered as the saphenous nerve block (in the adductor canal).

11.1.1. Study Drug Administration Considerations

As described in the EXPAREL Full Prescribing Information (November 2018), 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, 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 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 combined sciatic (in popliteal fossa) and adductor canal nerve block.

11.3. Method of Assigning Subjects to Treatment

11.3.1. Randomization Scheme

This is a randomized study. Cohort 1 will enroll approximately 60 total subjects undergoing bunionectomy surgery randomized 1:1:1 in the EXPAREL arm, EXPAREL admixed with 0.25% bupivacaine HCl arm (“admix” arm), and bupivacaine HCl arm.

Cohort 2 will enroll approximately 60 total subjects undergoing distal lower extremity surgery, 20 subjects in each treatment arm; EXPAREL arm, EXPAREL admix arm, and bupivacaine HCl arm. Subjects will be randomized 1:1:1 to treatment groups, by stratifying by surgery grouping. 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. In rare cases, if a subject has an early morning surgery and there would not be enough time to obtain study drug from the pharmacy, sites will be permitted to randomize the subject the day before the surgery (after contacting the subject the day before surgery to confirm eligibility details). The e-diary may be activated during the screening period in order to perform set-up and training, but no data entry may occur in the e-diary before the day of surgery. The subject will be considered randomized into the study once the study treatment assignment 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 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 developmental program, a pilot dose-escalation study (402-C-122) evaluating the PK, PD, and safety of EXPAREL as a sciatic nerve block in the popliteal fossa in subjects undergoing bunionectomy was conducted. The preliminary results for this study showed that compared to the EXPAREL 266 mg or 133 mg admixed groups, EXPAREL 266 mg had similar NRS pain scores, opioid consumption, and onset and duration of block, but produced lower PK concentrations of bupivacaine HCl. Thus, a total dose of 266 mg was deemed appropriate for the current study population administered in two halves as 133 mg EXPAREL in each of the sciatic and saphenous nerve blocks.

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, EXPAREL admixed with 0.25% bupivacaine HCl, 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 blocks.

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

At each site, only the designated unblinded pharmacist will receive unblinded randomization assignments; the designated unblinded pharmacist or administrator will be responsible for preparing 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 group by Anatomic Therapeutic Chemical class and preferred terms.

11.6.1. Prior to Study Drug Administration

Permitted Prior Medications and Therapy:

- Low-dose aspirin for cardioprotection
- 1 to 2 mg of midazolam (Versed)

Restricted Prior Medications and Therapy:

- Systemic glucocorticosteroids and neuromodulating agents (e.g., gabapentin, pregabalin [Lyrica], duloxetine [Cymbalta], etc.)
- Long-acting or sustained release opioid medications and NSAIDs (except for low-dose aspirin used for cardioprotection) are not permitted within 3 days of study drug administration.
- Dexmedetomidine HCl (Precedex) use is not permitted within 3 days of study drug administration.
- No opioid medications are permitted within 24 hours of study drug administration.
- Use of an investigational product within 30 days or 5 elimination half-lives of such investigational drug, whichever is longer, prior to study drug administration, or planned administration of another investigational product or procedure during the subject's participation in this study is not permitted.
- 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

Permitted Medications:

- Acceptable anesthetic techniques include general anesthesia or non-opioid sedation (except fentanyl, not to exceed 1 ug/kg unless deemed medically necessary). Neuroaxial or regional anesthesia technique (except the investigational related blocks) are not permitted.
- Single-dose administration of ondansetron or metoclopramide may be used intra-operatively for nausea/vomiting prevention.

Restricted Medications:

- 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

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.
- Patient Controlled Analgesia is not permitted.
- Dexmedetomidine HCl (Precedex) use is prohibited.
- Lidocaine and other local anesthetics will not be permitted to be locally administered in the area of the nerve block administration through POD 7.

11.7. Postsurgical Pain Medication for Breakthrough Pain

An unscheduled pain intensity assessment using the NRS (measured as “How much pain are you experiencing right now?”) must be completed immediately prior to administration of any breakthrough pain medication up to 96 hours post-surgery. All opioid and other analgesics (pain medications) administered post-surgery through POD 14 must be recorded.

Medications will be provided on an as needed (PRN) basis in relation to the breakthrough pain intensity. The intent is to use the guide below in a step-wise approach; acetaminophen or NSAIDs should be used for the initial treatment of post-surgical pain and escalation to opioids (and subsequent increased dose of opioids) should be implemented if the initial pain treatment (and initial opioid dose) is insufficient for pain relief. Opioids should not be the first choice for pain relief unless clinically indicated in the opinion of the investigator and should not be given on a schedule.

- For the initial treatment of post-surgical pain, subjects may receive either acetaminophen or NSAIDs without exceeding the maximum daily dose.
- If the initial pain treatment (acetaminophen or NSAIDs) is insufficient for pain relief, 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, 10 mg oxycodone may be offered.
- 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.

Post discharge, the subject may be provided with a prescription for oxycodone 5 mg. The subject may take acetaminophen, NSAIDs, or the prescribed oxycodone and will be given instructions on which medication to take PRN based on their pain intensity.

11.8. Treatment Compliance

Not applicable, since study drug (EXPAREL, EXPAREL admix, or bupivacaine HCl) will be administered preoperatively by the study staff.

11.9. Accountability of Study Drug

Any shipment of EXPAREL for the study will contain an investigational drug transmittal and receipt form to assist the Investigator or designee (e.g., pharmacist) in maintaining current and accurate inventory records. At a minimum, the Investigator or designee will maintain accurate records demonstrating dates and units of drug received, lot numbers, subjects to whom drug was administered, and accounts of any drug destroyed accidentally or deliberately. The Investigator must retain vials containing used, unused, or expired 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 “How much pain are you experiencing 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 21:00 (±3 h) from POD 1 to POD 14 measured as "What was your **worst** pain in the last 24 hours?"
- Pain intensity using the NRS once daily at 21:00 (±3 h) from POD 1 to POD 14 measured as "What was your **average** pain in the last 24 hours?"
- 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.

Subjects will be instructed to focus all NRS pain intensity ratings on the operative ankle/foot, and not other locations where they may be experiencing pain.

The following information shall be captured for data management purposes:

- Start and end time of block
- Start and stop time of surgery
- Start and stop of PACU admission and discharge
- Date and time of health care facility admission and discharge

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 comparing EXPAREL to 0.25% bupivacaine HCl

Secondary Endpoints:

- Total postsurgical opioid consumption in oral morphine equivalents (OMED) from 0 to 96 hours post-surgery comparing EXPAREL to 0.25% bupivacaine HCl
- Time to first opioid consumption comparing EXPAREL to 0.25% bupivacaine HCl
- The AUC of the NRS pain intensity scores from 0 to 96 hours post-surgery comparing EXPAREL to EXPAREL admixed with 0.25% bupivacaine HCl
- The duration of the motor block EXPAREL to EXPAREL admixed with 0.25% bupivacaine HCl

12.3. Safety Assessments

- Adverse events (AEs) and SAEs will be recorded from the time of informed consent 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 (Cohort 1 only)

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

12.6. Pharmacokinetic Endpoints (Cohort 1 only)

The following model-predicted PK endpoints will be determined:

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

12.7. Pharmacodynamic Assessments (Cohort 1 only)

Pharmacodynamic assessments must be performed by 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 functions (Light Touch Assessment and Cold Sensation Assessment):

- Sensory functions will be assessed using a wooden tongue depressor and ice. These assessments will evaluate light touch and cold sensation. The light touch assessment will be done first, followed by the cold sensation assessment. The tongue depressor application and ice application will be performed at predose (up to 15 min before block), 15 min (±5 min), 30 min (±5 min), 45 min (±5 min), 1 h (±15 min), 2 h (±30 min), 8 h (±30 min), 12 h (±30 min), 24 h (±1 h), 30 h (±1 h), 48 h (±1 h), 60 h (±2 h), 72 h (±2 h), 84 h (±2 h), 96 h (±3 h), 120 h (±3 h), 144 h (±3 h), and 168 h (±3 h) from the end of the nerve block procedures, or until full sensory function has returned to predose levels in two consecutive evaluations. Each light touch

assessment will be rated independently. Each cold sensation assessment will be rated independently. Additional unscheduled assessments may be performed, particularly around the surgery, if no onset of block is noted on the last scheduled assessment prior to surgery. For each sensory assessment performed, all 4 locations (as described in Appendix 4, Section 18.4) will be assessed for both light touch and cold (e.g., total of 8 independent ratings will be performed for each sensory assessment).

Onset of sensory block (sciatic and saphenous nerve tracked independently) will be defined as the earliest timepoint with loss of light touch sensation and/or cold sensation along the distribution of the target nerve distal to the site of the block.

Offset of sensory block (sciatic and saphenous nerve tracked independently) will be defined as recovery of light touch sensation and/or cold sensation along the distribution of the target nerve distal to the site of the block on 2 consecutive assessments. After offset of all sensory assessments are noted (on 2 consecutive assessments for all 4 areas for both touch and cold sensation), no subsequent assessments will be conducted.

Duration of sensory block will be defined as the time between onset and offset of light touch sensory and/or cold sensation block for each nerve individually (see Appendix 4, Section 18.4).

Assessment of motor function (onset and offset of motor block):

- 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 predose (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 end of block procedure, or until full motor function has returned to predose levels in two consecutive evaluations. 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 (sciatic) will be defined as the earliest timepoint with partial or no foot movement.

Offset of motor block (sciatic) will be defined as resolution of the motor block with complete foot movement on two consecutive assessments. After offset of motor block is noted (on 2 consecutive assessments), no subsequent assessments will be conducted.

Duration of motor block will be defined as time between onset and offset of motor block (see Appendix 3, Section 18.3).

12.8. Pharmacodynamic Endpoints (Cohort 1 only)

The following pharmacodynamics endpoints will be determined:

- Median time to onset of sensory block and motor block

- Median duration of sensory block and motor block

12.9. Appropriateness of Measures

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 (predose) 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 combined sciatic (in popliteal fossa) and saphenous (in the adductor canal) nerve blocks.

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.

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 through the primary endpoint will take place under the supervision of study staff at the site.

Subjects will be provided an e-diary on the day of surgery and instructed on duties and responsibilities with the e-diary.

13.1.1. Pain Intensity Assessment

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

- Pain intensity scores (using the NRS) measured as "How much pain are you experiencing 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
  - Subjects 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 scores (NRS) once daily at 21:00 (±3 h) from POD 1 to POD 14 measured as "What was your **worst** pain in the last 24 hours?"
- Pain intensity scores (NRS) once daily at 21:00 (±3 h) from POD 1 to POD 14 measured as "What was your **average** pain in the last 24 hours?"

Subjects will be instructed to focus all NRS pain intensity ratings on the operative ankle/foot, and not 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 (Cohort 1 only)

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

13.1.4. Pharmacodynamic assessment (Cohort 1 only)

Onset and duration of sensory block will be assessed using the light touch assessment and/or cold sensation to characterize the sensory block (see Appendix 4, Section 18.4).

Onset and duration of motor block will be assessed using the movement of the foot to characterize the motor block (see Appendix 3, Section 18.3).

Pharmacodynamic assessments must be performed by 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 one of the eligible surgeries will be approached by the investigator and/or the study staff for informed consent up to 30 days before the surgery. Subject 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 the questions answered by the investigator/study staff prior to providing informed consent.

13.2.2. Screening

Subjects may be screened up to 30 days prior to day of surgery but eligibility should be re-confirmed on 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 30-day time window. Any screening procedures that are not standard of care must be completed after written informed consent is provided and prior to surgery.

The following screening procedures should be performed after the ICF is signed:

- Explain study purpose and procedures, including responsibilities regarding the e-diary
- 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 lower extremity surgery, in which case all years should be recorded.
    - If a site's standard process includes detailed collection of all history (regardless of relevance/age), only the relevant items should be recorded in the eCRF as outlined above; an asterisk or similar indicator can be used in the source documentation to indicate the relevant items that should be included in the eCRF for source data verification purposes.
- Record prior and concomitant medications
- Record demographics and baseline characteristics including Pain Catastrophizing Scale (PCS) (see Appendix 5, Section 18.5).
- Record subject height and weight for BMI calculation
- Assess chronic opioid use in the past 30 days
- Conduct urine pregnancy test for women of childbearing potential
- Record AEs/SAEs from the time the ICF is signed
- Record concomitant medications for treatment of AEs

13.2.3. Baseline Procedures (Prior to Study Drug Administration)

- On the day of surgery, before administration of the block, the subject must record responses to the following pain assessments:
  - Pain intensity scores on the NRS as "What was your worst pain in the last 30 days?"
  - Pain intensity scores (using the NRS) "What was your average pain in the last 30 days?
- Conduct urine pregnancy test for women of childbearing potential
- Record changes to concomitant medications since screening
- Confirm eligibility and randomize subject
- Record AEs/ SAEs and any treatment(s) for the events
- Provide e-diary and instruct the subjects on duties and responsibilities for assessment completion
- For Cohort 1 only:
  - Perform sensory function assessment
  - Perform motor function assessment
  - 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.
- Administer study drug as combined sciatic (in popliteal fossa) and saphenous (in the adductor canal) nerve blocks using ultrasound 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 and any treatment(s) for the events

13.3.1. Procedures for Sciatic Nerve Block

A: Placement of ultrasound probe:

- Position the patient supine (with the leg placed on an elevated footrest) or lateral (operative side up). Place ultrasound probe in the popliteal fossa, 3 to 5 cm above the popliteal crease in the transverse orientation.
- Identify the sciatic nerve where it splits into the peroneal and tibial nerves but still enclosed in the connective tissue sheath (paraneural sheath).

B: Insertion of needle into paraneural sheath:

- Use a 100 mm, 21-gauge insulated needle
- Needle approach is from the lateral side
- The needle should be advanced in plane until the needle tip has pierced the sciatic nerve sheath (paraneural sheath), (i.e., advance needle underneath the peroneal nerve, and pop through the sheath that surrounds the tibial and peroneal nerves).

C: Hydrodissection of sciatic nerve block:

- Never advance the needle tip directly at either nerve, but rather use small aliquots of saline (1-2 ml) to hydrodissect and outline the nerves.

D: Study drug administration:

- Switch syringes and inject 20 mL of the study drug admixture in the sheath, between the two nerves.

13.3.2. Procedures for Adductor Canal Nerve Block

A: Placement of ultrasound probe:

- With the patient in the supine position, place ultrasound transducer at the midpoint between the inguinal crease and the superior pole of the patella. The femoral artery should be visible directly beneath the sartorius muscle.
- The saphenous nerve is frequently visible as a hyperechoic structure immediately lateral to the femoral artery.

B: Insertion of needle into adductor canal:

- From a lateral approach in plane using a 100 mm 21-gauge insulated needle, insert the needle until the tip is just lateral to the femoral artery and under the saphenous nerve.
- The injection will occur immediately lateral to the femoral artery, below the sartorius muscle.

C: Saline injection of adductor canal nerve block:

- Slowly start the saline injection to visualize the saphenous nerve so as not to injure it. The goal is to confirm needle tip position, and no more than 1-2 mL of saline should be required.

D: Study drug administration:

- Switch syringes and slowly start injecting the remaining 20 mL of study drug around the saphenous nerve as visualized during saline injection.

13.4. Post-Block Assessments

The following assessments will be conducted in Cohort 1 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), 1 h (±15 min), 2 h (±30 min), 8 h (±30 min), 12 h (±30 min), 24 h (±1 h), 30 h (±1 h), 48 h (±1 h), 60 h (±2 h), 72 h (±2 h), 84 h (±2 h), 96 h (±3 h), 120 h (±3 h), 144 h (±3 h), and 168 h (±3 h) from the end of the block procedure, or until full sensory/motor function has returned to predose levels in two consecutive evaluations. The light touch, cold sensation, and motor function tests will be rated independently from each other. For sensory function, the light touch assessment will be done first, followed by the cold sensation assessment.
- Collect scheduled PK blood samples. These samples will be obtained at predose (up to 15 min before block), and at 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 end of block procedure. (See Table 2).

In both Cohort 1 and Cohort 2 subjects:

- Record AEs/ SAEs
- Record any concomitant medications for treatment(s) for the events.

13.5. Intraoperative Procedures

- Record type of general anesthesia or sedation
- Record intraoperative drugs administered and doses
- Record date and start/end times of surgery
- Record AEs/ SAEs
- Record concomitant medications for treatment of AEs/ SAEs (if any)

13.6. Post-Anesthesia Care Unit Procedures

- Record date/time of admission to and discharge from the PACU
- For Cohort 1 only
  - Collect scheduled PK blood sample(s)
  - Perform sensory and motor function assessments
- Record AEs/ SAEs
- Record concomitant medications for treatment of AEs/ SAEs
- Subject to record NRS score (“How much pain are you experiencing now?”) upon arrival in the PACU (±5 min); every 15 minutes while in the PACU (±5 min); and at PACU discharge (±5 min)

- Subject to record NRS score ("How much pain are you experiencing now?") before administration of breakthrough pain medication
- Record date, time, and dosage of any breakthrough pain medication

13.7. Postsurgical Assessments from End of Surgery through Discharge

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- Record pain intensity scores (NRS) (see Appendix 1, Section 18.1) measured as "How much pain are you experiencing 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., 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.
  - Subjects 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.
  - An unscheduled NRS assessment will be obtained immediately prior to administration of any breakthrough pain medication until 96 hours post-surgery.
- Record pain intensity scores (NRS) measured as "What was your worst pain in the last 24 hours?" and "What was your average pain in the last 24 hours?"
  - Once daily at 21:00 (±3 h) starting on POD 1.
- Subject to record satisfaction with pain management using 1 question from the International Pain Outcome (IPO) questionnaire at 96 hours (±3 h) post-surgery.
- For Cohort 1 only:
  - Collect scheduled PK blood sample(s).
  - Perform sensory and motor function assessments.
- Record AEs/ SAEs.
- Record concomitant medications for treatment of AEs/ SAEs.

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.

13.8. Health Care Facility Discharge

- Subjects in Cohort 1 and Cohort 2 will be discharged after the completion of the 168 h and 96 h assessments, respectively.
- Record date and time of health care facility discharge.
- Re-instruct on duties and responsibilities with the e-diary and for breakthrough medications.

13.9. Postsurgical Assessments from Discharge through POD 14

- Record pain intensity scores (NRS) measured as "What was your worst pain in the last 24 hours?" and "What was your average pain in the last 24 hours?" once daily at 21:00 (±3 h) from the day after discharge (daily continuation from POD 1 to POD 14).

13.10. Unscheduled Visits

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

13.11. Postsurgical Day 14 Phone Call

- Remind subject to complete and return the e-diary, if applicable, after POD 14 assessment.
- Ask the subject about any new AE(s) and the resolution of any ongoing adverse event(s) since discharge. Record any adverse event information.
- Ask the subject about any medication(s) taken, that were not reported in the e-diary, 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 14.1.2, 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 ICF is signed and before the start of the study drug administration is identified as a pretreatment AE (PTAE). An AE that occurs after the administration of the study treatment is considered a 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 (i.e., PTAEs and TEAEs) 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 line should be recorded in the AE CRF; for example, an AE of nausea and vomiting would be listed as two separate events: the event of nausea and the event of vomiting. If a diagnosis is established after symptoms are recorded on the AE CRF, the diagnosis must be recorded, and the symptoms collapsed (removed; i.e., lined through and initialed). 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 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 study drug administration, 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

The severity of an AE must be categorized using the following guidelines:

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

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

Severe: An AE that prevents normal everyday activities.

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); 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 last assessment, the event was ongoing, with an undetermined outcome. Note: ongoing AEs are not to be considered resolved as a result of death
Recovering/Resolving:	At the time of last assessment, the event was decreasing in frequency, severity, etc., and a resolution was expected
Fatal:	The AE directly caused death
Unknown:	There was an inability to access the subject or the subject's records to determine the outcome (e.g., subject withdrew consent or was lost to follow-up)

14.1.6. Action Taken with Subject Due to an Adverse Event

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

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

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:

- Persistent tingling
- Persistent numbness
- Persistent weakness
- Hypersensitivity
- Seizures
- Tremors
- Dizziness
- Hematoma formation
- Cardiovascular depression
- Dyspnea
- Cardiovascular arrest
- Altered sensorium
- Visual disturbances
- Local anesthetic systemic toxicity

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 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 (drugsafety@pacira.com) or fax (858-408-3588). 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. Demographic and baseline characteristics will be summarized descriptively by treatment group for all subjects who receive study drug. Efficacy and safety endpoint analyses will be described in the SAP.

Efficacy data will be analyzed by randomized treatment group. Superiority of treatment with EXPAREL compared with bupivacaine HCl will be determined using analysis of variance (ANOVA) with treatment as main effect for the primary efficacy endpoint of AUC of the NRS pain intensity scores from 0 to 96 hours post-surgery. Additional factors such as site or surgery type may be included to adjust the model if deemed necessary. Other efficacy endpoints will be analyzed using ANOVA, logistic regression model, chi-square tests, and Kaplan-Meier and log-rank tests, as appropriate.

Safety and pharmacokinetic endpoints will be summarized descriptively by actual treatment received.

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 are not different between the EXPAREL and bupivacaine HCl treatment group.

The alternative hypothesis is:

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

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 sample size was calculated based on the primary efficacy endpoint of the AUC of the NRS pain intensity scores from 0 through 96 hours post-surgery comparing EXPAREL to bupivacaine HCl.

The sample size for Cohort 1 was based on the number of subjects necessary to characterize the PK following administration.

Cohort 1 and Cohort 2 subjects will be combined within treatment groups for the efficacy and safety analyses; therefore, the overall sample size was based on the primary efficacy endpoint of the AUC of the NRS pain intensity scores from 0 through 96 hours post-surgery. Assuming a 2-sided 0.05 alpha, common standard deviation (SD) of 170 a sample size of 40 subjects for EXPAREL and 40 subjects for bupivacaine HCl should have at least 90% power to detect a true difference of 150-units in the AUCs. Therefore, since Cohort 1 will have 60 subjects

(20 EXAPREL, 20 EXPAREL admixed with bupivacaine HCl and 20 bupivacaine HCl), Cohort 2 will need to enroll 60 subjects (20 EXAPREL, 20 EXPAREL admixed with bupivacaine HCl and 20 bupivacaine HCl) to meet the total requirements.

An efficacy interim analysis will occur when approximately 60 subjects have enrolled and provided complete data for the primary efficacy outcome.

15.4. Analysis Populations

The following analysis sets are planned:

Safety: The safety analysis set will include all 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 undergo the planned surgery. All analyses will be based on randomized treatment regardless of actual treatment received.

Pharmacokinetic: The pharmacokinetic analysis set will include all subjects 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 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 group.

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 group.

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 endpoint will be additionally analyzed by stratifying by surgery on the efficacy analysis set as a sensitivity analysis.

For continuous measures of efficacy, summary statistics (n, mean, median, standard deviation, minimum, and maximum) will be shown by treatment group. For categorical measures of efficacy, number and percentage of subjects in each category will be shown by treatment group. For time to

event measures of efficacy, medians and Kaplan-Meier estimates will be shown by treatment group.

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

All assessments will be presented in by-subject data listings.

15.6.3.1. Primary Efficacy Measure

The primary efficacy measure is the AUC of the NRS pain intensity scores from 0 to 96 hours post-surgery.

For the AUC of the NRS pain intensity scores from 0 to 96 hours post-surgery, EXPAREL will be compared to bupivacaine HCl using ANOVA with treatment as a main effect. Additional covariates may be included. Based on the model, the difference between treatment groups will be estimated along with the 2-sided 95% confidence intervals. The stratified sensitivity analysis will report similar statistics.

15.6.3.2. Secondary Efficacy Measures

The secondary efficacy measures are:

- Total postsurgical opioid consumption in oral morphine equivalents (OMED) from 0 to 96 hours post-surgery comparing EXPAREL to bupivacaine HCl
- Time to first opioid consumption comparing EXPAREL to bupivacaine HCl
- The AUC of the NRS pain intensity scores from 0 to 96 hours post-surgery comparing EXPAREL to EXPAREL admixed with bupivacaine HCl
- The duration of the motor block EXPAREL to EXPAREL admixed with bupivacaine HCl

For the total postsurgical opioid consumption endpoint, opioid medications will be converted to the oral morphine equivalents in mg amount. All opioids administered from 0 hours to 96 hours post-surgery will be included in the analysis. Prior to analysis, the natural logarithm transformation may be applied to the total amount. A minimal set value will be used for subjects that do not report opioid use. To test for a significant difference between EXPAREL and bupivacaine HCl, an ANOVA with treatment as a main effect will be used. Additional covariates may be included. Based on the model, the difference between treatment groups will be estimated along with the 2-sided 95% confidence intervals.

The time to event endpoints will be summarized with medians and Kaplan-Meier estimates. A log-rank test will be used to compare EXPAREL to bupivacaine HCl. Subjects that do not report any event will be censored at their last valid assessment respective to the endpoint.

For the endpoint AUC of the NRS pain intensity scores from 0 to 96 hours post-surgery, EXPAREL will be compared to EXPAREL admixed with bupivacaine HCl.

For the endpoint duration of the motor block, EXPAREL will be compared to EXPAREL admixed with bupivacaine HCl.

15.6.3.3. 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. Safety Analyses

All safety analyses will be based on actual treatment received.

15.6.4.1. Adverse Events

Adverse event verbatim terms will be mapped to preferred terms and related system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). Events that start prior to the start of study drug administration will be identified in 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 group. Incidence rates will also be displayed for each treatment group 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 group. All incidence rates will be categorized and displayed by system organ class and preferred term.

15.7. Significance Testing

All tests will be two-sided and based on a significance level of 0.05 unless otherwise specified.

15.8. Interim Analyses

An unblinded efficacy interim analysis conducted by an independent committee will occur when approximately 60 subjects (20 in each arm) have been randomized, treated and provided their primary efficacy outcome. An interim analysis will be conducted to evaluate and compare the clinical efficacy between EXAPREL only and bupivacaine HCl only. Primary purpose of this interim analysis is to evaluate the sample size assumptions and evaluate futility. Full details on the planned or additional interim analysis will be covered in a prospective interim analysis plan.

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17. INVESTIGATOR AGREEMENT

Printed Name of Investigator: _____

Printed Title/Position: _____

Printed Institution Address: _____

_____

_____

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

- To assume responsibility for the proper conduct of the study at this site;
- To conduct the study in compliance with this protocol, with any future amendments, and with any other study conduct procedures provided by Pacira Pharmaceuticals, Inc. 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

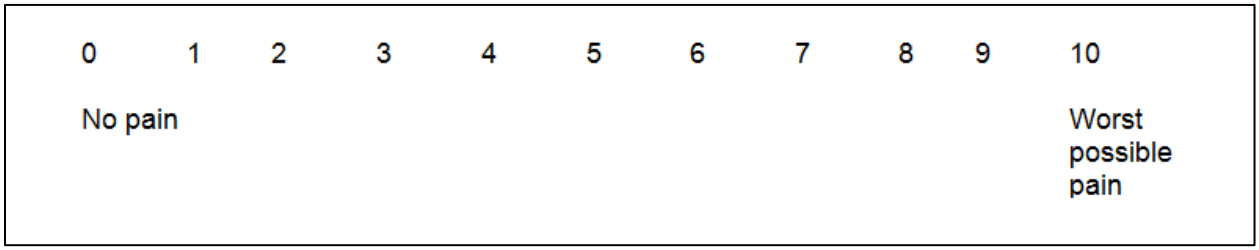
18. APPENDICES

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). Subjects will be instructed to focus all NRS pain intensity ratings on the operative ankle/foot, and not other locations where they may be experiencing pain.

- Pain intensity using the NRS measured as "What was your worst pain in the last 30 days?" and "What was your average pain in the last 30 days?" will be assessed at Baseline/Day of surgery
- Pain intensity using the NRS measured as "How much pain are you experiencing right now?" ** will be assessed:
  - Upon arrival in the PACU (±5 min)
  - Every 15 minutes in the PACU (±5 min)
  - At PACU discharge (±5 min)
  - Every 6 hours from the end of surgery until 96 hours post-surgery: 6 h (±2 h), 12 h (±2 h), 18 h (±2 h), 24 h (±2 h), 30 h (±2 h), 36 h (±2 h), 42 h (±2 h), 48 h (±2 h), 54 h (±2 h), 60 h (±2 h), 66 h (±2 h), 72 h (±2 h), 78 h (±3 h), 84 h (±3 h), 90 h (±3 h), and 96 h (±3 h)
  - If a subject is asleep, the subject will not be awakened to assess pain. If the subject awakens within the assessment window, a pain score will be collected then
  - Subjects 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 measured as "What was your worst pain in the last 24 hours?" and "What was your average pain in the last 24 hours?" will be assessed:
  - Once daily at 21:00 (±3 h) from POD 1 to POD 14

Numeric Rating Scale (NRS)



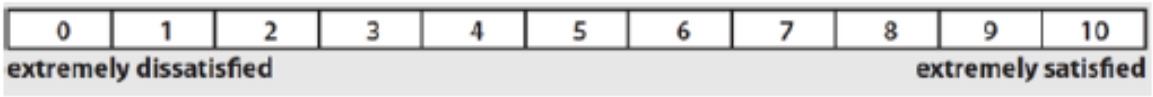
18.2. Appendix 2: Subject Satisfaction Questionnaire

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

Dear Sir/Madam,

Please answer the following questions about your pain control after surgery

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



18.3. Appendix 3: Motor Function Test (Cohort 1 only)

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 predose (up to 15 min before block), 15 min (±5 min), 30 min (±5 min), 45 min (±5 min), 1 h (±15 min), 2 h (±30 min), 8 h (±30 min), 12 h (±30 min), 24 h (±1 h), 30 h (±1 h), 48 h (±1 h), 60 h (±2 h), 72 h (±2 h), 84 h (±2 h), 96 h (±3 h), 120 h (±3 h), 144 h (±3 h), and 168 h (±3 h) from the end of the block procedures, or until full motor function has returned to the baseline (pre-block) level in two consecutive evaluations. 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.

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

18.4. Appendix 4: Light Touch Assessment and Cold Sensation Assessment (Cohort 1 only)

Sensory function for light touch will be assessed using a wooden tongue depressor. Sensory function for cold sensation will be assessed using ice. The light touch assessment will be done first, followed by the cold sensation assessment.

- The wooden tongue depressor light touch assessment and the cold sensation assessment will be performed at predose (up to 15 min before block), 15 min (±5 min), 30 min (±5 min), 45 min (±5 min), 1 h (±15 min), 2 h (±30 min), 8 h (±30 min), 12 h (±30 min), 24 h (±1 h), 30 h (±1 h), 48 h (±1 h), 60 h (±2 h), 72 h (±2 h), 84 h (±2 h), 96 h (±3 h), 120 h (±3 h), 144 h (±3 h), and 168 h (±3 h) from the end of the nerve block procedures, or until full sensory function has returned to baseline (pre-block) levels in two consecutive evaluations. Each light touch area of assessment will be rated independently. Each cold sensation assessment will be rated independently. Additional unscheduled assessments may be performed, particularly around the surgery, if no onset of block is noted on the last scheduled assessment prior to surgery. For each sensory assessment performed, all 4 locations below will be assessed for both light touch and cold (e.g., total of 8 independent ratings will be performed for each sensory assessment).

Sensory function assessment will include the following four locations:

1. Saphenous proximal - Medial aspect of the lower leg (3-4 cm below the knee)
2. Saphenous distal - Medial aspect of the lower leg (3-4 cm above ankle)
3. Sciatic proximal - Lateral aspect of the lower leg (3-4 cm above ankle)
4. Sciatic distal - Sole of the foot

The intent of applying the tongue depressor or ice 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).

Tongue Depressor Assessment

The tongue depressor assessment procedures are as follows:

- The subject should 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 three areas as above.

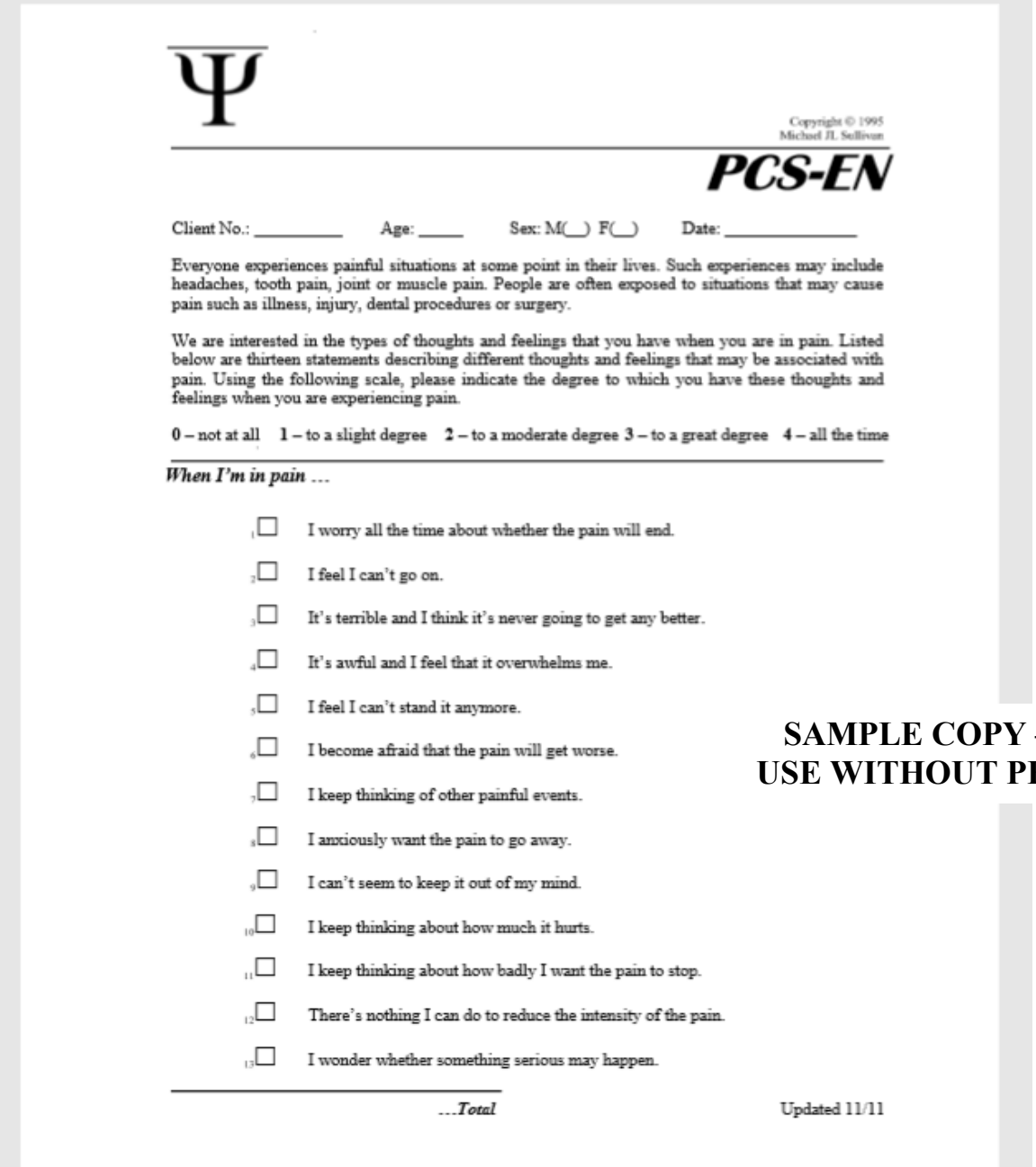
Ice Assessment

The ice assessment procedures are as follows:

- The subject should be instructed to close their eyes before the application of the ice (place ice in a small plastic bag to avoid any wet sensation).
- Instruct the subject you will be touching the subject on both legs and they will be asked if the cold sensation is the same (YES) or not the same (NO) when comparing each side.
- For the subject's reference, the ice is placed on the contralateral assessment area.
- The ice is then placed on the corresponding test assessment area.
- The subject will be asked if the cold sensation is the same (YES) or not the same (NO) when comparing each side.
- Record the subject's response (YES or NO) to the cold sensation in the assessment area.
- Proceed to test the other three areas as above.

18.5. Appendix 5: Pain Catastrophizing Scale

The Pain Catastrophizing Scale (PCS) is provided below.



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PCS-EN

Client No.: _____ Age: _____ Sex: M(__) F(__) Date: _____

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0 – not at all **1** – to a slight degree **2** – to a moderate degree **3** – to a great degree **4** – all the time

When I'm in pain …

1. ☐ I worry all the time about whether the pain will end.
2. ☐ I feel I can't go on.
3. ☐ It's terrible and I think it's never going to get any better.
4. ☐ It's awful and I feel that it overwhelms me.
5. ☐ I feel I can't stand it anymore.
6. ☐ I become afraid that the pain will get worse.
7. ☐ I keep thinking of other painful events.
8. ☐ I anxiously want the pain to go away.
9. ☐ I can't seem to keep it out of my mind.
10. ☐ I keep thinking about how much it hurts.
11. ☐ I keep thinking about how badly I want the pain to stop.
12. ☐ There's nothing I can do to reduce the intensity of the pain.
13. ☐ I wonder whether something serious may happen.

_____

…Total

Updated 11/11

The PCS contact information and permission to use: Mapi Research Trust, Lyon, France. Internet: https://eprovide.mapi-trust.org

18.6. Appendix 6: 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