Pacira Pharmaceuticals, Inc.
EXPAREL

Document:	Clinical Study Protocol
Official Title:	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Local Administration of EXPAREL for Prolonged Postsurgical Analgesia in Subjects Undergoing Third Molar Extraction
NCT Number:	NCT02517905
Document Date:	September 02, 2015

Clinical Study Protocol

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Local Administration of EXPAREL for Prolonged Postsurgical Analgesia in Subjects Undergoing Third Molar Extraction

Protocol No.:	402-C-329
EudraCT No.:	Not applicable
IND No.:	69,198
Study Phase:	3
Study Drug:	EXPAREL® (bupivacaine liposome injectable suspension)
Date:	02 September 2015 (Amendment 2) 27 July 2015 (Amendment 1) 27 May 2015 (original)
Study Sites:	Multicenter study in the United States
Sponsor:	Pacira Pharmaceuticals, Inc. 5 Sylvan Way Parsippany, NJ 07054 Tel: (973) 254-3560

Confidentiality Statement

The information contained in this document is confidential and the property of Pacira Pharmaceuticals, Inc. It should not be reproduced, revealed, or sent to third parties other than Institutional Review Boards/Independent Ethics Committees and the Investigator's research support staff participating in the conduct of the study without the prior written authorization of Pacira Pharmaceuticals, Inc.

SUMMARY OF CHANGES

Section 2 (Synopsis)

- Secondary Objectives:

  The text was changed

  from: "The secondary objectives of this study are to assess additional efficacy parameters, characterize the pharmacokinetic (PK) profile in this surgical model, and further assess the safety profile of EXPAREL."

  to: "The secondary objectives of this study are to assess additional efficacy parameters, characterize the pharmacokinetic (PK) profile in this surgical model, and further assess the safety and tolerability of EXPAREL."

- Methodology:
  - The sample size was increased from approximately 100 subjects (50 per treatment group) to approximately 175 subjects (100 subjects in the EXPAREL 133 mg group and 75 subjects in the placebo group).
  - The randomization was changed from 1:1 to 2:1.
  - The following text was added: "Subjects will be prohibited from smoking cigarettes or e-cigarettes from the time of randomization until discharge from the clinical research unit."
  - The interim analysis was removed.
  - A Day 7 follow-up visit was added.
  - The following text was changed

    from: "Adverse events will be recorded from the time the ICF is signed through Day 30. If a cardiac or neurological event occurs during the study, an unscheduled PK blood sample and ECG should be obtained within 2 hours of the time the event is noted."

    to: "Adverse events will be recorded from the time the ICF is signed through Day 30. If a cardiac event (e.g., myocardial depression, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmia, or cardiac arrest) or a neurological event (e.g., persistent anesthesia, paresthesia, weakness, or paralysis) occurs during the study, an unscheduled PK blood sample should be obtained and, for cardiac events, an ECG should be conducted within 2 hours of the time the event is noted."
  - The following text was added under postsurgical analgesia: "After 96 hours, the analgesic regimen may be adjusted."
  - The following text was changed

    from: "All postsurgical opioid analgesics administered must be documented through 96 hours."

    to: "All postsurgical analgesics administered must be documented through Day 10."

  - A Day 7 blood draw for PK analysis was added.
  - The following sentence was deleted: "However, blood samples from subjects randomized to the placebo group will not be analyzed."
- Number of Subjects Planned:

  The sample size was increased from approximately 100 subjects (50 per treatment group) to approximately 175 subjects (100 subjects in the EXPAREL 133 mg group and 75 subjects in the placebo group).
- Eligibility Criteria:

  For clarification of exclusion criterion 6, the semicolons were changed to commas.
- Efficacy Assessments:
  - The NRS pain intensity assessment timepoint of at first request for rescue pain medication was changed to immediately prior to each administration of rescue pain medication through 96 hours.
  - The final timepoint for the PoSSe scale questionnaire was changed from Day 10 to Day 7.
- Tertiary Efficacy Endpoints:
  - The AUC of the NRS pain intensity scores through 96 hours and Day 10 was changed to the AUC of the NRS pain intensity scores through 96 hours.
  - The NRS pain intensity scores at each assessed timepoint and at first request for rescue pain medication was changed to the NRS pain intensity scores at each assessed timepoint and immediately prior to each administration of rescue pain medication through 96 hours.
  - The sum of the pain intensity scores (SPIS) through 24, 48, 72, and 96 hours was added.
  - The PoSSe scale questionnaire mean total score at 72 hours and on Day 10 was changed to the PoSSe scale questionnaire mean total score at 72 hours and on Day 7.
- Pharmacokinetic Analysis:

  A Day 7 blood draw for PK analysis was added.
- Safety Assessments:

  A 96-hour timepoint (i.e., time of discharge) was added for vital signs.
- Statistical Methods:

  The interim analysis text was removed.

Table 1 (Time and Events Schedule of Study Procedures)

- A column was added for the Day 7 assessments.
- The timeframe for recording opioid rescue use was changed from 96 hours to Day 10.
- The Day 10 pain intensity assessment was deleted.

- A 96-hour timepoint (i.e., time of discharge) was added for vital signs.
- The final timepoint for the PoSSe scale questionnaire was changed from Day 10 to Day 7.
- Footnote 3: "Seated position" was changed to "supine position."
- Footnote 4: "NRS pain intensity scores also will be recorded at first request for rescue pain medication" was changed to "NRS pain intensity scores also will be recorded immediately prior to each administration of rescue pain medication through 96 hours."
- Footnote 6: Text was changed

  from: "If a cardiac or neurological event occurs during the study, an unscheduled PK blood sample and ECG should be obtained within 2 hours of the time that the event is noted."

  to: "If a cardiac event (e.g., myocardial depression, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmia, or cardiac arrest) or neurological event (e.g., persistent anesthesia, paresthesia, weakness, or paralysis) occurs during the study, an unscheduled PK blood sample should be obtained and, for cardiac events, an ECG should be conducted within 2 hours of the time that the event is noted."

Section 3 (Table of Contents)

The Table of Contents was updated.

Section 4.1 (List of Abbreviations)

The sum of pain intensity scores (SPIS) was added.

Section 8.2 (Secondary Objectives)

The text was changed

from: "The secondary objectives of this study are to assess additional efficacy parameters, characterize the pharmacokinetic (PK) profile in this surgical model, and further assess the safety profile of EXPAREL."

to: "The secondary objectives of this study are to assess additional efficacy parameters, characterize the pharmacokinetic (PK) profile in this surgical model, and further assess the safety and tolerability of EXPAREL."

Section 9 (Study Design and Plan)

- The sample size was increased from approximately 100 subjects (50 per treatment group) to approximately 175 subjects (100 subjects in the EXPAREL 133 mg group and 75 subjects in the placebo group).
- The randomization was changed from 1:1 to 2:1.

- The following text was added: "Subjects will be prohibited from smoking cigarettes or e-cigarettes from the time of randomization until discharge from the clinical research unit."
- The interim analysis was removed.
- A Day 7 follow-up visit was added.
- The following text was changed

  from: "Adverse events will be recorded from the time the ICF is signed through Day 30. If a cardiac or neurological event occurs during the study, an unscheduled PK blood sample and ECG should be obtained within 2 hours of the time the event is noted."

  to: "Adverse events will be recorded from the time the ICF is signed through Day 30. If a cardiac event (e.g., myocardial depression, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmia, or cardiac arrest) or neurological event (e.g., persistent anesthesia, paresthesia, weakness, or paralysis) occurs during the study, an unscheduled PK blood sample should be obtained and, for cardiac events, an ECG should be conducted within 2 hours of the time the event is noted."
- "All postsurgical opioid analgesics administered must be documented through 96 hours" was changed to "All postsurgical analgesics administered must be documented through Day 10."
- The following text was added under postsurgical analgesia: "After 96 hours, the analgesic regimen may be adjusted."
- A Day 7 blood draw for PK analysis was added.
- The following sentence was deleted: "However, blood samples from subjects randomized to the placebo group will not be analyzed."

Section 10.2 (Exclusion Criteria)

For clarification of exclusion criterion 6, the semicolons were changed to commas.

Section 11.1 (Treatment to be Administered)

The text was changed

from: "Subjects should only receive rescue pain medication (PO oxycodone 5-10 mg) upon request for breakthrough pain, as needed (maximum of every 4 hours). All postsurgical opioid analgesics administered must be documented through 96 hours. No other analgesic agents, including NSAIDs, are allowed during the 96-hour observation period."

to: "Subjects should only receive rescue pain medication (PO oxycodone 5-10 mg) upon request for breakthrough pain, as needed (maximum of every 4 hours). No other analgesic agents, including NSAIDs, are allowed during the 96-hour observation period. After 96 hours, the analgesic regimen may be adjusted. All postsurgical analgesics administered must be documented through Day 10."

Section 11.3.1 (Randomization Scheme)

The following text was changed

from: "Approximately 100 subjects (50 per treatment group) are planned for enrollment. Subjects will be randomized in a 1:1 ratio to receive local administration of a single dose of either EXPAREL (133 mg/10 mL) or placebo (normal saline, 10 mL)."

to: "Approximately 175 subjects (100 subjects in the EXPAREL 133 mg group and 75 subjects in the placebo group) are planned for enrollment. Subjects will be randomized in a 2:1 ratio to receive local administration of a single dose of either EXPAREL (133 mg/10 mL) or placebo (normal saline, 10 mL)."

Section 11.5.1 (Blinding Procedures)

The following text was added: "The site-specific blinding plan will outline the study treatment blinding process that will be followed at the site throughout the study."

Section 11.5.2 (Unblinding Procedures)

The first two paragraphs in the section were changed

from: "Subject treatment assignments should not be unblinded during the study by blinded study personnel. The Investigator will have the ability to unblind a subject 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. Any accidental unblinding events (i.e., through mishaps in the operating room or miscommunication among study staff) must be reported to Pacira immediately.

Only designated staff at Pacira will have the option to unblind treatment assignment through the randomization system, which will be designed to document such a transaction and notify the lead member of each functional group that such a transaction occurred."

to: "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. 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."

Section 11.6.1 (Prior and Concomitant Medications and Therapy)

Under concomitant medications, the following text was changed

from: "All medications taken within 3 days prior to study drug administration through Day 30 will be recorded on the CRF."

to: "All medications taken within 30 days prior to study drug administration through Day 30 will be recorded on the CRF."

Section 11.6.3 (Permitted and Restricted Therapy or Medications After Surgery Through 96 Hours)

This section was revised

from:

Permitted

Subjects should only receive rescue pain medication (PO oxycodone 5-10 mg) upon request for breakthrough pain, as needed (maximum of every 4 hours). All postsurgical opioid analgesics administered must be documented through 96 hours.

Restricted

No other analgesics are permitted within 96 hours after surgery. For study purposes, it is important to standardize pain management modalities during the first 96 hours following study drug administration. Therefore, the study staff must adhere closely to the treatment requirements noted in the protocol. After 96 hours, the analgesic regimen may be adjusted for each subject individually, as deemed appropriate by the physician responsible for the postsurgical care.

to:

Subjects should only receive rescue pain medication (PO oxycodone 5-10 mg) upon request for breakthrough pain, as needed (maximum of every 4 hours). No other analgesics are permitted within 96 hours after surgery.

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

All postsurgical analgesics administered must be documented through Day 10.

Section 12.1 (Efficacy Assessments)

- The NRS pain intensity assessment at first request for rescue pain medication was changed to immediately prior to each administration of rescue pain medication through 96 hours.
- The Day 10 pain intensity assessment was deleted.

- The final timepoint for the PoSSe scale questionnaire was changed from Day 10 to Day 7.

Section 12.2 (Efficacy Endpoints)

Tertiary efficacy endpoints:

- The AUC of the NRS pain intensity scores through 96 hours and Day 10 was changed to the AUC of the NRS pain intensity scores through 96 hours.
- "The NRS pain intensity scores at each assessed timepoint and at first request for rescue pain medication" was changed to "The NRS pain intensity scores at each assessed timepoint and immediately prior to each administration of rescue pain medication through 96 hours."
- The sum of the pain intensity scores (SPIS) through 24, 48, 72, and 96 hours was added.
- The PoSSe scale questionnaire mean total score at 72 hours and on Day 10 was changed to the PoSSe scale questionnaire mean total score at 72 hours and on Day 7.

Section 12.3 (Pharmacokinetic Analysis)

- A Day 7 blood draw for PK analysis was added.
- The following sentence was deleted: "However, blood samples from subjects randomized to the placebo group will not be analyzed."

Section 12.5 (Safety Assessments)

A 96-hour timepoint (i.e., time of discharge) was added for vital signs.

Section 13.1.3 (Vital Signs)

"Seated position" was changed to "supine position."

Section 13.1.4 (Electrocardiogram)

"Seated position" was changed to "supine position."

Section 13.1.6 (Postoperative Symptom Severity [PoSSe] Scale Questionnaire)

The final timepoint for the PoSSe scale questionnaire was changed from Day 10 to Day 7.

Section 13.2 (Screening Procedures)

"Measure vital signs (heart rate and blood pressure) after subject has rested in the seated position" was changed to "Measure vital signs (heart rate and blood pressure) after subject has rested in a supine position."

Section 13.3 (Baseline Procedures [Day 1])

"Measure vital signs (heart rate and blood pressure) after subject has rested in the seated position" was changed to "Measure vital signs (heart rate and blood pressure) after subject has rested in a supine position."

Section 13.5 (Procedures After Surgery Through 96 Hours)

- The NRS pain intensity assessment timepoint of at first request for rescue pain medication was changed to immediately prior to each administration of rescue pain medication through 96 hours.
- "Measure vital signs (heart rate and blood pressure) after subject has rested in the seated position at 1, 2, and 4 hours" was changed to "Measure vital signs (heart rate and blood pressure) after subject has rested in a supine position at 1, 2, 4, and 96 hours (i.e., prior to discharge)."
- The following text was changed

  from: "If a cardiac or neurological event occurs during the study, an unscheduled PK blood sample and ECG should be obtained within 2 hours of the time that the event is noted."

  to: "If a cardiac event (e.g., myocardial depression, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmia, or cardiac arrest) or neurological event (e.g., persistent anesthesia, paresthesia, weakness, or paralysis) occurs during the study, an unscheduled PK blood sample should be obtained and, for cardiac events, an ECG should be conducted within 2 hours of the time that the event is noted."

Section 13.6 (Day 7 Visit)

This section was added.

Section 13.7 (Day 10 Visit)

- The NRS pain intensity assessment was deleted.
- "Record date, time, and amount of all opioid pain medication administered" was deleted.
- The PoSSe scale questionnaire on Day 10 was deleted.

- "Document any unscheduled phone calls or office visits related to pain after discharge" was changed to "Document any unscheduled phone calls or office visits related to pain since Day 7."
- "Record concomitant medications" was changed to "Record concomitant medications including opioid rescue."

Section 14.1.2 (Recording Adverse Events)

- The following paragraph was changed:

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

  to: "All AEs will be followed through progression of their severity. For example, if an AE is reported as mild in severity but changes to moderate, the AE of mild will have an end date when the severity changes to moderate. A new AE record with a moderate severity will be created with a start date that is the same as the end date of the mild AE."

- The following text was changed

  from: "Any condition noted before the subject is randomized 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 randomization, or after study drug administration, it is considered an AE."

  to: "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 subject signs the ICF it is considered an AE."

- The following text was changed

  from: "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 study drug, action taken for the AE, and the outcome of the AE, including the date and time of resolution, if applicable."

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

Section 14.2.2 (Reporting Serious Adverse Events)

The following sentence was deleted: "Additional telephone contact information for Pacira Drug Safety/designee can be found in the regulatory binder."

Section 15.3 (Determination of Sample Size)

The following text was added: "However, the EXPAREL group will randomize approximately 100 subjects to lower the AE detection threshold for the safety database to 3%. The sample size for placebo was increased due to the additional collection of NRS pain intensity score immediately prior to all requests for rescue medication through 96 hours. The placebo sample size was increased to ensure that there are at least 50 subjects treated in both the EXPAREL and placebo under the current protocol amendment. It is expected that the sample size will be approximately 175 subjects resulting in a 2:1 ratio of EXPAREL to placebo subjects."

Section 15.8 (Interim Analysis)

This section was removed.

Section 16 (References)

The EXPAREL IB reference was updated from Edition 16 (23 October 2013) to Edition 17 (12 May 2015).

Section 18 (Appendix 1)

- The NRS pain intensity assessment timepoint of at first request for rescue pain medication was changed to immediately prior to each administration of rescue pain medication through 96 hours.
- The Day 10 pain intensity assessment was deleted.

Section 18 (Appendix 3)

- The final timepoint for the PoSSe scale questionnaire was changed from Day 10 to Day 7.
- Minor edits were made to the questionnaire.

Section 18 (Appendix 4)

The following text was added: "If the subject is not oriented, the event should be recorded as an AE."

1. SIGNATURE PAGE

James B. Jones, MD, PharmD, FACEP Sr. Vice President and Chief Medical Officer	03 September 2015 Date
George M. Wagner, Vice President Regulatory Affairs and Pharmacovigilance	02 September 2015 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 Products: EXPAREL® (bupivacaine liposome injectable suspension)		
Name of Active Ingredients: Bupivacaine free base, 1.3%, 13.3 mg/mL		

Title of Study: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Local Administration of EXPAREL for Prolonged Postsurgical Analgesia in Subjects Undergoing Third Molar Extraction

Principal Investigators: To be determined

Study Center(s): At least two study sites in the United States

Publications (Reference): None

Objectives:

Primary objective: The primary objective of this study is to demonstrate the analgesic efficacy of single-dose local administration of EXPAREL compared with placebo in subjects following bilateral third molar extraction.

Secondary objectives: The secondary objectives of this study are to assess additional efficacy parameters, characterize the pharmacokinetic (PK) profile in this surgical model, and further assess the safety and tolerability of EXPAREL.

Methodology:

This is a Phase 3, randomized, double-blind, placebo-controlled study in subjects scheduled to undergo elective bilateral third molar extraction (i.e., extraction of all four third molars) under local anesthesia. At least one lower mandibular third molar must involve full or partial bony impaction confirmed by visual or radiographic evidence.

Approximately 175 subjects (100 subjects in the EXPAREL 133 mg group and 75 subjects in the placebo group) are planned for enrollment. Subjects will be randomized in a 2:1 ratio to receive local administration of a single dose of either EXPAREL (133 mg/10 mL) or placebo (normal saline, 10 mL).

Screening

Subjects will be screened within 30 days prior to surgery. During the screening visit, subjects will be assessed for any past or present medical conditions that in the opinion of the Investigator would preclude them from study participation. After the informed consent form (ICF) is signed, a medical/surgical history, dental examination, physical examination, vital sign measurements, urine pregnancy test for women of childbearing potential, urine drug screen, and 12-lead electrocardiogram (ECG) will be conducted.

Day 1 (Day of Surgery)

On Day 1 prior to surgery, any adverse events (AEs) or changes to concomitant medications since screening will be recorded, vital signs will be measured, a drug screen will be conducted, and a urine pregnancy test will be conducted for women of childbearing potential. A pre-dose PK sample will be collected from all subjects eligible for randomization. Randomized subjects will receive a dental nerve block with lidocaine 2% with epinephrine 1:100,000 before undergoing bilateral third molar extraction under local anesthesia. In addition to the lidocaine nerve block, the Investigator may choose to add topical benzocaine or intraoperative nitrous oxide.

At the end of surgery and at least 20 minutes after the lidocaine administration, study drug will be infiltrated as follows to provide postsurgical analgesia:

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

- Maxilla – At the depth of the posterior buccal vestibule, two points of infiltration submucosal and supraperiosteal are identified at the apex of the extracted third molar. The sites are separated by 6-8 mm and 1 mL of EXPAREL infiltrated in each site (2 mL on each side), for a total of 4 mL in the maxilla.
- Mandible – After readaptation and closure of the mucoperiosteal flap, the external oblique ridge is palpated identifying the buccinator muscle attachment. Four infiltration points separated by 6-8 mm are selected along this line. The needle is inserted approximately 5 mm and 0.5 mL of EXPAREL is infiltrated into the muscle at each point (total of 2 mL per side for this step). At the point of greatest subperiosteal reflection, just lateral to the third molar socket, two infiltrations are taken deeper (1.5 cm) and 0.5 mL is infiltrated as the needle is withdrawn (total of 1 mL per side for this step). Thus, the total is 6 mL in the mandible.

Subjects will be required to remain in the research facility for 96 hours after study drug administration. Subjects will be prohibited from smoking cigarettes or e-cigarettes from the time of randomization until discharge from the clinical research unit.

After the first 30 subjects have completed the study through Day 10, the initial plasma samples from the subjects who received EXPAREL will be analyzed. Following a blinded review of the PK data, the protocol may be amended so that subsequent assessment and endpoints are collected beyond the median time to maximum plasma concentration (T_{max}).

Postsurgical Safety and Efficacy Assessments

Postsurgical assessments will include pain intensity scores using the 0-10 point numeric rating scale (NRS); use of supplemental opioid rescue medication; neurological assessment; 12-lead ECGs; vital signs; subject's satisfaction with postsurgical pain control; and the postoperative symptom severity (PoSSe) scale questionnaire. At timepoints when multiple assessments coincide, the NRS pain intensity assessment will be conducted first, if applicable.

All subjects will return for follow-up visits on Days 7 and 10. A phone call will be made to each subject on Day 30 for an AE assessment and to inquire as to whether the subject made any unscheduled phone calls or office visits related to pain.

Adverse events will be recorded from the time the ICF is signed through Day 30. If a cardiac event (e.g., myocardial depression, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmia, or cardiac arrest) or a neurological event (e.g., persistent anesthesia, paresthesia, weakness, or paralysis) occurs during the study, an unscheduled PK blood sample should be obtained and, for cardiac events, an ECG should be conducted within 2 hours of the time the event is noted. If there is a scheduled PK blood draw and ECG within 2 hours before or after the event, an additional PK blood draw and ECG are not needed.

Postsurgical Analgesia

Subjects should only receive rescue pain medication (oral [PO] oxycodone 5-10 mg) upon request for breakthrough pain, as needed (maximum of every 4 hours). No other analgesic agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), are allowed during the 96-hour observation period. After 96 hours, the analgesic regimen may be adjusted. All postsurgical analgesics administered must be documented through Day 10.

Pharmacokinetic Assessment

Blood samples for PK analysis will be obtained at baseline (prior to study drug administration); 15 minutes, 30 minutes, 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 84, and 96 hours after the beginning of study drug administration; and on Days 7 and 10. Blood samples will be collected from all subjects to maintain the treatment double-blind.

Number of Subjects (Planned): Approximately 175 subjects (100 subjects in the EXPAREL 133 mg group and 75 subjects in the placebo group) are planned for enrollment into the study.

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Name of Finished Products: EXPAREL® (bupivacaine liposome injectable suspension)		
Name of Active Ingredients: Bupivacaine free base, 1.3%, 13.3 mg/mL		

Eligibility Criteria:

Inclusion Criteria:

1. Male or female, ≥18 years of age at screening.
2. Scheduled to undergo bilateral third molar extractions (i.e., extraction of all four third molars) under local anesthesia. At least one lower mandibular third molar must involve full or partial bony impaction confirmed by visual or radiological evidence.
3. American Society of Anesthesiology (ASA) physical status 1, 2, or 3.
4. Female subjects must be either surgically sterile, using a medically acceptable method of birth control, or at least 2 years postmenopausal, and must have a documented negative pregnancy test result during screening and on Day 1 prior to surgery.
5. Able to provide informed consent, adhere to the study visit schedule, and complete all study assessments.

Exclusion Criteria:

1. History of hypersensitivity or idiosyncratic reaction to amide-type local anesthetics or opioids.
2. Contraindication to lidocaine, epinephrine, bupivacaine, or oxycodone.
3. History of significant drug allergy (e.g., anaphylaxis or hepatotoxicity).
4. Positive test result from the urine drug screen at screening or prior to the surgical procedure.
5. Currently pregnant, nursing, or planning to become pregnant during the study or within 1 month after study drug administration.
6. History or active psychiatric illness (including major depression, bipolar disorder, or anxiety), Type 1 or Type 2 diabetes, severe renal or hepatic impairment, significant cardiovascular disease (including cardiac rhythm disturbance), migraine headaches, frequent headaches, other pain conditions, or other medical condition that, in the opinion of the Investigator, may increase the risk of surgery or interfere with the evaluation of the study drug.
7. History of infection requiring intravenous (IV) antibiotics within 45 days or oral (PO) antibiotics within 30 days prior to study drug administration for reasons other than dental prophylaxis. Subjects must be afebrile, without signs or symptoms indicative of active infection.
8. Use of any of the following medications within the times specified before surgery: long-acting opioid medication, NSAIDs, aspirin (except for low-dose aspirin used for cardioprotection), or acetaminophen 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 norepinepherine 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 any concurrent therapy that could interfere with the evaluation of efficacy or safety, such as any drugs which in the Investigator's opinion may exert significant analgesic properties or act synergistically with the investigational product.
12. 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.

<table>
<tr><td>Name of Sponsor/Company:
Pacira Pharmaceuticals, Inc.
5 Sylvan Way
Parsippany, NJ 07054
(973) 254-3560</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
Volume:
Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
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<tr><td>Name of Active Ingredients:
Bupivacaine free base, 1.3%, 13.3 mg/mL</td></tr>
<tr><td colspan="3">Test Product, Dose, Mode of Administration, and Lot Number:
Name: EXPAREL® (bupivacaine liposome injectable suspension)
Active Ingredient: Bupivacaine 1.3%, 13.3 mg/mL
Dosage: Single administration of EXPAREL 133 mg in 10 mL
Lot Number: To be determined
Mode of Administration: Infiltration
Meal Relationship: None</td></tr>
<tr><td colspan="3">Test Product, Dose, Mode of Administration, and Lot Number:
Name: Placebo
Active Ingredient: Normal saline
Dosage: Single dose of 10 mL
Lot Number: Commercial product to be procured by the study site
Mode of Administration: Infiltration
Meal Relationship: None</td></tr>
<tr><td colspan="3">Duration of Subject Participation in Study:
Participation will begin upon signing of the ICF. No more than 30 days should pass between signing the ICF and surgery. A follow-up telephone call will occur on Day 30 (±4 days). Therefore, each subject may participate in the study for a maximum of 64 days.</td></tr>
<tr><td colspan="3">Efficacy Assessments (timepoints may change based on the mean T_{max} from the first 30 subjects):
The following efficacy measurements will be conducted at the times specified after the beginning of study drug administration:
Date, time of administration, and amount of all opioid rescue medication taken through 96 hours.
Pain intensity scores using the NRS at 15 minutes, 30 minutes, 1, 2, 4, 6, 8, 12, 24, 48, 72, and 96 hours, immediately prior to each administration of rescue pain medication through 96 hours (see Appendix 1).
Subject satisfaction with postsurgical pain control (using a 5-point Likert scale) at 24, 48, 72, and 96 hours, and on Day 10 (see Appendix 2).
Postoperative symptom severity (PoSSe) scale questionnaire at 72 hours and on Day 7 (see Appendix 3).
Unscheduled phone calls or office visits related to pain after discharge from the facility through Day 30.</td></tr>
</table>

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 Products: EXPAREL® (bupivacaine liposome injectable suspension)		
Name of Active Ingredients: Bupivacaine free base, 1.3%, 13.3 mg/mL		

Efficacy Endpoints:

Primary efficacy endpoint is the area under the curve (AUC) of the NRS pain intensity scores through 48 hours.

Secondary efficacy endpoints:

The following secondary endpoints will be analyzed in the following order using a hierarchical, fixed-sequence stepwise testing procedure:

1. The AUC of the NRS pain intensity scores through 24 hours.
2. The AUC of the NRS pain intensity scores through 72 hours.
3. Percentage of opioid-free subjects through 24 hours.
4. Percentage of opioid-free subjects through 48 hours.
5. Percentage of opioid-free subjects through 72 hours.

Tertiary efficacy endpoints:

- AUC of the NRS pain intensity scores through 96 hours.
- Sum of pain intensity scores (SPIS) through 24, 48, 72, and 96 hours.
- The NRS pain intensity scores at each assessed timepoint and immediately prior to each administration of rescue pain medication through 96 hours.
- The AUC of the NRS pain intensity scores from 24-48 and 48-72 hours.
- Percentage of pain-free subjects at each assessed timepoint using the NRS pain intensity score.
- Percentage of opioid-free subjects through 96 hours.
- Time to first opioid rescue medication.
- Integrated rank assessment using the NRS pain intensity score at 48 hours and the total amount of postsurgical opioids consumed through 48 hours (Silverman 1993).
- Overall assessment of the subject′s satisfaction with postsurgical pain control (using a 5-point Likert scale) at 24, 48, 72, and 96 hours, and on Day 10.
- PoSSe scale questionnaire mean total score at 72 hours and on Day 7.
- Number of unscheduled phone calls or office visits related to pain through Day 30.

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)*
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Name of Active Ingredients: Bupivacaine free base, 1.3%, 13.3 mg/mL		

Pharmacokinetic Analysis:

Pharmacokinetic parameters will be estimated from plasma bupivacaine measurements using non-compartmental analysis, based on the sampling schedule at baseline (prior to study drug administration); 15 minutes, 30 minutes, 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 84, and 96 hours after the beginning of study drug administration; and on Days 7 and 10.

The following parameters will be determined:

- Area under the plasma concentration-versus-time curve (AUC) from time 0 to the last collection time after drug administration ($AUC_{0\text{-last}}$).
- Area under the plasma concentration-versus-time curve from time 0 extrapolated to infinity after drug administration ($AUC_{0\text{-}\infty}$).
- Maximum plasma concentration (C_{max}).
- Time to maximum plasma concentration (T_{max}).
- The apparent terminal elimination rate constant (λ_z).
- The apparent terminal elimination half-life ($t_{1/2el}$).

Safety Assessments:

The following safety assessments will be conducted at the specified timepoints after the beginning of study drug administration:

- Neurological assessment at baseline (prior to study drug administration); 15 minutes, 30 minutes, 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 84, and 96 hours after the beginning of study drug administration; and on Day 10 (see Appendix 4).
- Cardiac assessment (i.e., 12-lead ECGs) at baseline (prior to study drug administration); 15 minutes, 30 minutes, 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 84, and 96 hours after the beginning of study drug administration; and on Day 10.
- Vital signs (resting heart rate and blood pressure) at baseline (approximately 1 hour prior to surgery) and 1, 2, 4, and 96 hours (i.e., time of discharge).
- Adverse events from the time the ICF is signed through Day 30.

Safety Endpoints:

- Summary of neurological assessments.
- Change from baseline in ECG data closest to the median T_{max}.
- Change from baseline in vital signs (resting heart rate and blood pressure) at each assessed timepoint.
- Incidence of treatment-emergent AEs (TEAEs) through Day 30.

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 Products: EXPAREL® (bupivacaine liposome injectable suspension)		
Name of Active Ingredients: Bupivacaine free base, 1.3%, 13.3 mg/mL		

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. EXPAREL will be compared with placebo using analysis of variance (ANOVA) with treatment as the main effect for the primary efficacy endpoint of AUC of the NRS pain intensity scores through 48 hours. Other efficacy endpoints will be analyzed using ANOVA, chi-square tests, and log-rank tests, as appropriate.

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.

Safety endpoints will be summarized descriptively by treatment group. The PK parameters will be calculated using non-compartmental analysis and summarized for the EXPAREL group.

Table 1. Time and Events Schedule of Study Procedures

	Screen Visit	Day 1	15 min	30 min	1h	2h	4h	6h	8h	12h	18h	24h	30h	36h	42h	48h	54h	60h	66h	72h	84h	96h	D7	D10	D30
Time Window	**Within 30 days**		**±5 min**	**±5 min**	**±5 min**	**±15 min**	**±15 min**	**±30 min**	**±30 min**	**±30 min**	**±30 min**	**±1h**	**±1h**	**±1h**	**±1h**	**±2h**	**±2h**	**±2h**	**±2h**	**±4h**	**±4h**	**±4h**	**±1d**	**±1d**	**±4d**
Obtain signed informed consent	X																								
Perform dental examination[1]	X																								
Assess/confirm eligibility	X	X[2]																							
Medical/surgical history	X	X[2]																							
Demographics and baseline characteristics	X																								
Physical examination including height and weight	X																								
Urine pregnancy test for women of childbearing potential	X	X[2]																							
Urine drug screen	X	X[2]																							
Vital signs[3]	X	X[2]			X	X	X															X			
Neurological assessment		X[2]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
12-lead electrocardiogram	X	X[2]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Randomize subject and prepare study drug		X[2]																							
Perform dental nerve block with lidocaine 2% with epinephrine 1:100,000		X[2]																							
Administer study drug; record start and stop time		X																							
Conduct NRS pain intensity assessment[4]			X	X	X	X	X	X	X	X		X				X				X		X			
Record times and amounts of opioid rescue medication administered[5]		◄----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----►	
Subject satisfaction with postsurgical pain control												X				X				X		X		X	
Complete PoSSe scale questionnaire																				X			X		
Collect scheduled PK blood sample		X[2]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Document any unscheduled phone calls or office visits related to pain after hospital discharge																							X	X	X
Phone call																									X
Record concomitant medications	◄----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----►
Record AEs (starting at signing of ICF)[6]	◄----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----►

Abbreviations: AE = adverse event; ICF = informed consent form; NRS = numeric rating scale; PK = pharmacokinetic; PoSSe = postoperative symptom severity.

* Postsurgical efficacy assessments will be conducted at the timepoints specified *after the beginning of study drug administration*. At timepoints when multiple assessments coincide, the NRS pain intensity assessment will be conducted first, if applicable.

[1] Or on Day 1 prior to surgery.

[2] Prior to surgery.

[3] Vital signs (heart rate and blood pressure) will be measured after subject has rested in a supine position.

[4] NRS pain intensity scores also will be recorded immediately prior to each administration of rescue pain medication through 96 hours.

[5] Subjects should only receive opioid rescue medication (oral oxycodone 5-10 mg) upon request for breakthrough pain, as needed (maximum of every 4 hours). During the 96-hour observation period, no other analgesic agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), are allowed. After 96 hours, the analgesic regimen may be adjusted.

[6] If a cardiac event (e.g., myocardial depression, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmia, or cardiac arrest) or neurological event (e.g., persistent anesthesia, paresthesia, weakness, or paralysis) occurs during the study, an unscheduled PK blood sample should be obtained and, for cardiac events, an ECG should be conducted within 2 hours of the time that the event is noted. If there is a scheduled PK blood draw and ECG within 2 hours before or after the event, an additional PK blood draw and ECG are not needed.

3. TABLE OF CONTENTS

LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

4.1. List of Abbreviations

AE	Adverse event
ANOVA	Analysis of variance
ASA	American Society of Anesthesiologists
AUC	Area under the curve
$AUC_{0\text{-tlast}}$	Area under the plasma concentration-time curve from the time of administration to the time of the last quantifiable concentration
$AUC_{0\text{-}\infty}$	Area under the plasma concentration-time curve from the time of administration extrapolated to infinity
CFR	Code of Federal Regulations
CI	Confidence interval
C_{max}	The maximum observed plasma concentration obtained directly from the experimental data without interpolation
CRF	Case Report Form
C_{tlast}	Time of the last quantifiable concentration
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
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
NRS	Numeric rating scale
NSAIDs	Non-steroidal anti-inflammatory drugs
PCA	Patient-controlled analgesia
PK	Pharmacokinetic
PO	Oral

PoSSe	Postoperative symptom severity
PTEA	Pretreatment adverse event
SAE	Serious adverse event
SAP	Statistical analysis plan
SNRI	Selective norepinephrine reuptake inhibitor
SPIS	Sum of the pain intensity scores
SSRI	Selective serotonin reuptake inhibitor
λ_z	The apparent terminal elimination rate constant
$t_{1/2el}$	The apparent terminal elimination half-life
TAP	Transversus abdominis plane
TEAE	Treatment-emergent adverse event
T_{max}	The time maximum plasma concentration
wWOCF	Windowed Worst-Observation-Carried-Forward
US	United States (of America)

4.2. Definition of Terms

Pharmacokinetic terms are defined in Section 12.4.

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. Attention is directed to the basic elements that are required to be incorporated into the informed consent form (ICF) under 21 CFR Part 50.25 and ICH GCP.

5.2. Ethical Conduct of the Study

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

5.3. Subject Information and Consent

Before a subject undergoes any study-specific screening procedures, the Investigator or designee will thoroughly explain to the subject the purpose of the study, the associated procedures, and any expected effects and potential adverse reactions. A copy of the IRB-approved ICF will be provided to the subject, who will be given sufficient time and opportunity to inquire about the details of the study and decide whether or not to participate. The subject, and the study staff with whom he/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/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 2000 [Edinburgh]).

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 extend pain relief with a single dose administration without the use of indwelling catheters and to decrease the requirement for supplemental opioid medications. 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 postoperative analgesia include infiltration with local anesthetic agents, and wound infiltration with local anesthetics combined with the systemic administration of analgesics (multimodal therapy). Multimodal therapy usually includes opioid medications, which have considerable drawbacks including time and resources required for monitoring opioid-related side effects. A reduction in the use of 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.

There are almost 12 billion units of opioids prescribed in the US every year, almost 2 billion of which are from the oral surgery arena. Third molar extraction is associated with a defined period of pain and discomfort that often leads to the need for opioid analgesics. Unfortunately, this has the drawback of subjecting the patient to opioid-related adverse events (AEs); depending on the specific event, this can occur in up to 50% of patients (Volkow 2011). Previous studies with the use of EXPAREL have shown significant reduction in pain as well as total opioid consumption following both hard and soft tissue surgical procedures, along with a significant increase in many studies in median time to first opioid use. This delay was also associated with fewer opioid related adverse effects.

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. Opioid-only regimens are common and intravenous (IV) patient-controlled analgesia (PCA) is a widely used delivery system for morphine sulfate. 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.

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.

7.4. Summary of Human Experience with EXPAREL

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

Across the entire clinical development program, in doses up to 665 mg, no adverse safety signal attributed to either CNS or cardiovascular system was reported with EXPAREL. Adverse events that are occasionally reported with high doses of standard bupivacaine solution have not been observed. In two rigorous QTc studies, EXPAREL did not cause significant QTc prolongation even at the highest dose evaluated.

The robust nature of the efficacy results in the Phase 3 wound infiltration studies (SKY0402-C-316 and SKY0402-C-317) and the Phase 2/3 nerve block study (402-C-323) was demonstrated across subgroups of subjects with various prognostic features and across demographic subgroups.

Following the NDA submission of EXPAREL, numerous clinical studies were conducted in which EXPAREL was administered via various routes of administration including infiltration into the transversus abdominis plane (TAP) (Sternlicht 2014, Feierman 2014) and intraoperative wound infiltration or instillation. Additionally, as of May 2015, more than one million patients have received EXPAREL in the postmarketing setting.

Please refer to the Investigator's Brochure for additional information regarding the completed studies. Please see the EXPAREL Full Prescribing Information for complete safety information regarding EXPAREL (liposome bupivacaine injectable suspension) in the setting of wound infiltration.

8. OBJECTIVES

8.1. Primary Objectives

The primary objective of this study is to demonstrate the analgesic efficacy of single-dose local administration of EXPAREL compared with placebo in subjects following bilateral third molar extraction.

8.2. Secondary Objectives

The secondary objectives of this study are to assess additional efficacy parameters, characterize the pharmacokinetic (PK) profile in this surgical model, and further assess the safety and tolerability of EXPAREL.

9. STUDY DESIGN AND PLAN

9.1. Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled study in subjects scheduled to undergo elective bilateral third molar extraction (i.e., extraction of all four third molars) under local anesthesia. At least one lower mandibular third molar must involve full or partial bony impaction confirmed by visual or radiographic evidence.

Approximately 175 subjects (100 subjects in the EXPAREL 133 mg group and 75 subjects in the placebo group) are planned for enrollment. Subjects will be randomized in a 2:1 ratio to receive local administration of a single dose of either EXPAREL (133 mg/10 mL) or placebo (normal saline, 10 mL).

Screening

Subjects will be screened within 30 days prior to surgery. During the screening visit, subjects will be assessed for any past or present medical conditions that in the opinion of the Investigator would preclude them from study participation. After the ICF is signed, a medical/surgical history, dental examination, physical examination, vital sign measurements, urine pregnancy test for women of childbearing potential, urine drug screen, and 12-lead electrocardiogram (ECG) will be conducted.

Day 1 (Day of Surgery)

On Day 1 prior to surgery, any AEs or changes in concomitant medications since screening will be recorded, vital signs will be measured, a urine drug screen will be conducted for all subjects, and a urine pregnancy test will be conducted for women of childbearing potential. A pre-dose PK sample will be collected from all subjects eligible for randomization. Randomized subjects will receive a dental nerve block with lidocaine 2% with epinephrine 1:100,000 before undergoing bilateral third molar extraction under local anesthesia. In addition to the lidocaine nerve block, the Investigator may choose to add topical benzocaine or intraoperative nitrous oxide.

At the end of surgery, and at least 20 minutes after the lidocaine administration, study drug will be infiltrated as follows to provide postsurgical analgesia:

- Maxilla – At the depth of the posterior buccal vestibule, two points of infiltration submucosal and supraperiosteal are identified at the apex of the extracted third molar. The sites are separated by 6-8 mm and 1 mL of EXPAREL infiltrated in each site (2 mL on each side), for a total of 4 mL in the maxilla.
- Mandible – After readaptation and closure of the mucoperiosteal flap, the external oblique ridge is palpated identifying the buccinator muscle attachment. Four infiltration points separated by 6-8 mm are selected along this line. The needle is inserted approximately 5 mm and 0.5 mL of EXPAREL is infiltrated into the muscle at each point (total of 2 mL per side for this step). At the point of greatest subperiosteal reflection, just lateral to the third molar socket, two infiltrations are taken deeper (1.5 cm) and 0.5

mL is infiltrated as the needle is withdrawn (total of 1 mL per side for this step). Thus, the total is 6 mL in the mandible.

Subjects will be required to remain in the research facility for 96 hours after study drug administration. Subjects will be prohibited from smoking cigarettes or e-cigarettes from the time of randomization until discharge from the clinical research unit.

After the first 30 subjects have completed the study through Day 10, the initial plasma samples from the subjects who received EXPAREL will be analyzed. Following a blinded review of the PK data, the protocol may be amended so that subsequent assessment and endpoints are collected beyond the median time to maximum plasma concentration (T_{max}).

Postsurgical Safety and Efficacy Assessments

Postsurgical assessments will include pain intensity scores using the 0-10 point numeric rating scale (NRS); use of supplemental opioid rescue medication; neurological assessment; 12-lead ECGs; vital signs; subject's satisfaction with postsurgical pain control; and the postoperative symptom severity (PoSSe) scale questionnaire (Ruta 2000). At timepoints when multiple assessments coincide, the NRS pain intensity assessment will be conducted first, if applicable.

All subjects will return for follow-up visits on Days 7 and 10. A phone call will be made to each subject on Day 30 for an AE assessment and to inquire as to whether the subject made any unscheduled phone calls or office visits related to pain.

Adverse events will be recorded from the time the ICF is signed through Day 30. If a cardiac event (e.g., myocardial depression, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmia, or cardiac arrest) or neurological event (e.g., persistent anesthesia, paresthesia, weakness, or paralysis) occurs during the study, an unscheduled PK blood sample should be obtained and, for cardiac events, an ECG should be conducted within 2 hours of the time the event is noted. If there is a scheduled PK blood draw and ECG within 2 hours before or after the event, an additional PK blood draw and ECG are not needed.

Postsurgical Analgesia

Subjects should only receive rescue pain medication (oral [PO] oxycodone 5-10 mg) upon request for breakthrough pain, as needed (maximum of every 4 hours). No other analgesics, including nonsteroidal anti-inflammatory drugs (NSAIDs) are allowed during the 96 hour observation period. After 96 hours, the analgesic regimen may be adjusted. All postsurgical analgesics administered must be documented through Day 10.

Pharmacokinetic Assessment

Blood samples for PK analysis will be obtained at baseline (prior to study drug administration); 15 minutes, 30 minutes, 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 84, and 96 hours after the beginning of study drug administration; and on Days 7 and 10. Blood samples will be collected from all subjects in order to maintain the treatment double-blind.

9.1.1. Duration of the Study and Subject Participation

Participation will begin upon signing of the ICF. No more than 30 days should pass between signing the ICF and surgery. A follow-up telephone call will occur on Day 30 (±4 days). Therefore, each subject may participate in the study for a maximum of 64 days.

9.1.2. Study Stopping Rules

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).

9.2. Discussion of Study Design

EXPAREL is approved for infiltration into a surgical site. This multicenter, randomized, double-blind, placebo-controlled study is designed to evaluate the safety, efficacy, and pharmacokinetics of local administration of EXPAREL for prolonged postsurgical analgesia in subjects undergoing third molar extraction. The double blind study design is intended to avoid potential bias resulting from subject or Investigator knowledge of the assigned treatment.

Third molar extraction is a frequently performed surgical procedure that causes considerable postsurgical pain, particularly following removal of impacted lower mandibular third molars. Standard postoperative analgesia following third molar extraction often includes combination opioid analgesics. In this study, all subjects will receive PO oxycodone, as needed, to control breakthrough postsurgical pain.

Neurological and cardiac assessments will be conducted to rule out bupivacaine toxicity related to high plasma exposure.

10. STUDY POPULATION

10.1. Inclusion Criteria

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

1. Male or female, ≥18 years of age at screening.
2. Scheduled to undergo bilateral third molar extractions (i.e., extraction of all four third molars) under local anesthesia. At least one lower mandibular third molar must involve full or partial bony impaction confirmed by visual or radiological evidence.
3. American Society of Anesthesiology (ASA) physical status 1, 2, or 3.
4. Female subjects must be either surgically sterile, using a medically acceptable method of birth control, or at least 2-years postmenopausal and must have a documented negative pregnancy test result during screening and on Day 1 prior to surgery.
5. 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. History of hypersensitivity or idiosyncratic reaction to amide-type local anesthetics or opioids.
2. Contraindication to lidocaine, epinephrine, bupivacaine, or oxycodone.
3. History of significant drug allergy (e.g., anaphylaxis or hepatotoxicity).
4. Positive test result from the urine drug screen at screening or prior to the surgical procedure.
5. Currently pregnant, nursing, or planning to become pregnant during the study or within 1 month after study drug administration.
6. History or active psychiatric illness (including major depression, bipolar disorder, or anxiety), Type 1 or Type 2 diabetes, severe renal or hepatic impairment, significant cardiovascular disease (including cardiac rhythm disturbance), migraine headaches, frequent headaches, other pain conditions, or other medical condition that, in the opinion of the Investigator, may increase the risk of surgery or interfere with the evaluation of the study drug.
7. History of infection requiring IV antibiotics within 45 days or PO antibiotics within 30 days prior to study drug administration for reasons other than dental prophylaxis. Subjects must be afebrile, without signs or symptoms indicative of active infection.
8. Use of any of the following medications within the times specified before surgery: long-acting opioid medication, NSAIDs, aspirin (except for low-dose aspirin used for cardioprotection), or acetaminophen 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 any concurrent therapy that could interfere with the evaluation of efficacy or safety, such as any drugs which in the Investigator's opinion may exert significant analgesic properties or act synergistically with the investigational product.
12. 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/her incapable of continuing with the remaining study assessments, then he/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/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 (heart rate and blood pressure), neurological assessment, 12-lead ECG, and any changes in the subject's health status will be assessed and recorded.

After termination from the study, the subject may be followed for safety including monitoring of AEs through Day 30.

11. TREATMENTS

11.1. Treatment to be Administered

Study Drug

Subjects will receive a single dose of either EXPAREL 133 mg or placebo in 10 mL volume according to the randomization schedule. Study drug administration will be performed in a blinded manner (e.g., utilizing a syringe masked by a finger cot).

Rescue Medication

Subjects should only receive rescue pain medication (PO oxycodone 5-10 mg) upon request for breakthrough pain, as needed (maximum of every 4 hours). No other analgesic agents, including NSAIDs, are allowed during the 96-hour observation period. After 96 hours, the analgesic regimen may be adjusted. All postsurgical analgesics administered must be documented through Day 10.

11.1.1. Administration Technique

Randomized subjects will receive a nerve block with lidocaine 2% with epinephrine 1:100,000 before undergoing bilateral third molar extraction under local anesthesia. In addition to the lidocaine nerve block, the Investigator may choose to add topical benzocaine or intraoperative nitrous oxide.

At the end of surgery, and at least 20 minutes after lidocaine administration, study drug (EXPAREL or placebo) will be infiltrated as follows to provide postsurgical analgesia:

Maxilla – At the depth of the posterior buccal vestibule, two points of infiltration submucosal and supraperiosteal are identified at the apex of the extracted third molar. The sites are separated by 6-8 mm and 1 mL of EXPAREL infiltrated in each site (2 mL on each side), for a total of 4 mL in the maxilla.

Mandible – After readaptation and closure of the mucoperiosteal flap, the external oblique ridge is palpated identifying the buccinator muscle attachment. Four infiltration points separated by 6-8 mm are selected along this line. The needle is inserted approximately 5 mm and 0.5 mL of EXPAREL is infiltrated into the muscle at each point (total of 2 mL per side for this step). At the point of greatest subperiosteal reflection, just lateral to the third molar socket, two infiltrations are taken deeper (1.5 cm) and 0.5 mL is infiltrated as the needle is withdrawn (total of 1 mL per side for this step). Thus, the total is 6 mL in the mandible.

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 site 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.

No agents are to be admixed with EXPAREL.

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

Placebo will consist of normal saline and will be supplied by the study sites. Subjects in the placebo group will receive 10 mL of placebo.

11.2.3. Description of Diluents

Not applicable.

11.3. Method of Assigning Subjects to Treatment

11.3.1. Randomization Scheme

Approximately 175 subjects (100 subjects in the EXPAREL 133 mg group and 75 subjects in the placebo group) are planned for enrollment. Subjects will be randomized in a 2:1 ratio to receive local administration of a single dose of either EXPAREL (133 mg/10 mL) or placebo (normal saline, 10 mL).

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 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. Clinical studies have shown that for wound infiltration a total dose of 266 mg (20 mL) of EXPAREL is safe and efficacious. Due to volume constraints at the surgical site, a dose of 133 mg (10 mL) will be utilized in this study.

11.5. Blinding

11.5.1. Blinding Procedures

EXPAREL and placebo are visually distinguishable; therefore, to maintain the double-blind study design, only unblinded study personnel who are NOT involved with protocol-specific, postsurgical assessments may prepare 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 a serious AE (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 individual(s) who are designated to receive unblinded randomization assignments will be responsible for preparing study drug.

Site surveys suggest that study sites will vary in their standard (and feasible) procedures for preparing sterile study drug in a blinded fashion. Therefore, each site will be responsible for providing their written blinding procedures for study drug preparation and transportation. This documentation (e.g., site-specific blinding plan) will be made available to Pacira for review before the site enrolls a subject into the study. The site-specific blinding plan will outline the study treatment blinding process that will be followed at the site throughout the study. Assignment of blinded and unblinded responsibilities regarding the preparation of study drug should take into account that **EXPAREL may not be held in a syringe for more than 4 hours after preparation for administration**.

Once the study drug is prepared in syringes as a sterile preparation, it will be placed under a sterile drape on a sterile tray for use when needed. The individuals preparing 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. Should administration of the study drug involve extension tubing or a butterfly needle, then any visible tubing needs to be covered with aluminum foil to maintain the blind.

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.

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. 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

11.6.1. Prior and Concomitant Medications and Therapy

Prior medications

- Long-acting opioid medications, NSAIDs, aspirin (except for low-dose aspirin used for cardioprotection), and acetaminophen are not permitted within 3 days of study drug administration.
- No opioid medications are permitted within 24 hours of study drug administration.
- 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.
- Use of systemic glucocorticosteroids is prohibited within 1 month of enrollment in this study.
- Use of any concurrent therapy that could interfere with the evaluation of efficacy or safety is prohibited, including any drugs which in the Investigator's opinion may exert significant analgesic properties or act synergistically with the investigational product.
- Subjects who have received an investigational product within 30 days before the scheduled dose of study medication are not eligible for study participation.

Concomitant medications

All medications taken within 30 days prior to study drug administration through Day 30 will be recorded on the CRF.

11.6.2. Permitted and Restricted Therapy or Medications During Surgery

Permitted

If needed, additional lidocaine 2% with epinephrine 1:100,000 may be administered as long as there is a separation of at least 20 minutes between the last administration of lidocaine and the administration of study drug. In addition to the lidocaine nerve block, the Investigator may choose to add topical benzocaine or intraoperative nitrous oxide.

Restricted

No agents are to be admixed with EXPAREL.

11.6.3. Permitted and Restricted Therapy or Medications After Surgery Through 96 Hours After Surgery

Subjects should only receive rescue pain medication (PO oxycodone 5-10 mg) upon request for breakthrough pain, as needed (maximum of every 4 hours). No other analgesics are permitted within 96 hours after surgery.

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

All postsurgical analgesics administered must be documented through Day 10.

11.7. Treatment Compliance

Not applicable, since study drug (EXPAREL or placebo) will be administered intraoperatively.

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 conducted at the times specified after the beginning of study drug administration (timepoints may change based on the median T_{max} from the first 30 subjects):

- Date, time of administration, and amount of all opioid rescue medication taken through 96 hours.
- Pain intensity scores using the NRS at 15 minutes, 30 minutes, 1, 2, 4, 6, 8, 12, 24, 48, 72, and 96 hours, and immediately prior to each administration of rescue pain medication through 96 hours (see Appendix 1).
- Subject satisfaction with postsurgical pain control (using a 5-point Likert scale) at 24, 48, 72, and 96 hours, and on Day 10 (see Appendix 2).
- Postoperative symptom severity (PoSSe) scale questionnaire at 72 hours and on Day 7 (see Appendix 3).
- Unscheduled phone calls or office visits related to pain after discharge from the facility through Day 30.

12.2. Efficacy Endpoints

The efficacy endpoints listed below will be assessed based on the efficacy measurements conducted at the specified timepoints after the beginning of study drug administration.

Primary efficacy endpoint:

The primary endpoint is the area under the curve (AUC) of the NRS pain intensity scores through 48 hours.

Secondary efficacy endpoints:

The following secondary endpoints will be analyzed in the following order using a hierarchical fixed-sequence stepwise testing procedure:

1. The AUC of the NRS pain intensity scores through 24 hours.
2. The AUC of the NRS pain intensity scores through 72 hours.
3. Percentage of opioid-free subjects through 24 hours.
4. Percentage of opioid-free subjects through 48 hours.
5. Percentage of opioid-free subjects through 72 hours.

Tertiary efficacy endpoints:

- The AUC of the NRS pain intensity scores through 96 hours.
- Sum of the pain intensity scores (SPIS) through 24, 48, 72, and 96 hours.

- The NRS pain intensity scores at each assessed timepoint and immediately prior to each administration of rescue pain medication through 96 hours.
- The AUC of the NRS pain intensity scores from 24-48 and 48-72 hours.
- Percentage of pain-free subjects at each assessed timepoint using the NRS pain intensity score.
- Percentage of opioid-free subjects through 96 hours.
- Time to first opioid rescue medication.
- Integrated rank assessment using the NRS pain intensity score at 48 hours and the total amount of postsurgical opioids consumed through 48 hours (Silverman 1993).
- Overall assessment of the subject's satisfaction with postsurgical pain control (using a 5-point Likert scale) at 24, 48, 72, and 96 hours, and on Day 10.
- PoSSe scale mean total score at 72 hours and on Day 7.
- Number of unscheduled phone calls or office visits related to pain through Day 30.

12.3. Pharmacokinetic Analysis

Blood samples for PK analysis will be obtained at baseline (prior to study drug administration); 15 minutes, 30 minutes, 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 84, and 96 hours after the beginning of study drug administration; and on Days 7 and 10. Blood samples will be collected from all subjects in order to maintain the treatment double-blind.

12.4. Pharmacokinetic Endpoints

Pharmacokinetic parameters will be estimated from the plasma bupivacaine measurements using non-compartmental analysis. The following parameters will be determined:

$AUC_{0\text{-}tlast}$	The area under the plasma concentration-time curve from the time of administration to the time of the last quantifiable concentration calculated using the log-linear trapezoidal rule.
$AUC_{0\text{-}\infty}$	The area under the plasma concentration-time curve from the time of administration extrapolated to infinity. The residual area from the time of the last quantifiable concentration (C_{tlast}) to infinity is to be calculated using the approximation: $AUC_{t\text{-}\infty} = Ct_{last}/ \lambda_z$.
C_{max}	The maximum observed plasma concentration obtained directly from the experimental data without interpolation.
T_{max}	The time to maximum plasma concentration (C_{max}).
λ_z	The apparent terminal elimination rate constant determined by log-linear regression of the terminal log-linear segment of the plasma concentration-time curve.
$t_{1/2el}$	The apparent terminal elimination half-life calculated as $0.693/\lambda_z$.

12.5. Safety Assessments

The following safety assessments will be conducted at the times specified after the beginning of study drug administration:

- Neurological assessment at baseline (prior to study drug administration); 15 minutes, 30 minutes, 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 84, and 96 hours; and on Day 10 (see Appendix 4).
- Cardiac assessment (i.e., 12-lead ECG) at baseline (prior to study drug administration); 15 minutes, 30 minutes, 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 84, and 96 hours; and on Day 10.
- Vital signs (resting heart rate and blood pressure) at baseline (approximately 1 hour prior to surgery), and 1, 2, 4, and 96 hours (i.e., prior to discharge).
- Adverse events from the time the ICF is signed through Day 30.

12.6. Safety Endpoints

The following safety endpoints will be assessed based on the safety measurements conducted at the specified timepoints:

- Summary of neurological assessments (proportion of subjects who are oriented, and proportion of subjects who have any of the neurological events).
- Change from baseline in ECG data closest to the median T_{max}.
- Change from baseline in vital signs (resting heart rate and blood pressure) at each assessed timepoint.
- Incidence of treatment-emergent AEs (TEAEs) through Day 30.

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.

The neurological and cardiac safety assessments are based on the known signs and symptoms associated with systemic bupivacaine toxicity.

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 safety, efficacy, and PK assessments conducted after baseline will be timed from the *beginning of study drug administration*.

At timepoints when multiple assessments coincide, the NRS pain intensity assessments will be conducted first, if applicable.

Day 1 is defined as the day on which study drug is administered. The beginning of surgery is defined as the time of the first incision. The end of surgery is defined as the time of the last suture. Postsurgical is defined as after the end of surgery.

Subjects will remain in the research facility for 96 hours after study drug administration; therefore, 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 Assessments

Pain intensity will be assessed using the NRS (see Appendix 1). To assess pain intensity, the subject will assume a resting position that does not exacerbate his or her postsurgical pain. The subject will rest in this position for at least 5 minutes before responding to the following question, "*On a scale of 0 to 10, where 0 = no pain and 10 = worst possible pain, how much pain are you having right now*?" The subject's response will be recorded.

13.1.2. Neurological Assessment

The neurological assessment will include the subject's orientation. Additionally, the subject will be asked whether he or she is experiencing any numbness of the lips, the tongue, or around the mouth; a metallic taste in the mouth; problems with hearing; problems with vision; or muscles twitching (see Appendix 4).

13.1.3. Vital Signs

Vital signs (heart rate and blood pressure) will be measured after the subject has rested in a supine position. The subject will remain in a supine position during the assessment.

13.1.4. Electrocardiogram

The 12-lead ECGs will be conducted after the subject has rested in a supine position for 5 minutes.

13.1.5. Subject Satisfaction with Postsurgical Pain Control

The subject's satisfaction with postsurgical pain control will be assessed using the Likert Scale at 24, 48, 72, and 96 hours, and on Day 10 (see Appendix 2).

13.1.6. Postoperative Symptom Severity (PoSSe) Scale Questionnaire

The PoSSe scale questionnaire will be completed at 72 hours and on Day 7 (see Appendix 3).

13.2. Screening Procedures

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

13.3. Baseline Procedures (Day 1)

- Confirm eligibility.
- Update relevant medical history.
- Perform urine pregnancy test for women of childbearing potential before study drug administration.
- Perform urine drug screen.
- Measure vital signs (heart rate and blood pressure) after subject has rested in a supine position.
- Perform neurological assessment (see Appendix 4).
- Conduct 12-lead ECG.
- Collect baseline (pre-dose) blood sample for PK analysis prior to study drug administration.
- Record changes to concomitant medications since screening.
- Record AEs.
- Randomize subject and prepare study drug.

13.4. Intraoperative Procedures (Day 1)

- Administer dental nerve block with lidocaine 2% with epinephrine 1:100,000.
- Perform bilateral third molar extraction under local anesthesia.
- At the end of surgery, administer study drug according to the randomization schedule.
- Record start and stop time of study drug administration.
- Record start and stop times of surgery.
- Record concomitant medications.
- Record AEs and any treatment(s) for the events.

13.5. Procedures After Surgery Through 96 Hours

- Collect scheduled blood samples for PK analysis at 15 minutes, 30 minutes, 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 84, and 96 hours.
- Administer rescue medication (PO oxycodone 5-10 mg) upon request for breakthrough pain, as needed (maximum of every 4 hours).
- Record date, time, and amount of all opioid rescue medication administered.
- Record subject's assessment of pain intensity using the NRS at the following timepoints: 15 minutes, 30 minutes, 1, 2, 4, 6, 8, 12, 24, 48, 72, and 96 hours, and immediately prior to each administration of rescue pain medication, if applicable (see Appendix 1).
- Perform neurological assessment at 15 minutes, 30 minutes, 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 84, and 96 hours (see Appendix 4).
- Conduct 12-lead ECG at 15 minutes, 30 minutes, 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 84, and 96 hours.
- Measure vital signs (heart rate and blood pressure) after subject has rested in a supine position at 1, 2, 4, and 96 hours (i.e., prior to discharge).
- Obtain overall rating of subject satisfaction with postsurgical pain control using the Likert scale at 24, 48, 72, and 96 hours (see Appendix 2).
- Have subject complete the PoSSe scale questionnaire at 72 hours (see Appendix 3).
- Record concomitant medications.
- Record AEs and any treatment(s) for the events.
- If a cardiac event (e.g., myocardial depression, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmia, or cardiac arrest) or neurological event (e.g., persistent anesthesia, paresthesia, weakness, or paralysis) occurs during the study, an unscheduled PK blood sample should be obtained and, for cardiac events, an ECG should be conducted within 2 hours of the time that the event is noted. If there is a scheduled PK blood draw and ECG within 2 hours before or after the event, an additional PK blood draw and ECG are not needed.
- Discharge subject after the 96-hour assessments have been completed.

13.6. Day 7 Visit

- Collect scheduled blood sample for PK analysis.
- Document any unscheduled phone calls or office visits related to pain after hospital discharge.
- Have subject complete the PoSSe scale questionnaire (see Appendix 3).
- Record concomitant medications including opioid rescue.
- Record AEs and any treatment(s) for the events.

13.7. Day 10 Visit

- Collect scheduled blood sample for PK analysis.
- Perform neurological assessment (see Appendix 4).
- Conduct 12-lead ECG.
- Document any unscheduled phone calls or office visits related to pain since Day 7.
- Obtain overall rating of subject satisfaction with postsurgical pain control using the Likert scale (see Appendix 2).
- Record concomitant medications including opioid rescue.
- Record AEs and any treatment(s) for the events.

13.8. Day 30 Phone Call

- Document any unscheduled phone calls or office visits related to pain since Day 10.
- Record concomitant medications.
- Record AEs and any treatment(s) for the events.

14. ADVERSE EVENT REPORTING

Consistent with the current regulatory guidance provided by the US CFR 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. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE.
A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug. Suspected adverse reactions are a subset of all AEs for which there is a reasonable possibility that the drug caused the event.

14.1.2. Recording Adverse Events

It is the responsibility of the Investigator to document all AEs (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 Day 30 after surgery 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).

All AEs will be followed through progression of their severity. For example, if an AE is reported as mild in severity but changes to moderate, the AE of mild will have an end date when the severity changes to moderate. A new AE record with a moderate severity will be created with a start date that is the same as the end date of the mild AE.

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 subject signs the ICF it is considered an AE. Note: A change in treatment for a pre-existing condition (e.g., new high blood pressure medication), does not necessarily indicate an AE.

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

14.1.3. Severity of Adverse Events

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

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

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

Severe: An AE that prevents normal everyday activities.

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 are provided below.

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 is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

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

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

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

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

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

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

14.2.2. Reporting Serious Adverse Events

Any SAE or death that occurs at any time after the subject signs the ICF through Day 30, whether or not related to EXPAREL, must be reported by the Investigator or designee to Pacira Drug Safety 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, at 908-342-1840.

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

If the Investigator is made aware of any SAEs after Day 30, these should also be reported to Pacira Drug Safety or designee provided the SAE is considered related to EXPAREL. The site would then provide a completed SAE form within 1 business day and the event would be followed until resolution, or until adequate stabilization is met.

15. STATISTICAL METHODS

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

15.1. Study Hypothesis

The primary null hypothesis is:

H_0: The means of the AUC of the NRS pain intensity scores through 48 hours are not different between the EXPAREL and placebo groups.

The alternative hypothesis is:

H_A: The mean AUC of the NRS pain intensity scores through 48 hours for the EXPAREL group is less than that of the placebo group.

15.2. Study Endpoints

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

15.3. Determination of Sample Size

In previous wound infiltrations studies in hemorrhoidectomy and bunionectomy, the difference between treatment groups in mean AUC from 0 to 48 hours or NRS pain intensity scores varied from 20 to 103. The standard deviations varied from 100 to 128. A sample size of 50 in each group will have 90% power to detect a difference in means of 66 assuming that the common standard deviation is 100 using a two group t-test with a 0.05 two-sided significance level. A sample size of 50 in each group will have 90% power to detect a difference in means of 86 assuming that the common standard deviation is 130 using a two group t-test with a 0.05 two-sided significance level.

However, the EXPAREL group will randomize approximately 100 subjects to lower the AE detection threshold for the safety database to 3%. The sample size for placebo was increased due to the additional collection of NRS pain intensity score immediately prior to all requests for rescue medication through 96 hours. The placebo sample size was increased to ensure that there are at least 50 subjects treated in both the EXPAREL and placebo under the current protocol amendment. It is expected that the sample size will be approximately 175 subjects resulting in a 2:1 ratio of EXPAREL to placebo subjects.

15.4. Analysis Populations

The following analysis sets are planned:

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

Efficacy: The efficacy analysis set will include all subjects in the safety analysis set who undergo the planned surgery and will be based on randomized treatment, regardless of actual treatment received.

Pharmacokinetic: The PK analysis set will include all subjects in the safety analysis set who receive EXPAREL, provide sufficient samples to allow for calculation of PK parameters required for analysis, and do not have significant protocol deviations that may invalidate or bias the results.

15.5. Handling Subject Dropouts and Discontinuations

For the calculation of the AUC of NRS pain intensity scores through any of the time periods, the following methods will be used for imputing missing data:

Missing scores before the first non-missing score will be replaced by the median score at the missing timepoint from other subjects in the same treatment group. Missing scores after the last non-missing score will be replaced by the last non-missing score (last observation carried forward). Missing scores between two non-missing scores will use linear interpolation to replace the missing score.

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

15.6. Statistical Analyses

15.6.1. Baseline Characteristics

Demographic and baseline characteristics will be summarized 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 measure in this study is the AUC of the NRS pain intensity scores through 48 hours.

For the AUC of the NRS pain intensity scores through 48 hours, EXPAREL will be compared to placebo using analysis of variance (ANOVA) with treatment as the main effect. Based on the model, the difference between the treatment groups will be estimated along with the 2-sided 95% confidence intervals (CI).

Handling of Subjects Requiring Rescue Medication

For the AUC of the NRS pain intensity scores, prior to analysis the windowed Worst-Observation-Carried-Forward (wWOCF) imputation method will be applied. For subjects who take opioid rescue pain medication, their NRS pain intensity scores recorded within the window of controlled type of rescue medication (6 hours for PO oxycodone) will be replaced by the 'worst' observation. The worst observation will be the highest score in the time interval from the end of surgery up to the time prior to taking their first rescue pain medication. Note that NRS

pain intensity scores in the window that are higher than the worst value prior to opioid rescue pain medication will not be overwritten. If no NRS pain intensity score is available prior to the first opioid rescue pain medication, the worst observation from all available measurements within the same treatment arm 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.

Continuous Measures of Efficacy

For the AUC of pain intensity scores, missing data will be imputed as described in Section 15.5 and fully described in the SAP.

For the integrated rank assessment that uses total amount of postsurgical opioids consumed through 48 hours, opioid medications will be converted to an IV morphine equivalent amount. All opioids consumed through 48 hours will be included in the analysis.

Summary statistics for each measure will be shown at each timepoint by treatment group. To test for significant differences between EXPAREL and placebo with respect to continuous measures of efficacy, an ANOVA with treatment as the main effect will be used. Based on the model, EXPAREL will be compared to placebo and two-sided CIs about the difference will be presented.

Categorical Measures of Efficacy

For categorizing subjects as pain-free, the NRS pain intensity score must be 0 or 1 at the assessed timepoint.

The proportion of subjects in each category will be calculated and summarized at each timepoint by treatment group. A chi-square test or Wilcoxon Rank Sum test will be used to compare EXPAREL to placebo.

Time to Event Measures of Efficacy

The time from start of study drug administration to the first use of an opioid rescue medication through 96 hours will be summarized with Kaplan-Meier estimates. A log-rank test will be used to compare EXPAREL to placebo.

15.6.4. Pharmacokinetic Analyses

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

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

Descriptive statistics will be used to summarize the PK parameters.

15.6.5. Safety Analyses

All safety analyses will be based on actual treatment received.

15.6.5.1 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.

15.6.5.2 Neurological Assessments

The proportion of subjects who are oriented at each timepoint will be summarized for each treatment group. The proportion of subjects who have at least one of the neurological events will be summarized for each treatment group.

15.6.5.3 Electrocardiograms

Descriptive statistics for each ECG parameter for baseline, each timepoint, and change from baseline at each timepoint will be summarized for each treatment group.

15.6.5.4 Vital Signs

Descriptive statistics for each vital sign for baseline, each timepoint, and change from baseline at each timepoint will be summarized for each treatment group.

15.7. Significance Testing

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

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 (Numeric Rating Scale)

Subjects will be evaluated for pain using the NRS at 15 minutes, 30 minutes, 1, 2, 4, 6, 8, 12, 24, 48, 72, and 96 hours after the beginning of study drug administration, and immediately prior to each administration of rescue pain medication through 96 hours.

Pain Intensity Scale

On a scale of 0 to 10, where 0 = no pain and 10 = worst possible pain, how much pain are you having right now? (Circle one number only.)

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst possible pain

Appendix 2: Subject Satisfaction with Postsurgical Pain Control (Likert Scale)

The subject's satisfaction with postsurgical pain control will be conducted at 24, 48, 72, and 96 hours after the beginning of study drug administration, and on Day 10.

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

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

Appendix 3: Postoperative Symptom Severity (PoSSe) Scale Questionnaire

Subjects will complete the PoSSe scale at 72 hours after the beginning of study drug administration and on Day 7.

PoSSe Scale

1. EATING

a. In the **last week**, has your operation affected your **enjoyment** of food?
(*Please mark **one** box*)
No, not at all ☐ Yes, a little ☐ Yes, very much ☐

b. In the **last week**, for how many days were you unable to **open your mouth** normally because of your operation?
(*Please mark **one** box*)
0 days ☐ 1-2 days ☐ 3-4 days ☐ 5-6 days ☐ 7 days ☐

2. SPEECH

a. In the **last week**, for how many days was your **voice** affected because of your operation?
(*Please mark **one** box*)
0 days ☐ 1-2 days ☐ 3-4 days ☐ 5-6 days ☐ 7 days ☐

b. On the **worst day** of the **last week**, how badly was your **speech** affected by your operation?
(*Please mark **one** box*)
Not at all ☐ Slightly ☐ Moderately ☐ Severely ☐ Unable to speak at all ☐

3. SENSATION

a. Thinking of the **last week**, for how many days were your lips or tongue feeling **tingling** because of your operation?
(*Please mark **one** box*)
None at all ☐ 1-2 days☐ 3-4 days ☐ 5-6 days ☐ 7 days ☐

b. Thinking of the **last week**, for how many days were your lips or tongue feeling **numb** because of your operation?
(*Please mark **one** box*)
None at all ☐ 1-2 days ☐ 3-4 days ☐ 5-6 days ☐ 7 days ☐

4. APPEARANCE

a. Thinking of the **last week**, for how many days were your face and/or neck **bruised** because of your operation?
(*Please mark **one** box*)
None at all ☐ 1-2 days ☐ 3-4 days ☐ 5-6 days ☐ 7 days ☐

b. Thinking of the **last week**, for how many days were your face and/or neck **swollen** because of your operation?
(*Please mark **one** box*)
None at all ☐ 1-2 days ☐ 3-4 days ☐ 5-6 days ☐ 7 days ☐

5. PAIN

a. Thinking of the **last week**, for how many days did you experience **pain** from your operation?
(*Please mark **one** box*)
None at all ☐ 1-2 days ☐ 3-4 days ☐ 5-6 days ☐ 7 days ☐

b. Thinking of the **last week**, has the pain from your operation been controlled by **painkillers**?
(*Please mark **one** box*)

I have had no pain. ☐
Yes, completely controlled. ☐
Controlled mostly but still some discomfort. ☐
Poorly controlled. ☐
Not controlled at all. ☐

6. SICKNESS

a. Thinking of the **last week**, for how many days did you **vomit** or **feel nauseated**?
(*Please mark **one** box*)
None at all ☐ 1-2 days ☐ 3-4 days ☐ 5-6 days ☐ 7 days ☐

b. On the **worse day** of the last week, **how many times** did you vomit or feel nauseated?
(*Please mark **one** box*)
Not at all ☐ One day ☐ 2-3 times ☐ More than 3 times ☐ All the time (all day long) ☐

7. INTERFERENCE WITH DAILY ACTIVITIES

a. In the **last week**, did the operation prevent you from carrying out **work/housework** and other **daily activities**?
(*Please mark **one** box*)

No, not at all. ☐
I could continue with my work, but my work suffered. ☐
Yes, for 1 day. ☐
Yes, for 2–6 days. ☐
Yes, for 7 days. ☐

b. In the **last week**, have your **leisure activities** been affected by your operation? (including sports, hobbies and social life)
(*Please mark **one** box*)

Not affected by the operation. ☐
Mildly affected by the operation. ☐
Moderately affected by the operation. ☐
Severely affected by the operation. ☐
The operation prevented any social life at all. ☐

c. Thinking of the **last week**, how badly did the pain affect your **life**?
(*Please mark **one** box*)

Not at all ☐ Slightly ☐ Moderately ☐ Severely ☐

Appendix 4: Neurological Assessment

A neurological assessment will be conducted at baseline (prior to study drug administration); 15 minutes, 30 minutes, 1, 2, 4, 8, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 84, and 96 hours after the beginning of study drug administration; and on Day 10.

The examination will include the subject's orientation.

- Is the subject oriented? □ Yes □ No

If the subject is not oriented, the event should be recorded as an AE.

Additionally, the subject will be asked the following questions:

- Do you have numbness of the lips, the tongue, or around the mouth?
  □ Yes □ No

- Do you have a metallic taste in your mouth?
  □ Yes □ No

- Are you having problems with your hearing not related to the use of a hearing aid?
  □ Yes □ No

- Are you having problems with your vision not related to the use of eye glasses?
  □ Yes □ No

- Are your muscles twitching?
  □ Yes □ No

If the subject answers "yes" to any of these questions, the event should be recorded as an AE.