Clinical Study Protocol
Amendment 2

A Multicenter, Randomized, Double-Blind, Controlled Trial Comparing Local Infiltration Analgesia with EXPAREL to Local Infiltration Analgesia without EXPAREL to Manage Postsurgical Pain Following Total Knee Arthroplasty

Protocol No.:	402-C-331
EudraCT No.:	2015-005229-38
IND No.:	69,198
Study Phase:	Phase 4
Study Drug:	EXPAREL® (bupivacaine liposome injectable suspension)
Date:	28 July 2016 22 February 2016 (Amendment 1) 16 November 2015 (Original)
Investigator(s) or Study Site(s):	Multicenter study in the US and Europe
Sponsor:	Pacira Pharmaceuticals, Inc. 5 Sylvan Way Parsippany, NJ 07054 Telephone: (973) 254-3560

SUMMARY OF CHANGES

Unless otherwise noted, the protocol clarifications and revisions stated below were made based on discussion with the Investigators.

Section 2 (Synopsis)

Methodology

- The following sentences were added:

  "Bupivacaine is preferred as the spinal anesthetic; however, if the spinal fails or cannot be completed, the patient may receive general anesthesia. Total intravenous anesthesia (TIVA) is then the preferred route. If TIVA is contraindicated or not preferable, then inhalational anesthetics may be used. The use of fentanyl or short-acting analogues will be permitted in both groups.

  The following medications will be allowed:

  - Anti-emetics may be used pre-operatively or intra-operatively.
    - Decadron 10 mg x 1 intra-op is permitted
    - Scopolamine patch will be permitted if used as a pre-medication or intra-operatively but should be removed post-operatively.
  - Lidocaine will be permitted, if used as a local anesthetic at the site of IV placement or as IV to stabilize heart rhythm.
  - Propofol is permitted for induction and intra-operatively, but not post-operatively.
  - Versed, 1-2 mg IV, may be used pre-operatively for anxiety or sedation."

- The following text was changed

  from: " Acetaminophen/paracetamol 1000 mg PO every 8 hours (q8h)"

  to: " Acetaminophen/paracetamol 975-1000 mg PO every 8 hours (q8h)"

- The following sentences were added:
  - "If a subject has an allergy to celecoxib, they may use the following alternative drugs: naproxen 500 mg PO or meloxicam 7.5 mg PO.

- The following text was changed

  from: "Pregabalin 300 mg PO"

  to: "Pregabalin up to 300 mg PO"

- The following text was changed

  from: "Tranexamic acid 1 gram, intravenously (IV)"

  to: "On Day 0, all eligible subjects will also receive tranexamic acid, up to 2 mg (IV), at the beginning of surgery or intra-operatively."

- The following text was changed

from: "Postsurgical rescue medication will consist of PO immediate-release oxycodone (initiating at 10 mg every 4 hours [q4h] or as needed [PRN]). If a subject cannot tolerate PO medication, IV morphine (2.5-5 mg) or hydromorphone (0.5-1 mg) may be administered q4h or PRN

to: "Postsurgical rescue medication will consist of PO immediate-release oxycodone initiating up to 10 mg. The subject may re-dose, per physician judgment, as needed (PRN), if the initial rescue medication fails. If a subject cannot tolerate PO medication or has repeated failure of the rescue medication with oxycodone (PO), IV morphine (2.5-5 mg) or hydromorphone (0.5-1 mg) may be administered q4h or PRN

- The following text was changed

from: " If a cardiac AE, neurological AE, fall, or serious AE (SAE) occurs during the study, a pharmacokinetic (PK) blood sample should be collected. Additionally, a 12-lead ECG, vital signs, and any appropriate clinical laboratory tests should be conducted."

to: " If a cardiac AE, neurological AE, fall, or serious AE (SAE) occurs during the study, a pharmacokinetic (PK) blood sample should be collected as close as possible to when the event occurs. Additionally, a 12-lead ECG, vital signs, and any appropriate clinical laboratory tests should be conducted as close as possible to when the event occurs. For out-of-hospital events, the medical monitor should be contacted to determine need for a PK sample and ECG."

<u>Eligibility Criteria</u>

- The following text was changed

from: " History of prior contralateral TKA or open knee surgery on the knee being considered for TKA."

to: " History of prior contralateral TKA within 1 year or open knee surgery on the knee being considered for TKA."

- The following text was removed from Exclusion Criteria #5

Currently pregnant, nursing, or planning to become pregnant during the study or within 1 month after study drug administration.

- The following text was changed

from: "Allergy, hypersensitivity, or contraindication to any of the study medications (i.e., bupivacaine, pregabalin, acetaminophen/paracetamol, celecoxib, oxycodone, morphine, hydromorphone, or tranexamic acid)."

to: "Allergy, hypersensitivity, intolerance, or contraindication to any of the study medications (i.e., bupivacaine, pregabalin, acetaminophen/paracetamol, or tranexamic acid"

- The following text was changed

from: " Rheumatoid or inflammatory arthritis or disease."

to: " Rheumatoid or inflammatory arthritis or disease that requires chronic analgesic treatment."

- The following text was changed

from: "Body weight <50 kg (110 pounds) or a body mass index >40 kg/m^2."

to: "Body weight <50 kg (110 pounds) or a body mass index >44 kg/m^2."

Efficacy Assessments

- The following text was changed

from: " Discharge readiness will be assessed q12h (at approximately 8:00 am and 8:00 pm [±2 hours]) from postsurgical Day 1 until hospital discharge."

to: "Discharge readiness will be assessed q12h (at approximately 8:00 am and 8:00 pm [±2 hours]) from postsurgical Day 0 up to the time of hospital discharge or up to reaching the discharge readiness score of 9, whichever comes first. Once a score of 9 is reached, no further discharge readiness assessments are required."

Time and Events Table

- The following text was changed

from: " Administer presurgical medications (i.e., acetaminophen/paracetamol 1000 mg orally (PO), celecoxib 200 mg PO, pregabalin 300 mg PO, and tranexamic acid 1 gram intravenously (IV) within 4 hours of surgery."

to: " Administer presurgical medications (i.e., acetaminophen/paracetamol 975-1000 mg orally (PO), celecoxib 200 mg PO (or in case of subject allergy, naproxen 500 mg PO or meloxicam 7.5 PO), and pregabalin up to 300 mg PO within 4 hours of surgery. Tranexamic acid up to 2 grams IV should be administrated at the beginning of surgery or intra-operatively."

- The following text was changed

from: "Administer scheduled post-surgical analgesics (i.e., acetaminophen/paracetamol 1000 mg PO every 8 hours [maximum of 3000 mg per day] and celecoxib 200 mg PO q12h)."

to: " Administer scheduled post-surgical analgesics (i.e., acetaminophen/paracetamol 975-1000 mg PO every 8 hours [maximum of 3000 mg per day] and celecoxib 200 mg PO q12h[or in case of subject allergy, naproxen 500 mg PO or meloxicam 7.5 PO])."

- The following text was changed

from: " If a cardiac AE, neurological AE, fall, or SAE occurs during the study, an unscheduled PK blood sample should be collected."

to: "If a cardiac AE, neurological AE, fall, or SAE occurs during the study, an unscheduled PK blood sample should be collected as close as possible to when the event occurs. For out-of-hospital events, the medical monitor should be contacted to determine need for a PK sample and ECG"

Section 9.1.1 (Duration of the Study and Subject Participation)

- The following sentences were added:

  "Bupivacaine is preferred as the spinal anesthetic; however, if the spinal fails or cannot be completed, the patient may receive general anesthesia. Total intravenous anesthesia (TIVA) is then the preferred route. If TIVA is contraindicated or not preferable, then inhalational anesthetics may be used. The use of fentanyl or short-acting analogues will be permitted in both groups.

  The following medications will be allowed:

  - Anti-emetics may be used pre-operatively or intra-operatively.
    - Decadron 10 mg x 1 intra-op is permitted
    - Scopolamine patch will be permitted if used as a pre-medication or intra-operatively but should be removed post-operatively.
  - Lidocaine will be permitted, if used as a local anesthetic at the site of IV placement or as IV to stabilize heart rhythm.
  - Propofol is permitted for induction and intra-operatively, but not post-operatively.
  - Versed, 1-2 mg IV, may be used pre-operatively for anxiety or sedation."

- The following text was changed

  from: " Acetaminophen/paracetamol 1000 mg PO every 8 hours (q8h)"

  to: " Acetaminophen/paracetamol 975-1000 mg PO every 8 hours (q8h)"

- The following sentences were added:
  - "If a subject has an allergy to celecoxib, they may use the following alternative drugs: naproxen 500 mg PO or meloxicam 7.5 mg PO.

- The following text was changed

  from: "Pregabalin 300 mg PO"

  to: "Pregabalin up to 300 mg PO"

- The following text was changed

  from: "Tranexamic acid 1 gram, intravenously (IV)"

  to: "On Day 0, all eligible subjects will also receive tranexamic acid, up to 2 mg (IV), at the beginning of surgery or intra-operatively."

- The following text was changed

  from: "Postsurgical rescue medication will consist of PO immediate-release oxycodone (initiating at 10 mg every 4 hours [q4h] or as needed [PRN]). If a subject cannot tolerate PO medication, IV morphine (2.5-5 mg) or hydromorphone (0.5-1 mg) may be administered q4h or PRN

  to: "Postsurgical rescue medication will consist of PO immediate-release oxycodone initiating up to 10 mg. The subject may re-dose, per physician judgment, as needed (PRN), if the initial rescue medication fails. If a subject cannot tolerate PO medication or has repeated failure of

the rescue medication with oxycodone (PO), IV morphine (2.5-5 mg) or hydromorphone (0.5-1 mg) may be administered q4h or PRN

Section 9.1.2 (Study Stopping Rules)

- The following text was changed

  from: "No formal stopping rules are planned for this study. If, however, 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)."

  to: "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).

  Blinded Data Review (BDR) of the subject data will be conducted by the Pacira Medical Monitoring Team after the first 60 subjects have completed Day 29 and subsequently on a bi-weekly basis throughout the conduct of this study. The Pacira Study Data Management and Biostatistics team will work in conjunction to provide blinded tables, figures, and listings for the BDR. Meeting notes will be compiled and filed at the end of each BDR session.

  The outcome of the BDR process will be the trigger for prompting the Safety Stopping Rules based on the incidence rate of all AESIs including the following:

  - Cardiac AESIs as defined in the protocol including cardiac arrest, hypertension, and hypotension exceeding 10%.
  - Neurologic AESIs as defined in the study protocol including dysgeusia and oral hypoaesthesia exceeding 10%.
  - Incidence rate of severe AESIs including cardiac AESIs and neurologic AESIsexceeding 5%.
  - Falls exceeding 5%.
  - Dizziness exceeding 25%.

  Unblinded review of the data and a relative risk data analysis will occur if any one of the events above should occur. If the risk relative to placebo is greater than 2, the next step will be any one of the following actions:

  - Halt subject dosing and/or study enrollment until the toxicity data can be further reviewed.
  - Revise eligibility criteria to exclude subjects who appear to be more at higher risk for a particular AE.

  Any unexplained death will be thoroughly reviewed and appropriate action taken."

Section 9.2 (Discussion of Study Design)

- The following text was changed

  from: " If a cardiac AE, neurological AE, fall, or SAE occurs during the study, a PK blood sample should be collected. Additionally, a 12-lead ECG, vital signs, and any appropriate clinical laboratory tests should be conducted."

  to: " If a cardiac AE, neurological AE, fall, or SAE occurs during the study, a PK blood sample should be collected as close as possible to when the event occurs. Additionally, a 12-lead ECG, vital signs, and any appropriate clinical laboratory tests should be conducted as close as possible to when the event occurs. For out-of-hospital events, the medical monitor should be contacted to determine need for a PK sample and ECG."

Section 10.2 (Exclusion Criteria)

- The following text was changed

  from: " History of prior contralateral TKA or open knee surgery on the knee being considered for TKA."

  to: " History of prior contralateral TKA within 1 year or open knee surgery on the knee being considered for TKA."

- The following text was changed

  from: "Allergy, hypersensitivity, or contraindication to any of the study medications (i.e., bupivacaine, pregabalin, acetaminophen/paracetamol, celecoxib, oxycodone, morphine, hydromorphone, or tranexamic acid)."

  to: "Allergy, hypersensitivity, intolerance, or contraindication to any of the study medications (i.e., bupivacaine, pregabalin, acetaminophen/paracetamol, or tranexamic acid"

- The following text was changed

  from: " Rheumatoid or inflammatory arthritis or disease."

  to: " Rheumatoid or inflammatory arthritis or disease that requires chronic analgesic treatment."

- The following text was changed

  from: "Body weight <50 kg (110 pounds) or a body mass index >40 kg/m^2."

  to: "Body weight <50 kg (110 pounds) or a body mass index >44 kg/m^2."

Section 11.1 (Treatment to be Administered)

- The following text was changed

  from: " Acetaminophen/paracetamol 1000 mg PO every 8 hours (q8h)"

  to: " Acetaminophen/paracetamol 975-1000 mg PO every 8 hours (q8h)"

- The following sentences were added:
    - "If a subject has an allergy to celecoxib, they may use the following alternative drugs: naproxen 500 mg PO or meloxicam 7.5 mg PO.
- The following text was changed

  from: "Pregabalin 300 mg PO"

  to: "Pregabalin up to 300 mg PO"
- The following text was changed

  from: "Tranexamic acid 1 gram, intravenously (IV)"

  to: "On Day 0, all eligible subjects will also receive tranexamic acid, up to 2 mg (IV), at the beginning of surgery or intra-operatively."
- The following text was changed

  from: "Postsurgical rescue medication will consist of PO immediate-release oxycodone (initiating at 10 mg q4h or PRN). If a subject cannot tolerate PO medication, IV morphine (2.5-5 mg) or hydromorphone (0.5-1 mg) may be administered q4h or PRN

  to: "Postsurgical rescue medication will consist of PO immediate-release oxycodone initiating up to 10 mg. The subject may re-dose, per physician judgment, PRN, if the initial rescue medication fails. If a subject cannot tolerate PO medication or has repeated failure of the rescue medication with oxycodone (PO), IV morphine (2.5-5 mg) or hydromorphone (0.5-1 mg) may be administered q4h or PRN

Section 12.1 (Efficacy Assessments)

- The following text was changed

  from: " Discharge readiness will be assessed q12h (at approximately 8:00 am and 8:00 pm [±2 hours]) from postsurgical Day 1 until hospital discharge."

  to: "Discharge readiness will be assessed q12h (at approximately 8:00 am and 8:00 pm [±2 hours]) from postsurgical Day 0 up to the time of hospital discharge or up to reaching the discharge readiness score of 9, whichever comes first. Once a score of 9 is reached, no further discharge readiness assessments are required."

Section 13.1.1 (Pain Intensity Assessment)

- The following sentence was added:

  "This does not apply to rescue medication VAS"

Section 13.1.7 (Adverse Events of Special Interest)

- The following text was changed

from: "If a cardiac AE, neurological AE, fall, or SAE occurs during the study, an unscheduled PK blood sample should be collected. In addition, a 12-lead ECG, vital signs, and any appropriate clinical laboratory tests should be conducted. ."

to: "If a cardiac AE, neurological AE, fall, or SAE occurs during the study, an unscheduled PK blood sample should be collected as close as possible to when the event occurs. In addition, a 12-lead ECG, vital signs, and any appropriate clinical laboratory tests should be conducted as close as possible to when the event occurs. For out-of-hospital events, the medical monitor should be contacted."

Section 13.3 (Baseline Procedures (Day 0 – Prior to Study Drug Administration)

- The following text was changed

from: "Administer acetaminophen/paracetamol 1000 mg PO, celecoxib 200 mg PO, pregabalin 300 mg PO, and tranexamic acid 1 gram IV within 4 hours prior to surgery."

to: "Administer acetaminophen/paracetamol 975-1000 mg PO, celecoxib 200 mg PO (in case of celecoxib allergy, naproxen 500 mg PO or meloxicam 7.5 mg PO may be administered), and pregabalin up to 300 mg PO within 4 hours prior to surgery. Tranexamic acid (up to 2 grams IV) should be administered either before surgery or intraoperatively."

Section 13.6 (Postsurgical Assessments through Hospital Discharge)

- The following text was changed

from: "Assess discharge readiness at 12, 24, 36, 48, 60, and 72 hours or discharge ready, whichever occurs first."

to: "Discharge readiness will be assessed q12h (at approximately 8:00 am and 8:00 pm [±2 hours]) from postsurgical Day 0 up to hospital discharge or up to reaching the discharge readiness score of 9, whichever comes first. Once a score of 9 is reached no further discharge readiness assessments are required."

Appendix 4 (Discharge Readiness)

- The following text was changed

from: "Only subjects who achieve a score of 9 or higher are considered ready for discharge. Discontinue assessing discharge readiness once a score of 9 or higher is reached."

to: "Discharge readiness will be assessed q12h (at approximately 8:00 am and 8:00 pm [±2 hours]) from postsurgical Day 0 up to hospital discharge or up to reaching the discharge readiness score of 9, whichever comes first. Once a score of 9 is reached no further discharge readiness assessments are required."

- The following table was updated for clarification:

from:

Parameter	Score
Vital Signs	
≤20% of preoperative value	2
20%-40% of preoperative value	1
>40% of preoperative value	0
Ambulation	
Steady gait/no dizziness	2
With assistance	1
None/dizziness	0
Nausea and Vomiting	
Minimal	2
Moderate	1
Severe	0
Pain	
Minimal	2
Moderate	1
Severe	0
Surgical Bleeding	
Minimal	2
Moderate	1
Severe	0

to:

Parameter	Score
Vital Signs: Measure Systolic Blood Pressure, Heart Rate, Respiratory Rate, Temperature	
ALL 4 vital signs are within 20% of the preoperative values	2
ANY of the 4 vital signs are within 20-40% of preoperative values and none of the vital signs exceed 40% of the preoperative values	1
ANY of the 4 vital signs are >40% of the preoperative valuess	0
Ambulation	
Steady gait/no dizziness	2
With assistance	1
None/dizziness	0
Nausea and Vomiting	
Minimal: no nausea/vomiting or nausea not requiring treatment	2
Moderate: nausea without vomiting and can tolerate liquids	1
Severe: nausea/vomiting and unable to tolerate oral liquids	0
Pain	
Minimal: requiring one or less pain rescue in the prior 12 hours	2
Moderate: requiring more than one pain rescue in the prior 12 hours	1
Severe: requiring supplemental IV analgesia for pain rescue	0
Surgical Bleeding	
Minimal: no action required	2

Moderate: requires dressing chage because it has soaked through or a compressive dressing	1
Severe: requires a suture or a return to the OR	0

1. SIGNATURE PAGE

James B. Jones, MD, PharmD, FACEP Sr. Vice President and Chief Medical Officer	28 July 2016 Date
Michael Rozycki, Vice President/ Regulatory Affairs and Pharmacovigilance	28 JULY 2016 Date
James P. Nezamis, MS Sr. Director, Biostatistics	28 July 2016 Date

2. SYNOPSIS

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

Title of Study: A Multicenter, Randomized, Double-Blind, Controlled Trial Comparing Local Infiltration Analgesia with EXPAREL to Local Infiltration Analgesia without EXPAREL to Manage Postsurgical Pain Following Total Knee Arthroplasty

Principal Investigator(s): To be determined

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

Publications (Reference): None

Objectives:

Primary Objective: The primary objective of this study is to compare pain control and total opioid consumption following local infiltration analgesia (LIA) with EXPAREL to LIA without EXPAREL in adult subjects undergoing primary unilateral total knee arthroplasty (TKA).

Secondary Objectives: The secondary objectives of this study are to compare additional efficacy, safety, and health economic outcomes following LIA with EXPAREL to LIA without EXPAREL in adult subjects undergoing primary unilateral TKA.

Methodology:

This is a Phase 4, multicenter, randomized, double-blind, controlled trial in approximately 300 adult subjects undergoing primary unilateral TKA under spinal anesthesia with bupivacaine HCl (10-15 mg).

Bupivacaine is preferred as the spinal anesthetic; however, if the spinal fails or cannot be completed, the patient may receive general anesthesia. Total intravenous anesthesia (TIVA) is then the preferred route. If TIVA is contraindicated or not preferable, then inhalational anesthetics may be used. The use of fentanyl or short-acting analogues will be permitted in both groups.

The following medications will be allowed:

- Anti-emetics may be used pre-operatively or intra-operatively.
  - Decadron 10 mg x 1 intra-op is permitted
  - Scopolamine patch will be permitted if used as a pre-medication or intra-operatively but should be removed post-operatively.
- Lidocaine will be permitted, if used as a local anesthetic at the site of IV placement or as IV to stabilize heart rhythm.
- Propofol is permitted for induction and intra-operatively, but not post-operatively.
- Versed, 1-2 mg IV, may be used pre-operatively for anxiety or sedation

Subjects will be screened within 30 days prior to study drug administration. During the screening visit, which must take place at least 1 day prior to surgery, subjects will be assessed for past or present neurologic, cardiac, and general medical conditions that in the opinion of the Investigator would preclude them from study participation. After the informed consent form (ICF) is signed, a medical history, surgical history, physical examination, physical therapy assessment, 12-lead electrocardiogram (ECG), vital sign measurements, urine drug screen, and urine pregnancy test for women of childbearing potential will be conducted.

On Day 0, all eligible subjects will receive the following medications within 4 hours prior to surgery:

- Acetaminophen/paracetamol 975-1000 mg, orally (PO).

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- Celecoxib 200 mg, PO.
    - If a subject has an allergy to celecoxib, they may use the following alternative drugs: naproxen 500 mg PO or meloxicam 7.5 mg PO.
- Pregabalin up to 300 mg, PO.

On Day 0, all eligible subjects will also receive tranexamic acid, up to 2 grams (intravenously [IV]), at the beginning of surgery or intra-operatively.

Subjects will be randomized 1:1 to two treatment groups. Subjects in Group 1 will receive LIA with EXPAREL 266 mg in 20 mL admixed with bupivacaine HCl 0.5% in 20 mL and expanded in volume with 80 mL normal saline (total volume of 120 mL). Subjects in Group 2 will receive LIA with bupivacaine HCl 0.5% in 20 mL expanded in volume with 100 mL normal saline (total volume of 120 mL).

Trained and qualified Investigators (see Appendix 5) will use their usual surgical technique to perform the TKA. Use of tourniquets and drains, if used, will be recorded. The case is to be completed at a time that will allow for a postsurgical physical therapy assessment on Day 0.

Subjects will be required to remain at the hospital facility for a minimum of 48 hours after surgery. The subjects must still complete the 72-hour assessments if they are discharged from the hospital facility prior to 72 hours after surgery.

The use of fentanyl or analogues will be permitted (during surgery only) in both groups. Intraoperative administration of other opioids or any other analgesic, local anesthetics, or anti-inflammatory agents will be prohibited in both groups, unless needed to treat an AE.

Study drug will be administered using six 20 cc syringes with 22-gauge needles prior to wound closure. Each stick should deliver approximately 1-1.5 cc to the intended area. The tissue should visibly expand with minimal leakage. Study drug should be injected in the prescribed locations based on the areas of highest nerve density.

Prior to cementation

- Syringe #1: Posterior capsule (8-10 sticks medial and 8-10 sticks lateral).
- Syringe #2: Femur – medial and lateral periosteum, posterior periosteum, suprapatellar/quadriceps tendon (20 sticks).
- Syringe #3: Tibia – fat pad (5 sticks); pes anserinus, medial collateral ligament, and gutter (15 sticks).
- Syringe #4: Circumferential periosteum (15-20 sticks).

After cementation

- Syringe #5: Midline quadriceps tendon (10 sticks); retinaculum, medial gutter, femoral to tibia (10 sticks).
- Syringe #6: Lateral gutter, femoral to tibial (10 sticks); subcutaneous/closure (10 sticks).

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

Postsurgically, all subjects will receive the following scheduled medications until hospital discharge:

- Acetaminophen/paracetamol 975-1000 mg PO every 8 hours (q8h). The total daily dose is not to exceed 3000 mg.
- Celecoxib 200 mg PO every 12 hours (q12h).
    - If a subject has an allergy to celecoxib, they may use the following alternative drugs: naproxen

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500 mg PO or meloxicam 7.5 mg PO.

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

Postsurgical Rescue Medication

Subjects should only receive rescue medication upon request for pain control, as needed. Postsurgical rescue medication will consist of PO immediate-release oxycodone initiating up to 10 mg. The subject may re-dose, per physician judgment, as needed (PRN), if the initial rescue medication fails. If a subject cannot tolerate PO medication or has repeated failure of the rescue medication with oxycodone (PO), IV morphine (2.5-5 mg) or hydromorphone (0.5-1 mg) may be administered q4h or PRN. **Patient-controlled analgesia (PCA) is not permitted**. No other rescue analgesic agents, including NSAIDs, are permitted until hospital discharge. After discharge, the analgesic regimen may be adjusted for each subject individually as deemed appropriate by the physician responsible for the postsurgical care.

Postsurgical Assessments

Postsurgical clinical assessments will include pain intensity scores using a 10-cm visual analog scale (VAS) (see Appendix 1); overall benefit of analgesia score (OBAS) questionnaire (see Appendix 2); total postsurgical opioid consumption; physical therapy assessment (see Physical Therapy Assessment Manual); nurse's satisfaction with overall analgesia (see Appendix 3); and discharge readiness (see Appendix 4).

Adverse events will be recorded from the time the ICF is signed through postsurgical Day 29. If a cardiac AE, neurological AE, fall, or serious AE (SAE) occurs during the study, a pharmacokinetic (PK) blood sample should be collected as close as possible to when the event occurs. Additionally, a 12-lead ECG, vital signs, and any appropriate clinical laboratory tests should be conducted as close as possible to when the event occurs. For out-of-hospital events, the medical monitor should be contacted to determine need for a PK sample and ECG.

Cardiac AEs of special interest include chest pain (angina, myocardial infarction), abnormal/irregular heart rate (bradycardia, tachycardia, extrasystoles), and shortness of breath requiring intervention. Neurologic AEs of special interest include altered mental status/altered sensorium, rigidity, dysarthria, seizure, tremors, metallic taste, tinnitus, perioral numbness, and visual disturbance. Additionally, the following events are of special interest if they persist or occur beyond 72-hours postdose: dizziness, hyperesthesia, muscular twitching, and tingling/paresthesia.

Postsurgical health economic outcome assessments will include hospital length of stay (LOS), use of skilled nursing facility, outpatient physical therapy use, hospital readmissions, and use of other health services following discharge (phone calls related to postsurgical pain, unscheduled visits related to postsurgical pain, and visits to emergency department) through postsurgical Day 29.

A follow-up visit will be scheduled for all subjects on postsurgical Day 14. A follow-up phone call will be made on postsurgical Day 29 to all subjects who received study drug to assess for AEs.

Number of Subjects (Planned):

Approximately 300 subjects (150 subjects per treatment group) are planned for enrollment in this study in order to have at least 260 evaluable subjects.

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

Eligibility Criteria:

Inclusion Criteria:

1. Male or female, at least 18 years of age at screening.
2. Scheduled to undergo primary, unilateral, tricompartmental TKA under spinal anesthesia.
3. Primary indication for TKA is degenerative osteoarthritis of the knee.
4. American Society of Anesthesiologists (ASA) physical status 1, 2, or 3.
5. Female subjects must be surgically sterile; or at least 2 years postmenopausal; or have a monogamous partner who is surgically sterile; or practicing double-barrier contraception; or practicing abstinence (must agree to use double-barrier contraception in the event of sexual activity); or using an insertable, injectable, transdermal, or combination oral contraceptive approved by the FDA for greater than 2 months prior to screening and commit to the use of an acceptable form of birth control for the duration of the study and for 30 days after completion of the study.
6. Able to provide informed consent, adhere to the study visit schedule, and complete all study assessments.

Exclusion Criteria:

1. Currently pregnant, nursing, or planning to become pregnant during the study or within 1 month after study drug administration.
2. History of prior contralateral TKA within 1 year or open knee surgery on the knee being considered for TKA. Prior arthroscopy is permitted.
3. Planned concurrent surgical procedure (e.g., bilateral TKA).
4. Undergoing unicompartmental TKA or revision TKA.
5. Concurrent painful physical condition that may require analgesic treatment (such as an NSAID or opioid) in the postsurgical period for pain that is not strictly related to the knee surgery and which may confound the postsurgical assessments (e.g., significant pain from other joints including the non-index knee joint, chronic neuropathic pain, concurrent or prior contralateral TKA, concurrent foot surgery).
6. Comorbidity impacting current physical function of Investigator opinion that it may impact postsurgical rehabilitation.
7. Allergy, hypersensitivity, intolerance, or contraindication to any of the study medications (i.e., bupivacaine, pregabalin, acetaminophen/paracetamol, or tranexamic acid).
8. Use of any of the following medications within the times specified before surgery: long-acting opioid medication or NSAIDs (except for low-dose aspirin used for cardioprotection) within 3 days, or any opioid medication within 24 hours.
9. Initiation of treatment with any of the following medications within 1 month of study drug administration or if the medication(s) are being given to control pain: selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin (Lyrica®), or duloxetine (Cymbalta®). If a subject is taking one of these medications for a reason other than pain control, he or she must be on a stable dose for at least 1 month prior to study drug administration.
10. Current use of systemic glucocorticosteroids within 1 month of enrollment in this study.
11. Use of dexmedetomidine HCl (Precedex®) within 3 days of study drug administration.
12. History of coronary or vascular stent placed within the past 3 months (may be extended to 1 year if medically

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Name of Finished Product: EXPAREL (bupivacaine liposome injectable suspension)		
Name of Active Ingredient: Bupivacaine, 1.3%, 13.3 mg/mL		

indicated per physician discretion).

13. Have been treated for a deep vein thrombosis, pulmonary embolism, myocardial infarction, or ischemic stroke within the past 6 months (may be extended to 1 year if medically indicated per physician discretion).
14. Rheumatoid or inflammatory arthritis or disease that requires chronic analgesic treatment.
15. Severely impaired renal or hepatic function (e.g., serum creatinine level >2 mg/dL [176.8 µmol/L], blood urea nitrogen level >50 mg/dL [17.9 mmol/L], serum aspartate aminotransferase [AST] level >3 times the upper limit of normal [ULN], or serum alanine aminotransferase [ALT] level >3 times the ULN.)
16. Any neurologic or psychiatric disorder that might impact postsurgical pain or interfere with study assessments.
17. Malignancy in the last 2 years, per physician discretion.
18. History of misuse, abuse, or dependence on opioid analgesics, other prescription drugs, illicit drugs, or alcohol.
19. Failure to pass the alcohol breath test or urine drug screen.
20. Body weight <50 kg (110 pounds) or a body mass index >44 kg/m^2.
21. Previous participation in an EXPAREL study.
22. Administration of an investigational drug within 30 days or 5 elimination half-lives of such investigational drug, whichever is longer, prior to study drug administration, or planned administration of another investigational product or procedure during the subject's participation in this study.

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

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

Active ingredients: Bupivacaine

Dosage: Single dose of EXPAREL 266 mg in 20 mL admixed with bupivacaine HCl 0.5% in 20 mL and expanded in volume with 80 mL normal saline (total volume of 120 mL)

Lot number: To be determined

Mode of administration: Intraoperative local infiltration

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

Name: Bupivacaine HCl 0.5% (Group 2)

Active ingredients: Bupivacaine

Dosage: Single dose of bupivacaine HCl 0.5% in 20 mL expanded in volume with 100 mL normal saline (total volume of 120 mL)

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

Mode of administration: Intraoperative local infiltration

Duration of Subject Participation in Study:

Participation will begin at the signing of the ICF. No more than 30 days should pass between signing of the ICF and the administration of study drug. The time from study drug administration through the end of participation is 30 ± 3 days. Therefore, subjects may participate in the study for up to 63 days.

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Name of Finished Product: EXPAREL (bupivacaine liposome injectable suspension)		
Name of Active Ingredient: Bupivacaine, 1.3%, 13.3 mg/mL		

Efficacy Assessments:

The following efficacy measurements will be assessed at the times specified after the end of surgery:

- Pain intensity scores using the VAS upon arrival at the post-anesthesia care unit (PACU); at 4, 6, 8, 10, 12, 24, 28, 32, 36, 48, 52, 56, 60, and 72 hours or until hospital discharge; immediately prior to each administration of rescue pain medication; and just prior to hospital discharge (see Appendix 1).
- Amount of all opioid rescue analgesics taken through postsurgical Day 29.
- The OBAS questionnaire at 24, 48, and 72 hours or upon hospital discharge (see Appendix 2).
- Physical therapy assessments (timed up and go test, stair climbing test, and timed walk test) will be conducted once postsurgically on Day 0; at approximately 8:00 am and 8:00 pm (±2 hours) from postsurgical Day 1 through hospital discharge; and on postsurgical Day 14 (see Physical Therapy Assessment Manual). Preemptive use of opioids or NSAIDs prior to the physical therapy assessment is not permitted.
- Nurse's satisfaction with overall analgesia will be assessed at 24, 48, and 72 hours or upon hospital discharge (see Appendix 3).
- Discharge readiness will be assessed q12h (at approximately 8:00 am and 8:00 pm [±2 hours]) from postsurgical Day 0 up to the time of hospital discharge or up to reaching the discharge readiness score of 9, whichever comes first. Once a score of 9 is reached, no further discharge readiness assessments are required (see Appendix 4).

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

Efficacy Endpoints:

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

Primary Efficacy Endpoint:

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

Secondary Endpoints:

- Proportion of subjects who are pain free (defined as a VAS pain intensity score of ≤1.5 and no prior rescue medication) at each assessed timepoint.
- The VAS pain intensity scores at each assessed timepoint.
- The AUC of the VAS pain intensity scores through 24, 36, 48, 60, and 72 hours.
- The AUC of the VAS pain intensity scores from 24–48 and 48–72 hours.
- The sum of the pain intensity scores (SPIS) through 24, 48, and 72 hours.
- SPIS from 24–48 and 48–72 hours.
- Total inpatient postsurgical opioid consumption (in mg) through 24 and 72 hours or hospital discharge.
- Total postsurgical opioid consumption (in mg) from hospital discharge through postsurgical Day 29.
- Percentage of opioid-free subjects through 24, 48, and 72 hours or hospital discharge.
- Time to first opioid rescue through 72 hours or hospital discharge.
- The OBAS total score at 24, 48, and 72 hours or upon hospital discharge.
- Proportion of subjects meeting Modified Postanesthesia Discharge Scoring System (MPADSS) criteria for discharge readiness at each assessed timepoint.
- Nurse's satisfaction with overall analgesia at 24, 48, and 72 hours or upon hospital discharge.

Health Economic Outcomes Assessments:

The health economic outcomes will include:

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

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Health Economic Outcomes Endpoints:

- Hospital LOS, defined as the time from completion of the wound closure until the hospital discharge order is written or through postsurgical Day 29, whichever is sooner.
- Incidence of hospital readmission through postsurgical Day 29.
- Incidence of skilled nursing facility use.
- Total time spent in skilled nursing facility.
- Number of postsurgical physical therapy visits.
- Number of phone calls related to postsurgical pain.
- Number of unscheduled visits related to postsurgical pain.
- Number of visits to the emergency department.

Safety Assessment:

- Adverse events from the time the ICF is signed through postsurgical Day 29.

Safety Endpoint:

- Incidence of treatment-emergent AEs (TEAEs) and SAEs through postsurgical Day 29.

Statistical Methods:

A comprehensive statistical analysis plan will be developed for this study. Demographic and baseline characteristics will be summarized descriptively by treatment group. Efficacy data will be summarized by treatment group. Superiority of treatment with EXPAREL (Group 1) versus treatment without EXPAREL (Group 2) will be determined using an analysis of variance (ANOVA) with treatment as the main effect on the AUC of the VAS pain intensity scores through 48 hours. If superiority of pain control is demonstrated, then the total opioid use (in morphine equivalent doses) through 48 hours in Group 1 will be compared to that of Group 2 using an ANOVA. This hierarchical testing procedure will protect the type 1 error rate. Secondary efficacy endpoints will be analyzed using ANOVA, chi-square tests, and log-rank tests, as appropriate. Safety endpoints will be summarized descriptively by treatment group.

Sample Size

A sample size of 130 subjects in each group is needed to have at least 90% power to detect a −0.3 unit difference in the geometric means for total opioid dose assuming the common standard deviation (SD) is 0.670 using a two group t-test with a 0.025 two-sided significance level. A sample size of 78 is needed in each group to have at least 90% power to detect a difference in $AUC_{(12\text{-}48)}$ of the VAS pain intensity score means of −40 assuming the common SD is 70 using a two group t-test with a 0.025 two-sided significance level. Three hundred subjects (150 per treatment arm) will be randomized into this study in order to have 260 evaluable subjects.

Table 1: Time and Events Schedule of Study Procedures

	Screen Visit**	D0 Preop	0 min	OR	PACU Arrival	4h	6h	8h	10h	12h	24h	28h	32h	36h	48h	52h	56h	60h	72h	D14 Visit	D29 Call
Time Window	**Within 30 days**					**±15 min**	**±30 min**	**±30 min**	**±1h**	**±1h**	**±1h**	**±2h**	**±2h**	**±2h**	**±2h**	**±2h**	**±2h**	**±2h**	**±4h**	**±3d**	**±3d**
Obtain signed ICF	X																				
Assess/confirm eligibility	X	X																			
Record medical and surgical history	X	X																			
Record demographics and baseline characteristics	X																				
Conduct pregnancy test for WOCBP	X	X																			
Conduct urine drug screen	X	X																			
Conduct alcohol breath test		X																			
Perform physical examination	X																			X	
Measure vital signs (heart rate and blood pressure)[1]	X	X																			
Perform 12-lead ECG	X																				
Perform PT assessment (at approximately 8:00 am and 8:00 pm ±2h); record date and time[2]	X					◄	-	-	-	-	-	-	-	-	-	-	-	-	►	X	
Record VAS pain intensity score[3,4,5,6]		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Randomize subject, prepare study drug		X																			
Administer scheduled presurgical medications[7]		X																			
Administer study drug according to randomization schedule; record start and stop times			X																		
Record intraoperative opioids administered and doses				X																	
Record start and end time of tourniquet use and maximum pressure (mmHg) used				X																	
Record date and time of insertion of drain(s), if used				X																	
Record surgery start and stop times				X																	
Record date and time of removal of drain(s), if used						◄	-	-	-	-	-	-	-	-	-	-	-	-	►		
Record times and doses of all analgesic medication administered					◄	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	►
Administer scheduled postsurgical analgesics[3,8]					◄	-	-	-	-	-	-	-	-	-	-	-	-	-	►		
Complete OBAS questionnaire[6]											X				X				X		
Nurse's satisfaction with postsurgical pain control[6]											X				X				X		
Assess discharge readiness q12h (at approximately 8:00 am and 8:00 pm ±2h); record date and time[3]					◄	-	-	-	-	-	-	-	-	-	-	-	-	-	►		
Record date and time of actual discharge											◄	-	-	-	-	-	-	-	-	►	
Document any hospital readmissions																				X	X
Document post-surgical outpatient PT visits																				X	X

Document use of skilled nursing facility																			X	X
Document any unscheduled phone calls or office visits related to pain after discharge																			X	X
Document any unscheduled visits to the ER after discharge																			X	X
Record prior and concomitant medications[9]	←	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	→
Record AEs (beginning at the time ICF is signed)[10]	←	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	→

Abbreviations: AE = adverse event; d = day; D = day; ECG = electrocardiogram; ER = emergency room; h = hours; ICF = informed consent form; min = minutes; OBAS = overall benefit of analgesia score; OR = operating room; PACU = post-anesthesia care unit; Preop = preoperative; PT = physical therapy; q12h = every 12 hours; VAS = visual analog scale; WOCBP = women of childbearing potential.

* Postsurgical assessments will be conducted at the timepoints specified after the end of surgery. **At timepoints when multiple assessments coincide, the VAS pain intensity assessment will be conducted first and the physical therapy assessment will be conducted last**.

** The screening visit must take place at least 1 day prior to surgery.

[1] Vital signs will be measured after the subject has rested in a supine position for at least 5 minutes.

[2] Physical therapy assessments (timed up and go test, stair climbing test, and timed walk test) will be conducted once postsurgically on Day 0; q12h from postsurgical Day 1 through hospital discharge; and on postsurgical Day 14. Preemptive use of opioids or NSAIDs prior to the physical therapy assessment is not permitted.

[3] Timepoints shown through 72 hours or until hospital discharge.

[4] The preoperative pain intensity assessment should be conducted prior to administration of any premedication.

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

[6] And just prior to hospital discharge.

[7] Administer presurgical medications (i.e., acetaminophen/paracetamol 975-1000 mg orally (PO), celecoxib 200 mg PO (or in case of subject allergy, naproxen 500 mg PO or meloxicam 7.5 PO), and pregabalin up to 300 mg PO within 4 hours of surgery. Tranexamic acid up to 2 grams IV should be administrated at the beginning of surgery or intra-operatively.

[8] Administer scheduled post-surgical analgesics (i.e., acetaminophen/paracetamol 975-1000 mg PO every 8 hours [maximum of 3000 mg per day] and celecoxib 200 mg PO q12h[or in case of subject allergy, naproxen 500 mg PO or meloxicam 7.5 PO]).

[9] Instruct subject to discontinue prohibited medications. Record date and time of all medications starting at least 30 days prior to study drug administration until hospital discharge. Record medications administered for treatment of an AE through postsurgical Day 29.

[10] If a cardiac AE, neurological AE, fall, or SAE occurs during the study, an unscheduled PK blood sample should be collected as close as possible to when the event occurs. For out-of-hospital events, the medical monitor should be contacted to determine need for a PK sample and ECG. In addition, a 12-lead ECG, vital signs, and any appropriate clinical laboratory tests should be conducted. Cardiac AEs of special interest include chest pain (angina, myocardial infarction), abnormal/irregular heart rate (bradycardia, tachycardia, extrasystoles), and shortness of breath requiring intervention. Neurologic AEs of special interest include altered mental status/altered sensorium, rigidity, dysarthria, seizure, tremors, metallic taste, tinnitus, perioral numbness, and visual disturbance. Additionally, the following events are of special interest if they persist or occur beyond 72-hours postdose: dizziness, hyperesthesia, muscular twitching, and tingling/paresthesia.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

4.1. List of Abbreviations

AE	Adverse event
ANOVA	Analysis of variance
AUC	Area under the curve
CFR	Code of Federal Regulations
CI	Confidence interval
CRF	Case Report Form
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
LIA	Local infiltration analgesia
LOS	Length of stay
MPADSS	Modified Postanesthesia Discharge Scoring System
NDA	New Drug Application
NRS	Numeric rating scale
NRS-R	Numeric rating scale at rest
NSAIDs	Non-steroidal anti-inflammatory drugs
OBAS	Overall benefit of analgesia score
PACU	Post-anesthesia care unit
PCA	Patient-controlled analgesia
PK	Pharmacokinetic
PO	Oral
PRN	As needed
PT	Preferred term
PTAE	Pretreatment adverse event

q4h	Every 4 hours
q8h	Every 8 hours
q12h	Every 12 hours
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SNRI	Selective norepinephrine reuptake inhibitor
SPIS	Sum of the pain intensity scores
SSRI	Selective serotonin reuptake inhibitor
TEAE	Treatment-emergent adverse event
TKA	Total knee arthroplasty
ULN	Upper limit of normal
US	United States (of America)
VAS	Visual analog scale

4.2. Definition of Terms

Not applicable.

5. ETHICS

5.1. Institutional Review Board/Independent Ethics Committee

Prior to screening subjects into this study, each study site will obtain the approval of an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) that complies with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and/or the United States (US) Food and Drug Administration (FDA) Title 21 Code of Federal Regulations (CFR) Part 56. For study sites with IECs that comply with ICH GCP, but not US FDA 21 CFR Part 56, a waiver request will be submitted to FDA. If granted, then FDA's letter documenting the waiver will be provided to the Investigator to be maintained with the signed Investigator statement (Form FDA 1572) in the Investigator's study binder. 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, the Directive 2001/20/EC of the European Parliament and of the Council of 04 April 2001 and amendments, the Commission Directive 2005/28/EC of 08 April 2005 and amendments, 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) is free to withdraw the subject at any time for safety or administrative reasons. Any other requirements necessary for the protection of the human rights of the subject will also be explained, according to the current ICH GCP (E6) and the Declaration of Helsinki (1964, and as amended through 2013).

6. INVESTIGATORS AND STUDY ADMINISTRATION STRUCTURE

Information regarding the Investigators, sites, laboratories, and other service providers is available upon request to the IRB/IECs and regulatory agencies.

7. INTRODUCTION

7.1. Indication

EXPAREL® was developed to provide a prolonged period of decreased pain and decreased opioid use with a single dose administration without the use of indwelling catheters. It is indicated for use as an analgesic injected into the surgical site for postsurgical pain relief.

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

7.2. Current Therapies/Treatments

Current modalities of postsurgical analgesic treatment include wound infiltration and nerve block with local anesthetic agents, usually combined with the systemic administration of analgesics (multimodal therapy). Multimodal therapy usually includes opioid medications, nonsteroidal anti-inflammatory drugs (NSAIDs), and/or acetaminophen provided through a variety of routes including intravenous (IV), transdermal patch, and oral (PO) administration. Opioids are widely used and considered some of the most powerful analgesics; however, they also have considerable drawbacks including time and resources required for monitoring opioid-related side effects. A reduction in the use of postoperative opioids is desirable to decrease the incidence and severity of opioid-induced adverse effects, such as respiratory depression, nausea, vomiting, constipation, somnolence, pruritus, and urinary retention.

Total knee arthroplasty (TKA) is a common surgical procedure that causes postsurgical pain of considerable intensity and duration. While the standard analgesic medications administered prior to the TKA procedure and used to provide analgesic relief immediately after surgery can vary, most experts agree that multimodal pain control has become the standard of care. In TKA, that may include local analgesics (i.e., wound infiltration) combined with acetaminophen and an NSAID or a cyclooxygenase-2 selective inhibitor with opioids reserved as rescue analgesics. This approach has been shown to significantly reduce opioid requirements and opioid-related adverse events (AEs). It is clear that opioid-related AEs increase perioperative morbidity, including delay in ambulation and participation in rehabilitation therapy programs. Also, analgesic adjuncts, such as dexamethasone (single intraoperative dose) and gabapentinoids (i.e., gabapentin and pregabalin) may provide further benefit (Joshi 2015). Following surgery, additional analgesic treatment often includes opioids. Therefore, TKA was selected as an appropriate pain model for investigating a sustained-release formulation of bupivacaine, which has the potential to overcome the limitation reported in previous studies with regard to the duration of the analgesic effect obtained with commercially-available products.

With over 70 million surgeries performed annually in the US, postoperative pain is a ubiquitous condition among our population. While it is a predictable component of the postoperative process, such pain is often poorly managed, resulting in clinical and physiological changes that increase morbidity and mortality (inability to ambulate early, etc.), diminish quality of life,

and extend length of stay, thereby increasing hospital expenditures (Oderda 2007) and reducing patient satisfaction. Effective relief of acute pain with minimal opioid complications, on the other hand, may improve clinical outcomes, avoid complications (like delay in regaining bowel function or an inability to tolerate liquid and solid oral intake, etc.), and conserve healthcare resources. As such, the Joint Commission on Accreditation of Healthcare Organizations 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 postoperative pain, and are currently considered the mainstay of treatment. Adverse events related to opioid administration (e.g., nausea, vomiting, ileus, confusion), however, represent one important reason that there is a need to develop opioid-sparing strategies. Indeed, fear of gastrointestinal side effects such as nausea and vomiting, as well as respiratory depression, present major limitations for the widespread use of opioid analgesics (Chernin 2001 and Viscusi 2009). Furthermore, management of opioid-related events often requires medical attention (e.g., opioid antagonists, antiemetic agents) and increased pharmacy/nursing time, which may raise healthcare expenses (Carroll 1994).

7.3. EXPAREL (bupivacaine liposome injectable suspension)

Bupivacaine is one of the longer-acting local anesthetics, but even so it has a limited duration of action after local administration, usually reported as less than 8 hours. EXPAREL (Pacira Pharmaceuticals, Inc., Parsippany, NJ) is a bupivacaine liposome injectable suspension. It consists of microscopic spherical, multivesicular liposomes (DepoFoam® drug delivery system), organized in a honeycomb-like structure comprising numerous non-concentric internal aqueous chambers containing a bupivacaine base at a concentration of 13.3 mg/mL. Each chamber is separated from adjacent chambers by lipid membranes. The lipids (phospholipids, cholesterol, and triglycerides) are naturally occurring or close analogs of endogenous lipids. Bupivacaine is slowly released from the DepoFoam particles by a complex mechanism involving reorganization of the barrier lipid membranes and subsequent diffusion of the drug over an extended period of time. A small amount of extra-liposomal bupivacaine (i.e., not bound within the DepoFoam particles) enables EXPAREL to have a similar onset of action to standard bupivacaine HCl. Because of this, EXPAREL has been noted in wound infiltration studies to have a bimodal curve (Apseloff 2013), with an initial peak at approximately 0-2 hours and a second peak at approximately 24-48 hours (Hu 2013).

EXPAREL was approved by the US FDA in 2011 for administration into the surgical site to produce postsurgical analgesia. The active ingredient (bupivacaine) and inactive ingredient (DepoFoam) of EXPAREL are each contained, though separately, in FDA-approved products:

- Bupivacaine HCl solution, a well-characterized anesthetic/analgesic, with more than 35 years of its use in the US.
- DepoFoam, a liposomal extended-release formulation contained in the marketed product DepoCyt® (1999). The form of DepoFoam used in each of the products – DepoCyt and EXPAREL – has a slightly different mixture of lipid components.

7.3.1. Summary of Human Experience with EXPAREL

7.3.1.1. Wound Infiltration New Drug Application (NDA)

During the original clinical development program (wound infiltration), Pacira conducted 21 clinical studies and one observational follow-up study to investigate EXPAREL (formerly known as SKY0402™). Across these studies, a total of 1307 human subjects received EXPAREL at doses ranging from 10-750 mg (or 9-665 mg free base) and by various routes: local administration into the surgical wound, subcutaneous, perineural, and epidural. The investigational drug product has been well tolerated and the reported AEs occurred at a similar rate as the corresponding bupivacaine HCl controls in the active comparator studies.

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

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

EXPAREL was demonstrated to produce statistically significant and clinically meaningful analgesia in two pivotal placebo-controlled Phase 3 studies (SKY0402-C-317 and SKY0402-C-316) involving both orthopedic and soft tissue procedures over 36 and 72 hours, respectively. In addition to meeting their primary endpoints (area under the curve [AUC] of the numeric rating scale [NRS] at rest [NRS-R] pain intensity scores through 72 hours [Study SKY0402-C-316] and through 24 hours [Study SKY0402-C-317]), key secondary endpoints also were met, demonstrating prolonged analgesia and reduction of opioid use by various measures (percentage of subjects who received no supplementary opioid medication; total amount of postoperative consumption of opioid medication; and time to first use of opioid medication). The robust nature of the efficacy results in both pivotal studies SKY0402-C-316 and SKY0402-C-317 was demonstrated across subgroups of subjects with various prognostic features and across demographic subgroups.

An analysis was performed to compare the incidence of opioid-related AEs between the EXPAREL and bupivacaine HCl groups in all bupivacaine-controlled, parallel-group wound infiltration studies (SIMPLE TKA 311, SKY0402-C-208, SIMPLE Hemorrhoidectomy 312, SKY0402-C-209, SKY0402-C-207, SKY0402-C-201, and SIMPLE Breast Augmentation 315). There was a statistically significantly lower incidence of opioid-related AEs in the EXPAREL ≤300 mg group compared to the bupivacaine HCl group through 72 hours postdose. This was consistent with the statistically significantly lower total postoperative consumption of opioids in the EXPAREL ≤300 mg group through 72 hours postdose. Fewer subjects in the EXPAREL ≤300 mg group had at least one opioid-related AE compared to the bupivacaine HCl group (25.6% versus 45.6%; $p<0.0001$). The total opioid medication administered (adjusted geometric mean) through 72 hours postdose was statistically significantly lower in the EXPAREL ≤300 mg group (7.94 mg) compared to the bupivacaine HCl group (15.84 mg); $p<0.0001$. The EXPAREL >300 mg group did not show a statistically significant advantage favoring EXPAREL; the mean

(standard deviation [SD]) of the average number of opioid-related AEs per subject was 0.58 (0.522), and the total opioid medication administered (adjusted geometric mean) through 72 hours postdose was 22.82 mg in the EXPAREL >300 mg group.

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

7.3.1.2. Nerve Block Supplemental NDA

A total of 335 human subjects received EXPAREL as a nerve block over six clinical studies (SKY0402-002, SKY0402-C-111, SKY0402-C-203, SKY0402-C-211, 402-C-322, and 402-C-323) utilizing three different surgical models (femoral nerve block, intercostal nerve block, and ankle nerve block). Doses administered ranged from 2 mg to 310 mg. The data from three of these studies (SKY0402-002, SKY0402-C-203, and SKY0402-C-211) were included in the wound infiltration NDA as well as the nerve block supplemental NDA.

Phase 3 Nerve Block Studies

Study 402-C-322 was a Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled study to investigate the efficacy and safety of EXPAREL (total of 266 mg in 20 mL) divided into three equal doses in three syringes of approximately 88 mg in 6.6 mL volume per nerve and administered to each of three nerve segments (index nerve, nerve above, and nerve below) compared with saline placebo nerve block. The primary objective was to evaluate the efficacy of intercostal nerve block using EXPAREL compared with placebo in subjects undergoing posterolateral thoracotomy.

Intercostal nerve block with EXPAREL was well tolerated in subjects undergoing posterolateral thoracotomy. However, the study did not meet its primary efficacy endpoint: there was no statistically significant difference in the mean AUC of the NRS-R pain intensity scores through 72 hours between subjects in the EXPAREL group and in the placebo group although a treatment effect was evident through 12 to 24 hours based upon a post hoc analysis.

Fifty-six subjects (59.6%) in the EXPAREL group and 46 subjects (50.5%) in the placebo group experienced one or more TEAEs. Most of the TEAEs were mild or moderate in severity. Three subjects (3.2%) in the EXPAREL group and no subjects in the placebo group experienced a TEAE that were assessed by the Investigator as related to study drug. Twelve subjects (12.8%) in the EXPAREL group and 9 subjects (9.9%) in the placebo group experienced one or more treatment-emergent serious AEs (SAEs). Two of these subjects in the EXPAREL group and four of these subjects in the placebo group died. None of the SAEs or deaths was assessed by the Investigator as related to study drug. Two subjects (2.1%) in the EXPAREL group and seven subjects (7.4%) in the placebo group were withdrawn from the study due to an AE.

Study 402-C-323 was a Phase 2/3, multicenter, randomized, double-blind, parallel-group, placebo-controlled, dose-ranging study in subjects undergoing primary unilateral TKA under general or spinal anesthesia. The primary objectives of Part 1 were to (1) evaluate three dose levels of EXPAREL versus placebo with respect to the magnitude and duration of the analgesic effect achieved following single dose injection femoral nerve block with EXPAREL, and (2) select a single therapeutic dose of EXPAREL from the three dose levels to be tested in Part 2.

The primary objective of Part 2 was to compare the magnitude and duration of the analgesic effect of single injection femoral nerve block of a single dose level of EXPAREL (selected from Part 1) with placebo (preservative-free normal saline for injection).

Femoral nerve block with EXPAREL at 67 mg, 133 mg, and 266 mg was well tolerated in subjects undergoing TKA. There were no discernible safety differences across the treatment groups. There was a dose response in EXPAREL-treated subjects. A dose of 266 mg was selected for Part 2.

Part 2 of the study met its primary efficacy endpoint: the difference in the AUC of the NRS-R pain intensity scores through 72 hours between the EXPAREL group and the placebo group was statistically significant. Additionally, the difference in the total postsurgical opioid consumption (mg) through 72 hours between the EXPAREL 266 mg group and the placebo group was statistically significant indicating lower opioid consumption in the EXPAREL group.

In Part 1, there were no discernible safety differences across the treatment groups. In Part 2, the incidences of TEAEs and treatment-emergent SAEs were similar between the EXPAREL 266 mg group and the placebo group. There were no deaths or withdrawals due to an AE during the study.

During Part 2 of the study, three subjects experienced a fall; each subject was in the EXPAREL 266 mg group. Each of the three subjects was able to complete the 20-meter walk test at 24 hours, 72 hours, and on Day 30. The rate of inpatient falls in study 402-C-323, 1.8%, was very similar to the overall incidence of inpatient falls in TKA patients (between 1% and 2%).

The 20-meter walk test was used to determine whether there was any significant degree of motor blockade with use of EXPAREL. The percentage of subjects who were able to complete the walk test at 24 hours and 72 hours did not differ significantly across the EXPAREL and placebo groups in Part 1. In Part 2, the percentage of subjects who were able to complete the walk test was comparable between EXPAREL 266 mg and placebo groups at 24 hours (53.0% vs. 58.5%, respectively) and 72 hours (83.1% vs. 92.6%, respectively). This suggested a lack of significant motor blockade with EXPAREL. This is confirmed by physician satisfaction with return of sensory/motor function.

Pooled Nerve Block Safety Data

In the All Studies pool, 335 subjects received EXPAREL (All Doses), 33 subjects received bupivacaine HCl, and 207 subjects received placebo.

Overall, 184/335 subjects (54.9%) in the EXPAREL All Doses group, 15/35 subjects (45.5%) in the bupivacaine HCl group, and 99/207 subjects (47.8%) in the placebo group experienced at least one TEAE in a preferred term (PT) that had an incidence of ≥2%. The incidence and types of TEAEs (PTs) were similar between the EXPAREL All Doses group and the placebo group.

In the EXPAREL All Doses group, the TEAEs reported with an incidence ≥2% were anemia (5.1%), bradycardia (2.1%), sinus tachycardia (2.1%), constipation (13.4%), feeling cold (3.3%), local swelling (2.1%), pyrexia (20.3%), procedural hypotension (5.1%), body temperature increased (2.4%), headache (4.5%), hypoesthesia (7.8%), paresthesia (2.1%), urinary retention (4.2%), and pruritus (12.2%).

In the EXPAREL 266 mg group, the TEAEs reported with an incidence ≥2% were anemia (5.7%), sinus tachycardia (2.4%), constipation (18.1%), feeling cold (4.8%), local swelling (2.9%), pyrexia (24.3%), procedural hypotension (6.2%), body temperature increased (3.8%), mobility decreased (2.9%), headache (3.3%), hypoesthesia (2.4%), urinary retention (5.7%), and pruritus (16.7%).

In the bupivacaine HCl group (N=33 subjects), the TEAEs reported with an incidence ≥2% were abdominal pain (3.0%), diarrhea (6.1%), flatulence (3.0%), chills (3.0%), injection site discomfort (3.0%), injection site erythema (9.1%), pyrexia (6.1%), drug hypersensitivity (3.0%), procedural hypotension (3.0%), back pain (6.1%), joint swelling (3.0%), headache (6.1%), hypoesthesia (24.2%), paresthesia (12.1%), nasal congestion (3.0%), and oropharyngeal pain (3.0%).

In the placebo group, the TEAEs reported with an incidence ≥2% were anemia (3.9%), constipation (16.9%), feeling cold (3.9%), local swelling (2.4%), pyrexia (18.8%), procedural hypotension (2.9%), mobility decreased (2.4%), headache (3.4%), urinary retention (2.9%), and pruritus (15.9%).

There were 17 TEAEs (anemia, bradycardia, sinus tachycardia, constipation, diarrhea, feeling cold, injection site erythema, pyrexia, postoperative wound infection, procedural hypotension, back pain, cluster headache, hypoesthesia, paresthesia, urinary retention, and pruritus) that occurred at an incidence of ≥5% in the EXPAREL 266 mg group where the incidence was greater in the EXPAREL group than in the placebo group.

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

7.4. Postmarketing Exposure

As of February 2016, more than 1.7 million patients have received EXPAREL in the postmarketing setting.

8. OBJECTIVES

8.1. Primary Objectives

The primary objective of this study is to compare pain control and total opioid consumption following local infiltration analgesia (LIA) with EXPAREL to LIA without EXPAREL in adult subjects undergoing primary unilateral TKA.

8.2. Secondary Objectives

The secondary objectives of this study are to compare additional efficacy, safety, and health economic outcomes following LIA with EXPAREL to LIA without EXPAREL in adult subjects undergoing primary unilateral TKA.

9. STUDY DESIGN AND PLAN

9.1. Study Design

This is a Phase 4, multicenter, randomized, double-blind, controlled trial in approximately 300 adult subjects undergoing primary unilateral TKA under spinal anesthesia with bupivacaine HCl (10-15 mg).

Bupivacaine is preferred as the spinal anesthetic; however, if the spinal fails or cannot be completed, the patient may receive general anesthesia. Total intravenous anesthesia (TIVA) is then the preferred route. If TIVA is contraindicated or not preferable, then inhalational anesthetics may be used. The use of fentanyl or short-acting analogues will be permitted in both groups.

The following medications will be allowed:

- Anti-emetics may be used pre-operatively or intra-operatively.
    - Decadron 10 mg x 1 intra-op is permitted
    - Scopolamine patch will be permitted if used as a pre-medication or intra-operatively but should be removed post-operatively.
- Lidocaine will be permitted, if used as a local anesthetic at the site of IV placement or as IV to stabilize heart rhythm.
- Propofol is permitted for induction and intra-operatively, but not post-operatively.
- Versed, 1-2 mg IV, may be used pre-operatively for anxiety or sedation

Subjects will be screened within 30 days prior to study drug administration. During the screening visit, which must take place at least 1 day prior to surgery, subjects will be assessed for past or present neurologic, cardiac, and general medical conditions that in the opinion of the Investigator would preclude them from study participation. After the ICF is signed, a medical history, surgical history, physical examination, physical therapy assessment, 12-lead electrocardiogram (ECG), vital sign measurements, urine drug screen, and urine pregnancy test for women of childbearing potential will be conducted.

On Day 0, all eligible subjects will receive the following medications within 4 hours prior to surgery:

- Acetaminophen/paracetamol 975-1000 mg, PO.
- Celecoxib 200 mg, PO.
    - If a subject has an allergy to celecoxib, they may use the following alternative drugs: naproxen 500 mg PO or meloxicam 7.5 mg PO.
- Pregabalin up to 300 mg, PO.

On Day 0, all eligible subjects will also receive tranexamic acid, up to 2 grams (IV), at the beginning of surgery or intra-operatively.

Subjects will be randomized 1:1 to two treatment groups. Subjects in Group 1 will receive LIA with EXPAREL 266 mg in 20 mL admixed with bupivacaine HCl 0.5% in 20 mL and expanded in volume with 80 mL normal saline (total volume of 120 mL). Subjects in Group 2 will receive LIA with bupivacaine HCl 0.5% in 20 mL expanded in volume with 100 mL normal saline (total volume of 120 mL).

Trained and qualified Investigators (see Appendix 5) will use their usual surgical technique to perform the TKA. Use of tourniquets and drains, if used, will be recorded. The case is to be completed at a time that will allow for a postsurgical physical therapy assessment on Day 0.

Subjects will be required to remain at the hospital facility for a minimum of 48 hours after surgery. The subjects must still complete the 72-hour assessments if they are discharged from the hospital facility prior to 72 hours after surgery.

The use of fentanyl or analogues will be permitted (during surgery only) in both groups. Intraoperative administration of other opioids or any other analgesic, local anesthetics, or anti-inflammatory agents will be prohibited in both groups, unless needed to treat an AE.

Study drug will be administered using six 20 cc syringes with 22-gauge needles prior to wound closure. Each stick should deliver approximately 1-1.5 cc to the intended area. The tissue should visibly expand with minimal leakage. Study drug should be injected in the prescribed locations based on the areas of highest nerve density.

Prior to cementation

- Syringe #1: Posterior capsule (8-10 sticks medial and 8-10 sticks lateral).
- Syringe #2: Femur – medial and lateral periosteum, posterior periosteum, suprapatellar/ quadriceps tendon (20 sticks).
- Syringe #3: Tibia – fat pad (5 sticks); pes anserinus, medial collateral ligament, and gutter (15 sticks)
- Syringe #4: Circumferential periosteum (15-20 sticks).

After cementation

- Syringe #5: Midline quadriceps tendon (10 sticks); retinaculum, medial gutter, femoral to tibia (10 sticks).
- Syringe #6: Lateral gutter, femoral to tibial (10 sticks); subcutaneous/closure (10 sticks).

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

Postsurgically, all subjects will receive the following scheduled medications until hospital discharge:

- Acetaminophen/paracetamol 975-1000 mg PO every 8 hours (q8h). The total daily dose is not to exceed 3000 mg.
- Celecoxib 200 mg PO every 12 hours (q12h).
    - If a subject has an allergy to celecoxib, they may use the following alternative drugs: naproxen 500 mg PO or meloxicam 7.5 mg PO.

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

Postsurgical Rescue Medication

Subjects should only receive rescue medication upon request for pain control, as needed. Postsurgical rescue medication will consist of PO immediate-release oxycodone initiating up to 10 mg. The subject may re-dose, per physician judgment, as needed (PRN), if initial medication fails. If a subject cannot tolerate PO medication, or has repeated failure of the rescue medication with oxycodone (PO), IV morphine (2.5-5 mg) or hydromorphone (0.5-1 mg) may be administered q4h or PRN. **Patient-controlled analgesia (PCA) is not permitted**. No other rescue analgesic agents, including NSAIDs, are permitted until hospital discharge. After discharge, the analgesic regimen may be adjusted for each subject individually as deemed appropriate by the physician responsible for the postsurgical care.

Postsurgical Assessments

Postsurgical clinical assessments will include pain intensity scores using a 10-cm visual analog scale (VAS) (see Appendix 1); overall benefit of analgesia score (OBAS) questionnaire (see Appendix 2); total postsurgical opioid consumption; physical therapy assessment

(see Physical Therapy Assessment Manual); nurse's satisfaction with overall analgesia (see Appendix 3); and discharge readiness (see Appendix 4).

If a cardiac AE, neurological AE, fall, or SAE occurs during the study, an unscheduled PK blood sample should be collected as close as possible to when the event occurs. In addition, a 12-lead ECG, vital signs, and any appropriate clinical laboratory tests should be conducted as close as possible to when the event occurs. For out-of-hospital events, the medical monitor should be contacted to determine need for a PK sample and ECG. Cardiac AEs of special interest include chest pain (angina, myocardial infarction), abnormal/irregular heart rate (bradycardia, tachycardia, extrasystoles), and shortness of breath requiring intervention. Neurologic AEs of special interest include altered mental status/altered sensorium, rigidity, dysarthria, seizure, tremors, metallic taste, tinnitus, perioral numbness, and visual disturbance. Additionally, the following events are of special interest if they persist or occur beyond 72-hours postdose: dizziness, hyperesthesia, muscular twitching, and tingling/paresthesia.

Postsurgical health economic outcome assessments will include hospital length of stay (LOS), use of skilled nursing facility, outpatient physical therapy use, hospital readmissions, and use of other health services following discharge (phone calls related to postsurgical pain, unscheduled visits related to postsurgical pain, and visits to emergency department) through postsurgical Day 29.

A follow-up visit will be scheduled for all subjects on postsurgical Day 14. A follow-up phone call will be made on postsurgical Day 29 to all subjects who received study drug to assess for AEs.

9.1.1. Duration of the Study and Subject Participation

Participation will begin at the signing of the ICF. No more than 30 days should pass between signing of the ICF and the administration of EXPAREL. The time from study drug administration through the end of participation is 30 ± 3 days. Therefore, subjects may participate in the study for up to 63 days.

9.1.2. Study Stopping Rules

If Pacira, the Investigator, or officials from regulatory authorities discover conditions during the study that indicate that the study or study site should be terminated, this action may be taken after Pacira has consulted with appropriate regulatory authorities and notified the Investigator(s).

Blinded Data Review (BDR) of the subject data will be conducted by the Pacira Medical Monitoring Team after the first 60 subjects have completed Day 29 and subsequently each block of 10 subjects complete through Day 29 throughout the conduct of this study. The Pacira Study Data Management and Biostatistics team will work in conjunction to provide blinded tables, figures, and listings for the BDR. Meeting notes will be compiled and filed at the end of each BDR session.

The outcome of the BDR process will be the trigger for prompting the Safety Stopping Rules based on the incidence rate of all AESIs including the following:

- Cardiac AESIs as defined in the protocol including cardiac arrest, hypertension, and hypotension exceeding 10%.

- Neurologic AESIs as defined in the study protocol including dysgeusia and oral hypoaesthesia exceeding 10%.
- Incidence rate of severe AESIs including cardiac AESIs and neurologic AESIsexceeding 5%.
- Falls exceeding 5%.
- Dizziness exceeding 25%.

Unblinded review of the data and a relative risk data analysis will occur if any one of the events above should occur. If the risk relative to placebo is greater than 2 at the 5% level or all of the AESI appear in the EXPAREL arm and meet the criteria above, the next step will be any one of the following actions:

- Halt subject dosing and/or study enrollment until the toxicity data can be further reviewed.
- Revise eligibility criteria to exclude subjects who appear to be more at higher risk for a particular AE.

Any unexplained death will be thoroughly reviewed and appropriate action taken.

9.2. Discussion of Study Design

EXPAREL is approved for infiltration into a surgical site. This Phase 4, multicenter, randomized, double-blind, controlled trial in approximately 300 adult subjects undergoing primary unilateral TKA is designed to further evaluate the efficacy and safety of LIA with EXPAREL for postsurgical analgesia in subjects undergoing TKA. The double-blind study design is intended to avoid potential bias resulting from subject or Investigator knowledge of the assigned treatment.

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

If a cardiac AE, neurological AE, fall, or SAE occurs during the study, an unscheduled PK blood sample should be collected as close as possible to when the event occurs. In addition, a 12-lead ECG, vital signs, and any appropriate clinical laboratory tests should be conducted as close as possible to when the event occurs. For out-of-hospital events, the medical monitor should be contacted to determine need for a PK sample and ECG. Cardiac AEs of special interest include chest pain (angina, myocardial infarction), abnormal/irregular heart rate (bradycardia, tachycardia, extrasystoles), and shortness of breath requiring intervention. Neurologic AEs of special interest include altered mental status/altered sensorium, rigidity, dysarthria, seizure, tremors, metallic taste, tinnitus, perioral numbness, and visual disturbance. Additionally, the following events are of special interest if they persist or occur beyond 72-hours postdose: dizziness, hyperesthesia, muscular twitching, and tingling/paresthesia.

10. STUDY POPULATION

10.1. Inclusion Criteria

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

1. Male or female, at least 18 years of age at screening.
2. Scheduled to undergo primary, unilateral, tricompartmental TKA under spinal anesthesia.
3. Primary indication for TKA is degenerative osteoarthritis of the knee.
4. American Society of Anesthesiologists (ASA) physical status 1, 2, or 3.
5. Female subjects must be surgically sterile; or at least 2 years postmenopausal; or have a monogamous partner who is surgically sterile; or practicing double-barrier contraception; or practicing abstinence (must agree to use double-barrier contraception in the event of sexual activity); or using an insertable, injectable, transdermal, or combination oral contraceptive approved by the FDA for greater than 2 months prior to screening and commit to the use of an acceptable form of birth control for the duration of the study and for 30 days after completion of the study.
6. Able to provide informed consent, adhere to the study visit schedule, and complete all study assessments.

10.2. Exclusion Criteria

A subject will not be eligible for the study if he or she meets any of the following criteria:

1. Currently pregnant, nursing, or planning to become pregnant during the study or within 1 month after study drug administration.
2. History of prior contralateral TKA within 1 year or open knee surgery on the knee being considered for TKA. Prior arthroscopy is permitted.
3. Planned concurrent surgical procedure (e.g., bilateral TKA).
4. Undergoing unicompartmental TKA or revision TKA.
5. Concurrent painful physical condition that may require analgesic treatment (such as an NSAID or opioid) in the postsurgical period for pain that is not strictly related to the knee surgery and which may confound the postsurgical assessments (e.g., significant pain from other joints including the non-index knee joint, chronic neuropathic pain, concurrent or prior contralateral TKA, concurrent foot surgery).
6. Comorbidity impacting current physical function of Investigator opinion that it may impact postsurgical rehabilitation.
7. Allergy, hypersensitivity, intolerance, or contraindication to any of the study medications (i.e., bupivacaine, pregabalin, acetaminophen/paracetamol, or tranexamic acid).

8. Use of any of the following medications within the times specified before surgery: long-acting opioid medication or NSAIDs (except for low-dose aspirin used for cardioprotection) within 3 days, or any opioid medication within 24 hours.
9. Initiation of treatment with any of the following medications within 1 month of study drug administration or if the medication(s) are being given to control pain: selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin (Lyrica®), or duloxetine (Cymbalta®). If a subject is taking one of these medications for a reason other than pain control, he or she must be on a stable dose for at least 1 month prior to study drug administration.
10. Current use of systemic glucocorticosteroids within 1 month of enrollment in this study.
11. Use of dexmedetomidine HCl (Precedex®) within 3 days of study drug administration.
12. History of coronary or vascular stent placed within the past 3 months (may be extended to 1 year if medically indicated per physician discretion).
13. Have been treated for deep vein thrombosis, pulmonary embolism, myocardial infarction, or ischemic stroke within the past 6 months (may be extended to 1 year if medically indicated per physician discretion)
14. Rheumatoid or inflammatory arthritis or disease that requires chronic analgesic treatment.
15. Severely impaired renal or hepatic function (e.g., serum creatinine level >2 mg/dL [176.8 µmol/L], blood urea nitrogen level >50 mg/dL [17.9 mmol/L], serum aspartate aminotransferase [AST] level >3 times the upper limit of normal [ULN], or serum alanine aminotransferase [ALT] level >3 times the ULN.)
16. Any neurologic or psychiatric disorder that might impact postsurgical pain or interfere with study assessments.
17. Malignancy in the last 2 years, per physician discretion.
18. History of misuse, abuse, or dependence on opioid analgesics, other prescription drugs, illicit drugs, or alcohol.
19. Failure to pass the alcohol breath test or urine drug screen.
20. Body weight <50 kg (110 pounds) or a body mass index >44 kg/m^2.
21. Previous participation in an EXPAREL study.
22. Administration of an investigational drug within 30 days or 5 elimination half-lives of such investigational drug, whichever is longer, prior to study drug administration, or planned administration of another investigational product or procedure during the subject's participation in this study.

10.3. Removal of Subjects from Therapy or Assessment

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

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

10.3.1. Withdrawal Secondary to Adverse Events

If a subject experiences an AE that renders him or her incapable of continuing with the remaining study assessments, then he or she will be discontinued from further participation in the study. A final evaluation should be performed so that the subject's study participation can be terminated in a safe and orderly manner.

10.3.2. Voluntary or Study Investigator Withdrawal

Subjects are free to discontinue from the study at any time, without prejudice to future treatment. Nevertheless, subjects will be encouraged to complete at least the study safety assessments. In addition, a subject may be discontinued from the study if he or she refuses to comply with study procedures. Reasons for discontinuation from the study will be recorded.

If a subject is discontinued by the Investigator or voluntarily withdraws from the study after receiving study drug, the subject will be asked to complete a final evaluation so that he or she can be withdrawn in a safe and orderly manner. In the final evaluation, vital signs and any changes in the subject's health status will be recorded.

After termination from the study, the subject may be followed for safety including monitoring of AEs through postsurgical Day 29.

11. TREATMENTS

11.1. Treatment to be Administered

Prior to Surgery

On Day 0, all eligible subjects will receive the following medications within 4 hours prior to surgery:

- Acetaminophen/paracetamol 975-1000 mg, PO.
- Celecoxib 200 mg, PO.
    - If a subject has an allergy to celecoxib, they may use the following alternative drugs: naproxen 500 mg PO or meloxicam 7.5 mg PO.
- Pregabalin up to 300 mg, PO.

On Day 0, all eligible subjects will also receive tranexamic acid, up to 2 grams (IV) at the beginning of surgery or intra-operatively.

During Surgery

Subjects in Group 1 will receive LIA with EXPAREL 266 mg in 20 mL admixed with bupivacaine HCl 0.5% in 20 mL and expanded in volume with 80 mL normal saline (total volume of 120 mL). Subjects in Group 2 will receive LIA with bupivacaine HCl 0.5% in 20 mL expanded in volume with 100 mL normal saline (total volume of 120 mL).

After Surgery

Postsurgically, all subjects will receive the following scheduled medications until hospital discharge:

- Acetaminophen/paracetamol 975-1000 mg PO q8h. The total daily dose is not to exceed 3000 mg.
- Celecoxib 200 mg PO q12h.
    - If a subject has an allergy to celecoxib, they may use the following alternative drugs: naproxen 500 mg PO or meloxicam 7.5 mg PO.

Rescue Medication

Subjects should only receive rescue medication upon request for pain control, as needed. Postsurgical rescue medication will consist of PO immediate-release oxycodone initiating up to 10 mg. The subject may re-dose, per physician judgment, PRN, if initial rescue medication fails. If a subject cannot tolerate PO medication or has repeated failure of the rescue medication with oxycodone (PO), IV morphine (2.5-5 mg) or hydromorphone (0.5-1 mg) may be administered q4h or PRN. **PCA is not permitted**. No other rescue analgesic agents, including NSAIDs, are permitted until hospital discharge. After discharge, the analgesic regimen may be adjusted for each subject individually as deemed appropriate by the physician responsible for the postsurgical care.

11.1.1. Administration Technique

Study drug will be administered using six 20 cc syringes with 22-gauge needles prior to wound closure. Each stick should deliver approximately 1-1.5 cc to the intended area. The tissue should visibly expand with minimal leakage. Study drug should be injected in the prescribed locations based on the areas of highest nerve density.

Prior to cementation

- Syringe #1: Posterior capsule (8-10 sticks medial and 8-10 sticks lateral).
- Syringe #2: Femur – medial and lateral periosteum, posterior periosteum, suprapatellar/quadriceps tendon (20 sticks).
- Syringe #3: Tibia – fat pad (5 sticks); Pes anserinus, medial collateral ligament, and gutter (15 sticks)
- Syringe #4: Circumferential periosteum (15-20 sticks).

After cementation

- Syringe #5: Midline quadriceps tendon (10 sticks); retinaculum, medial gutter, femoral to tibia (10 sticks).
- Syringe #6: Lateral gutter, femoral to tibial (10 sticks); subcutaneous/closure (10 sticks).

11.1.2. Study Drug Administration Considerations

Since there is a potential risk of severe adverse effects associated with the administration of bupivacaine, the study sites must be equipped to manage subjects with any evidence of cardiac toxicity.

EXPAREL may not be administered to a subject if it has been held in a syringe for more than 4 hours after preparation. In order to prevent the study drug from settling, gently inverting and re-inverting the syringe several times prior to administration is recommended.

11.2. Identity of Investigational Product(s)

11.2.1. Description of EXPAREL

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

11.2.2. Description of Reference Product

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

11.2.3. Description of Diluents

Normal saline for injection (80 mL) will be added to the admixed study drug for Group 1 to achieve a total volume of 120 mL. Normal saline for injection (100 mL) will be added to the study drug in Group 2 (bupivacaine HCl 0.5% in 20 mL) to achieve a total volume of 120 mL.

11.3. Method of Assigning Subjects to Treatment

11.3.1. Randomization Scheme

Approximately 300 subjects (150 per treatment group) are planned for enrollment. Subjects will be randomized in a 1:1 ratio to receive either LIA with EXPAREL 266 mg admixed with bupivacaine HCl 0.5% (Group 1) or LIA with bupivacaine HCl 0.5% (Group 2).

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

11.3.2. Randomization Procedures

Once a subject is identified as being qualified for the study per the eligibility criteria (see Section 10.1 and Section 10.2), and is at the study site for surgery, the unblinded research pharmacist or designee will obtain a randomization assignment. The subject will be considered randomized into the study once the study treatment assignment is received.

11.3.3. Replacement of Subjects

Subjects who are randomized but are withdrawn from the study before receiving study drug or do not undergo the surgical procedure may be replaced. Once assigned, subject numbers will not be reused; subjects enrolled to replace those who withdraw will be assigned a unique subject number and randomized to treatment according to the procedures outlined above.

11.4. Selection of Doses in the Study

During the clinical development of EXPAREL, single doses ranging from 2 mg to 665 mg have been safely administered via various routes. Pharmacokinetic studies have shown that because EXPAREL releases bupivacaine gradually as the lipid structure breaks down, administration of EXPAREL 266 mg results in a maximum plasma concentration (C_{max}) equivalent to that seen with standard bupivacaine HCl 100 mg. EXPAREL 266 mg, the FDA-approved and marketed dose, was selected for this study. Based on current clinical practice, bupivacaine HCl 0.5% was selected for this study, consistent with standard of care (Brener 2013).

11.5. Blinding

11.5.1. Blinding Procedures

To maintain the double-blind study design, only the unblinded study personnel who are NOT involved with protocol-specific, postsurgical assessments may prepare and administer the study drug. Staff members conducting study-specific, postsurgical assessments and the subjects will

remain blinded to the assigned treatment throughout the study. 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 the unblinded randomization assignments and be responsible for preparing study drug.

Assignment of blinded and unblinded responsibilities regarding the preparation of study drug should take into account that **EXPAREL must be administered within 4 hours of opening the vial**.

The individuals preparing and administering study drug will not be allowed to perform any of the study assessments or reveal the assigned study treatment to any other members of the study team at any time. 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 (see Pharmacy Manual for additional details).

No crossover will be permitted between the blinded and unblinded study site personnel during the study period. The assignment of site monitors will also be segregated. Blinded monitors will review case report forms (CRFs), clinic charts, and all other study-related documents that do not disclose the allocation of study treatment. Care should be taken in recording and review of operating room 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.

11.5.2. Unblinding Procedures

Subject treatment assignments should not be unblinded during the study by blinded study personnel. The Investigator will have the ability to unblind a subject through the randomization system if he or she feels that subject safety warrants such unblinding. However, the Investigator should discuss the safety issues with the Medical Monitor before attempting such unblinding, if possible. Any unblinding will be documented through immediate notification of the Pacira study team and the Investigator within the interactive response technology (IRT) system used for randomization. The reason for unblinding will be documented. Any accidental unblinding events (i.e., through mishaps in the operating room or miscommunication among study staff) must be reported to Pacira immediately.

Any unblinding performed through the randomization system will be recorded as a transaction and the appropriate study personnel will be notified that such a transaction occurred.

Any incidence(s) of unblinding will be noted in the clinical study report with a full discussion of the events leading to the decision to unblind.

11.6. Prior and Concomitant Therapy and Medications

All medications taken within 30 days prior to study drug administration through hospital discharge or until the subject is withdrawn from the study, whichever is sooner, will be recorded

on the CRF. All postsurgical analgesics administered must be documented through postsurgical Day 29. Additionally, any medications administered in association with an AE will be recorded through postoperative Day 29.

11.6.1. Before Study Drug Administration

Permitted Prior Medications

- Low-dose aspirin for cardioprotection.
- Presurgical medications are described in Section 11.1.

Restricted Prior Medications and Therapy

- Systemic glucocorticosteroids are prohibited within 1 month of enrollment in this study.
- Initiation of treatment with any of the following medications is prohibited within 1 month of study drug administration or if the medication(s) are being given to control pain: SSRIs, SNRIs, gabapentin, pregabalin (Lyrica), or duloxetine (Cymbalta). If a subject is taking one of these medications for a reason other than pain control, he or she must be on a stable dose for at least 1 month prior to study drug administration.
- Long-acting opioid medications or 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.

11.6.2. During Surgery

Permitted

- The use of fentanyl or analogs will be permitted during surgery.

Restricted

- No drugs (e.g., epinephrine, dexamethasone, clonidine) other than bupivacaine are to be admixed with study drug.
- Lidocaine and other local anesthetics will not be permitted to be locally administered during surgery because they are known to interact with EXPAREL resulting in the displacement of bupivacaine and elevated plasma levels.
- Intrathecal opioids.
- The use of long-acting opioids (e.g., morphine, hydromorphone HCl), acetaminophen/ paracetamol, ketorolac, or other NSAIDs will not be permitted intraoperatively except for emergency use to treat an AE.

11.6.3. During Hospitalization

Permitted

- The permitted rescue medications are described in Section 11.1.
- Scheduled postsurgical medications are described in Section 11.1.

Restricted

- No other rescue analgesics, including postsurgical use of fentanyl, are permitted during hospitalization.
- PCA is not permitted.
- Anesthetics in the "caine" family are prohibited.
- Dexmedetomidine HCl (Precedex) use is prohibited.

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

All postsurgical analgesics administered must be documented through postsurgical Day 29.

11.7. Treatment Compliance

Not applicable, since study drug will be administered intraoperatively by the study staff.

11.8. Accountability of Study Drug

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

12. STUDY ENDPOINTS AND MEASUREMENTS

12.1. Efficacy Assessments

The following efficacy measurements will be assessed at the times specified after the end of surgery:

- Pain intensity scores using the VAS upon arrival at the post-anesthesia care unit (PACU); at 4, 6, 8, 10, 12, 24, 28, 32, 36, 48, 52, 56, 60, and 72 hours or until hospital discharge; just prior to hospital discharge; and immediately prior to each administration of rescue pain medication (see Appendix 1).
- Amount of all opioid rescue analgesics taken through postsurgical Day 29.
- The OBAS questionnaire at 24, 48, and 72 hours or upon hospital discharge (see Appendix 2).
- Physical therapy assessments (timed up and go test, stair climbing test, and timed walk test) will be conducted once postsurgically on Day 0; at approximately 8:00 am and 8:00 pm (±2 hours) from postsurgical Day 1 through hospital discharge; and on postsurgical Day 14 (see Physical Therapy Assessment Manual). Preemptive use of opioids or NSAIDs prior to the physical therapy assessment is not permitted.
- Nurse's satisfaction with overall analgesia will be assessed at 24, 48, and 72 hours or upon hospital discharge (see Appendix 3).
- Discharge readiness will be assessed q12h (at approximately 8:00 am and 8:00 pm [±2 hours]) from postsurgical Day 0 up to hospital discharge or up to reaching the discharge readiness score of 9, whichever comes first. Once a score of 9 is reached no further discharge readiness assessments are required (see Appendix 4).

12.2. Efficacy Endpoints

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

Primary Efficacy Endpoint:

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

Secondary Endpoints:

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

- SPIS from 24–48 and 48–72 hours.
- Total inpatient postsurgical opioid consumption (in mg) through 24, 48, and 72 hours or hospital discharge.
- Total postsurgical opioid consumption (in mg) from hospital discharge through postsurgical Day 29.
- Percentage of opioid-free subjects through 24, 48, and 72 hours or hospital discharge.
- Time to first opioid rescue through 72 hours or hospital discharge.
- The OBAS total score at 24, 48, and 72 hours or upon hospital discharge.
- Proportion of subjects meeting Modified Postanesthesia Discharge Scoring System (MPADSS) criteria for discharge readiness at each assessed timepoint.
- Nurse's satisfaction with overall analgesia at 24, 48, and 72 hours or upon hospital discharge.

12.3. Health Economic Outcome Assessments

The health economic outcomes will include:

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

12.4. Health Economic Endpoints

- Hospital LOS, defined as the time from completion of the wound closure until the hospital discharge order is written or through postsurgical Day 29, whichever is sooner.
- Incidence of hospital readmission through postsurgical Day 29.
- Incidence of skilled nursing facility use.
- Total time spent in skilled nursing facility.
- Number of postsurgical physical therapy visits.
- Number of phone calls related to postsurgical pain.
- Number of unscheduled visits related to postsurgical pain.
- Number of visits to the emergency department.

12.5. Safety Assessment

The following safety assessment will be conducted at the time specified:

- Adverse events from the time the ICF is signed through postsurgical Day 29.

12.6. Safety Endpoint

The following safety endpoint will be assessed based on the safety assessment:

- Incidence of TEAEs and SAEs through postsurgical Day 29.

12.7. Appropriateness of Measures

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

13. STUDY PROCEDURES

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

13.1. Instructions for Conducting Procedures and Measures

All assessments conducted after baseline (i.e., study drug administration) will be timed from the end of surgery.

At timepoints when multiple assessments coincide, the VAS pain intensity assessment will be conducted first and the physical therapy assessment will be conducted last.

Day 0 is defined as the day on which study drug is administered. The beginning of surgery is defined as the time of the first incision. The end of surgery is defined as the time of the last suture. 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.

13.1.1. Pain Intensity Assessment

Pain intensity will be assessed using a 10-cm VAS (Carlsson 1983, McCormack 1988, and Scott 1976) at baseline (Day 0 prior to surgery); upon arrival at the PACU; at 4, 6, 8, 10, 12, 24, 28, 32, 36, 48, 52, 56, 60, and 72 hours; immediately prior to each administration of rescue pain medication; and just prior to hospital discharge (see Appendix 1).

If ice or passive extenders are used, these must be stopped at least 15 minutes prior to the pain intensity assessment. If subjects are in immobilizers, these must be removed at least 15 minutes prior to the pain intensity assessment. This does not apply to rescue medication VAS.

13.1.2. Overall Benefit of Analgesia Score Questionnaire

The OBAS questionnaire will be completed at 24, 48, and 72 hours, or upon hospital discharge (see Appendix 2).

13.1.3. Nurse's Satisfaction with Postsurgical Pain Control

The nurse's satisfaction with postsurgical pain control will be assessed using the Likert Scale at 24, 48, and 72 hours, or upon hospital discharge (see Appendix 3).

13.1.4. Vital Signs

The scheduled vital signs (heart rate and blood pressure) will be measured after the subject has rested in a supine position for at least 5 minutes at screening and baseline (Day 0 prior to surgery). Vital signs will also be measured if a subject experiences an AE of special interest (i.e., cardiac AE, neurological AE, or fall) or an SAE (see Section 13.1.7). The subject will remain in a supine position during the assessment.

13.1.5. Physical Examination

A full physical examination will be conducted at screening. Superficial abnormalities that may interfere with participation in the study will be noted. A targeted physical examination of the lower extremity and the knee itself will be conducted on Day 14.

13.1.6. Electrocardiogram

A 12-lead ECG will be conducted at screening after the subject has rested in a supine position for at least 5 minutes. A 12-lead ECG will also be conducted if a subject experiences an AE of special interest (i.e., cardiac AE, neurological AE, or fall) or an SAE (see Section 13.1.7).

13.1.7. Adverse Events of Special Interest

If a cardiac AE, neurological AE, fall, or SAE occurs during the study, an unscheduled PK blood sample should be collected as close as possible to when the event occurs. In addition, a 12-lead ECG, vital signs, and any appropriate clinical laboratory tests should be conducted as close as possible to when the event occurs. For out-of-hospital events, the medical monitor should be contacted.

Cardiac AEs of special interest include:

- Chest pain (angina, myocardial infarction)
- Abnormal/irregular heart rate (bradycardia, tachycardia, extrasystoles)
- Shortness of breath requiring intervention.

Neurologic AEs of special interest include:

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

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

- Dizziness
- Hyperesthesia
- Muscular twitching
- Tingling/paresthesia

13.2. Screening Procedures

- Explain study purpose and procedures.
- Obtain signed ICF.
- Assess eligibility.
- Record relevant medical/surgical history, demographics, and baseline characteristics.
- Conduct urine drug screen.
- Conduct urine pregnancy test for women of childbearing potential.
- Perform physical examination.
- Measure vital signs (heart rate and blood pressure) after subject has rested in a supine position.
- Conduct 12-lead ECG after subject has rested in a supine position.
- Conduct physical therapy assessment (see Physical Therapy Assessment Manual).
- Record concomitant medications.
- Record AEs starting at signing of the ICF.

13.3. Baseline Procedures (Day 0 - Prior to Study Drug Administration)

- Confirm eligibility.
- Update relevant medical and surgical history.
- Conduct alcohol breath test and urine drug screen.
- Conduct urine pregnancy test for women of childbearing potential.
- Record baseline VAS pain intensity score prior to any premedication (see Appendix 1).
- Administer acetaminophen/paracetamol 975-1000 mg PO, celecoxib 200 mg PO (in case of celecoxib allergy, naproxen 500 mg PO or meloxicam 7.5 mg PO may be administered), and pregabalin up to 300 mg PO within 4 hours prior to surgery. Tranexamic acid (up to 2 grams IV) should be administered either before surgery or intraoperatively.
- Measure vital signs (heart rate and blood pressure) after subject has rested in a supine position.
- Record changes to concomitant medications since screening.
- Randomize subject and prepare study drug (see Section 11).
- Record AEs and any treatment(s) for the events.

13.4. Intraoperative Procedures

- Record intraoperative opioids administered and doses.

- Administer blinded study drug per Section 11.
- Record start and stop times of study drug administration.
- Record start and stop times of tourniquet use and the maximum pressure (mmHg).
- Record time of insertion of drain(s), if used.
- Record start and stop times of surgery.
- Record concomitant medications.
- Record AEs and any treatment(s) for the events.
- Refer to Section 13.1.7 for additional procedures in the event a cardiac AE, neurological AE, fall, or SAE occurs.

13.5. Upon Arrival at the Post-Anesthesia Care Unit

- Record VAS pain intensity score (see Appendix 1).
- Administer rescue medication upon request, as needed (see Section 11.1).
- Record times and doses of all opioid rescue medication administered.
- Record other concomitant medications.
- Record AEs and any treatment(s) for the events.
- Refer to Section 13.1.7 for additional procedures in the event a cardiac AE, neurological AE, fall, or SAE occurs.

13.6. Postsurgical Assessments through Hospital Discharge

- Record VAS pain intensity scores at 4, 6, 8, 10, 12, 24, 28, 32, 36, 48, 52, 56, 60, and 72 hours; immediately prior to each administration of rescue pain medication; and just prior to discharge (see Appendix 1).
- Complete OBAS questionnaire at 24, 48, and 72 hours or upon hospital discharge (see Appendix 2).
- Conduct physical therapy assessment once postsurgically on Day 0, and at approximately 8:00 am and 8:00 pm (±2 hours) from postsurgical Day 1 until hospital discharge (see Physical Therapy Assessment Manual).
- Obtain overall rating of nurse's satisfaction with postsurgical pain control using the Likert scale at 24, 48, and 72 hours or upon hospital discharge (see Appendix 3).
- Administer rescue medication upon request, as needed (see Section 11.1).
- Record date, time, and amount of all opioid rescue medication administered.
- Administer scheduled postsurgical analgesics.
- Record time of removal of drain(s), if used.
- Record other concomitant medications.
- Record AEs and any treatment(s) for the events.

- Discharge readiness will be assessed q12h (at approximately 8:00 am and 8:00 pm [±2 hours]) from postsurgical Day 0 up to hospital discharge or up to reaching the discharge readiness score of 9, whichever comes first. Once a score of 9 is reached no further discharge readiness assessments are required (see Appendix 4).
- Record date and time of discharge from hospital.
- Refer to Section 13.1.7 for additional procedures in the event a cardiac AE, neurological AE, fall, or SAE occurs.

13.7. Postsurgical Day 14 Visit

- Conduct targeted physical examination.
- Record date and time of discharge, if applicable.
- Record times and doses of all analgesic medication administered since hospital discharge.
- Document any unscheduled phone calls or office visits related to pain after discharge.
- Document any visits to the emergency department.
- Document any outpatient physical therapy visits.
- Document any use of a skilled nursing facility.
- Document any hospital readmissions.
- Record AEs and any treatment(s) for the events.

13.8. Postsurgical Day 29 Phone Call

- Document any unscheduled phone calls or office visits related to pain after discharge.
- Record times and doses of all analgesic medication administered since the postsurgical Day 14 visit.
- Document any visits to the emergency department.
- Document any outpatient physical therapy visits.
- Document any use of a skilled nursing facility.
- Document any hospital readmissions.
- Record AEs and any treatment(s) for the events.

14. ADVERSE EVENT REPORTING

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

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

14.1. Adverse Events

14.1.1. Definitions

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

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

An AE that occurs after the 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 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 postsurgical Day 29 must be recorded regardless of whether or not they are considered related to study drug. Whenever feasible, AE terms should be documented as medical diagnoses (highest

possible level of integration); otherwise, the AEs should be reported separately as individual signs or symptoms. Only one AE per line should be recorded in the AE CRF; for example, an AE of nausea and vomiting should be listed as two separate events: the event of nausea and the event of vomiting. If a diagnosis is established after symptoms are recorded on the AE CRF, the diagnosis should be recorded and the symptoms collapsed (removed; i.e., lined through and initialed). Whenever possible, abnormal laboratory results should be reported as their clinical corollary (e.g., low potassium should be recorded as hypokalemia).

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

Any condition noted before the subject signs the ICF will be listed as Medical History and is considered a pre-existing condition. If a pre-existing condition changes (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 an AE, and the outcome of the AE, including the date and time of resolution, if applicable.

14.1.3. Severity of Adverse Events

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

Mild:	An AE that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
Moderate:	An AE that is discomforting and interferes with normal everyday activities.
Severe:	An AE that prevents normal everyday activities.

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

14.1.4. Relationship of Adverse Events to Study Drug

The Investigator will assess the relationship of the AE to study drug after careful medical consideration on a case-by-case basis. General guidelines for determining the AE's causality to the study drug are provided below.

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

Unlikely:	A clinical event with a temporal relationship to study drug administration which makes a causal relationship improbable and in which other drugs, chemicals, or underlying disease provide a plausible explanation;
Possible:	A clinical event with a reasonable time sequence to administration of the study drug but which could also be explained by a concurrent disease or other drugs or chemicals;
Probable:	A clinical event with a reasonable time sequence to administration of the study drug unlikely to be attributed to a concurrent disease or other drugs or chemicals and which follows a clinically reasonable response on withdrawal (dechallenge); or
Definite:	The pharmacological properties of the study drug(s) or of the substance class, and the course of the AE after dechallenge and, if applicable, after rechallenge, and/or specific test indicate involvement of the study drug(s) in the occurrence/worsening of the AE, and no indication of other causes exists.

14.1.5. Outcome of Adverse Events

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

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

14.1.6. Action Taken with Subject due to an Adverse Event

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

- None.
- Medication.

- Non-pharmaceutical therapy. (The specific therapy used must be recorded in the CRF.)
- Discontinued from study.
- Other. (The specific action taken must be recorded.)

14.2. Serious Adverse Events

14.2.1. Definition of a Serious Adverse Event

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

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

[1]**Death:** Any event resulting in a subject's death must be reported as an SAE. However, death, in and of itself, is not an AE; it is an outcome. The cause of death is the AE. Therefore, the Investigator should make every effort to obtain and document the cause of death for all subjects who die during the study. If, despite all efforts, the cause of death remains unknown, the AE should be documented as an "unspecified fatal event."

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

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

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

[5]**Medically Significant**: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medically significant events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

14.2.2. Reporting Serious Adverse Events

Any SAE or death that occurs at any time after the subject signs the ICF through postsurgical Day 29, whether or not related to EXPAREL, must be reported by the Investigator or designee to Pacira Drug Safety within 24 hours of discovery by either email (drugsafety@pacira.com) or fax (973-201-0649). In addition, the Investigator or designee is encouraged to contact the Medical Monitor to discuss the case, as needed.

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

If the Investigator is made aware of any SAEs after postsurgical Day 29, these should also be reported to Pacira Drug Safety or designee provided the SAE is considered related to EXPAREL. The site would then provide a completed SAE form within 1 business day and the event would be followed until resolution, or until adequate stabilization is met.

15. STATISTICAL METHODS

A comprehensive statistical analysis plan (SAP) will be developed for this study.

15.1. Study Hypothesis

The first primary null hypothesis is $H_{01}: \mu_1 = \mu_2$ versus the alternative hypothesis $H_{A1}: \mu_1 < \mu_2$. If the first primary null hypothesis is rejected, then the second primary hypotheses will be tested.

The second primary null hypothesis is $H_{02}: \gamma_1 = \gamma_2$ versus the alternative hypothesis $H_{A2}: \gamma_1 < \gamma_2$.

Where μ1 and μ2 are the mean VAS $AUC_{(12\text{-}48)}$ and γ_1 and γ_2 are the mean total opioid consumption (IV morphine equivalents) through 48 hours for treatment group 1 and treatment group 2 respectively.

15.2. Study Endpoints

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

15.3. Determination of Sample Size

A sample size of 130 subjects in each group is needed to have at least 90% power to detect a –0.3 unit difference in the geometric means for total opioid dose assuming the common standard deviation (SD) is 0.670 using a two group t-test with a 0.025 two-sided significance level. A sample size of 78 is needed in each group to have at least 90% power to detect a difference in $AUC_{(12\text{-}48)}$ of the VAS pain intensity score means of –40 assuming the common SD is 70 using a two group t-test with a 0.025 two-sided significance level. Three hundred subjects (150 per treatment arm) will be randomized into this study in order to have 260 evaluable subjects.

15.4. Analysis Populations

The following analysis sets are planned:

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

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

15.5. Handling Subject Dropouts and Discontinuations

For the calculation of the AUC of VAS pain intensity scores through any of the time periods, missing data will be imputed using a multiple imputation scheme. Details for the multiple imputation scheme will be provided 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 Compliance

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

15.6.3. Efficacy Analyses

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

15.6.3.1 Primary Efficacy Measures

The primary efficacy measures in this study are the AUC of the VAS pain intensity scores from hour 12 through 48 hours and total opioid consumption from hour 0 thru 48 hours. For the AUC of the VAS pain intensity scores through 48 hours, EXPAREL will be compared to placebo using analysis of variance (ANOVA) with treatment and site as main effects. Total opioid consumption will be log transformed then analyzed using ANOVA with treatment and site as main effects. To protect the type 1 error rate, total opioid consumption will be tested only if the comparison between EXPAREL and placebo for AUC is significant. All comparisons will be at the 5% alpha level. For the AUC comparison, the difference between the treatment groups will be estimated along with the 2-sided 95% confidence intervals (CIs). For the total opioid consumption comparison, the ratio of EXPAREL to placebo along with the 2-sided 95% CI for the ratio will be estimated.

Handling of Subjects Requiring Rescue Medication

For AUC of the VAS pain intensity scores, prior to analysis the windowed Worst-Observation-Carried-Forward (wWOCF) imputation method will be applied. For subjects who take rescue pain medication, their pain intensity scores recorded within the window of controlled type of rescue medication will be replaced by the 'worst' observation. All pain scores within that window will be replaced by the 'worst' observation. The worst observation will be the highest score in the time interval from the end of surgery to first rescue medication or, for subsequent rescue medication intervals, the end of the previous rescue window to the rescue medication. The VAS score at the time of rescue and end of previous rescue window are included in the determination of worst observation. If the rescue medication intervals overlap, then worst observation may be the value carried from the prior interval. Note that pain intensity scores in the window that are higher than the worst value prior to rescue pain medication will not be overwritten. If no pain intensity score is available prior to the first rescue pain medication, the worst observation from all available measurements will be used instead.

15.6.3.2 Secondary Efficacy Measures

The secondary efficacy measures will be analyzed using a hierarchical fixed-sequence stepwise testing procedure. To protect the Type 1 error rate, the testing will be performed in a

sequentially rejective fashion. If the first test is significant at the 0.05 level, then, and only then, the next secondary efficacy measure will be tested, and so forth. The results will be declared statistically significant at the 0.05 significance level. The secondary endpoints and order of the hierarchy will be defined in the SAP.

The secondary VAS AUCs selected for analysis will be analyzed as described for the primary AUC.

The secondary total opioid consumption endpoints selected for analysis will be analyzed as described for total opioid consumption through 48 hours.

The secondary endpoints measuring proportions of subjects selected for analysis will be analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by site.

The secondary times to event endpoints selected for analysis will be analyzed using logistic regression and Kaplan-Meier methods.

All other secondary endpoints will be summarized or tabulated as appropriate without testing for a treatment difference.

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 listings only. Incidence rates of TEAEs and the proportion of subject prematurely withdrawn from the study due to a TEAE will be shown for each treatment group. Incidence rates will also be displayed for each treatment group for study drug-related TEAEs and by severity. Incidence rates of SAEs will also be shown for each treatment group. All incidence rates will be categorized and displayed by system organ class and preferred term.

15.6.5. Health Economic Outcomes

Health economic outcomes will be summarized or tabulated as appropriate without testing for a treatment difference.

15.7. Significance Testing

All statistical comparisons will be at the 5% alpha level.

16. REFERENCES

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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. (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.

_____ _____

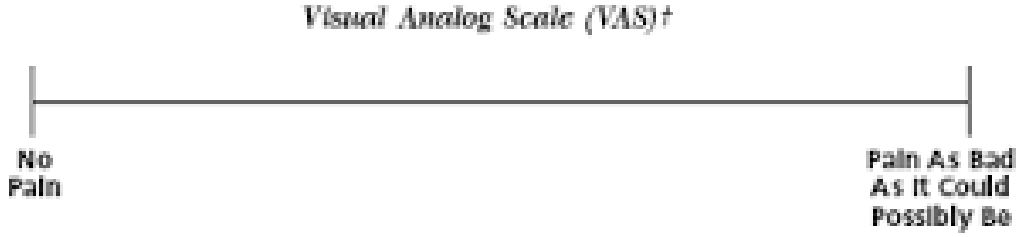
Signature of Investigator Date

18. APPENDICES

Appendix 1: Subject's Reported Pain (Visual Analog Scale)

Subjects will be evaluated for pain using a 10 cm VAS at baseline (Day 0 prior to any premedication before surgery); upon arrival at the PACU; at 4, 6, 8, 10, 12, 24, 28, 32, 36, 48, 52, 56, 60, and 72 hours or until hospital discharge; immediately prior to each administration of rescue pain medication; and just prior to hospital discharge.

Subjects will be asked "How much pain are you experiencing right now? Please place a vertical mark on the line below to indicate the level of pain you are experiencing right now."



(For reference only; not for clinical use.)

Appendix 2: Overall Benefit of Analgesia Score Questionnaire

The OBAS questionnaire will be completed at 24, 48, and 72 hours after surgery or upon hospital discharge (Lehmann 2010).

1. Please rate your current pain at rest on a scale between 0=minimal pain and 4=maximum imaginable pain
2. Please grade any distress and bother from vomiting in the past 24 h (0=not at all to 4=very much)
3. Please grade any distress and bother from itching in the past 24 h (0=not at all to 4=very much)
4. Please grade any distress and bother from sweating in the past 24 h (0=not at all to 4=very much)
5. Please grade any distress and bother from freezing in the past 24 h (0=not at all to 4=very much)
6. Please grade any distress and bother from dizziness in the past 24 h (0=not at all to 4=very much)
7. How satisfied are you with your pain treatment during the past 24 h (0=not at all to 4=very much)

Appendix 3: Nurse's Satisfaction with Postsurgical Pain Control (Likert Scale)

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

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

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

Appendix 4: Discharge Readiness

The subject's discharge readiness will be assessed q12h using the MPADSS below (Chung 1995a; Chung 1995b). This discharge readiness assessment will be used for data collection only and is not intended to interfere with the surgical center's policy for determining when the subject should be discharged from the site. Discharge readiness will be assessed q12h (at approximately 8:00 am and 8:00 pm [±2 hours]) from postsurgical Day 0 up to hospital discharge or up to reaching the discharge readiness score of 9, whichever comes first. Once a score of 9 is reached no further discharge readiness assessments are required

Modified Postanesthesia Discharge Scoring System (MPADSS)

Parameter	Score
Vital Signs: Measure Systolic Blood Pressure, Heart Rate, Respiratory Rate, Temperature	
ALL 4 vital signs are within 20% of the preoperative values	2
ANY of the 4 vital signs are within 20-40% of preoperative values and none of the vital signs exceed 40% of the preoperative values	1
ANY of the 4 vital signs are >40% of the preoperative valuess	0
Ambulation	
Steady gait/no dizziness	2
With assistance	1
None/dizziness	0
Nausea and Vomiting	
Minimal: no nausea/vomiting or nausea not requiring treatment	2
Moderate: nausea without vomiting and can tolerate liquids	1
Severe: nausea/vomiting and unable to tolerate oral liquids	0
Pain	
Minimal: requiring one or less pain rescue in the prior 12 hours	2
Moderate: requiring more than one pain rescue in the prior 12 hours	1
Severe: requiring supplemental IV analgesia for pain rescue	0
Surgical Bleeding	
Minimal: no action required	2
Moderate: requires dressing chage because it has soaked through or a compressive dressing	1
Severe: requires a suture or a return to the OR	0

Appendix 5: Training Qualifications for Investigators

1. Determine if Investigator is experienced in periarticular infiltration of bupivacaine HCl or EXPAREL.
2. In order to qualify, potential Investigators must read:
    a) Best infiltration practices: local analgesia infiltration techniques – hip & knee arthroplasty (Cushner 2014),
    b) Periarticular regional analgesia in total knee arthroplasty: A review of the neuroanatomy and injection technique (Guild 2015),
    c) Techniques for periarticular infiltration with liposomal bupivacaine for the management of pain after hip and knee arthroplasty: A consensus recommendation (Joshi 2015),
    d) and watch Dr. Dysart's infiltration video.
3. Pass brief quiz on the above.
4. Have training by Medical Affairs Team.
5. Undergo intraoperative observation to assess competency in a standardized approach by all investigators. Inexperienced investigators shall be observed during a minimum of five cases to confirm the technique is completed as per protocol. Experienced investigators shall be observed as well; the number of cases will be at the discretion of the Medical Affairs team.