Clinical Study Protocol

Amendment 3

A Multicenter, Randomized, Double-blind, Active-controlled Study to Evaluate the Safety and Efficacy of EXPAREL When Administered via Infiltration into the Transversus Abdominis Plane (TAP) Versus Bupivacaine Alone in Subjects Undergoing Elective Cesarean Section

Protocol No.:	402-C-411
EudraCT No.:	Not applicable
IND No.:	069,198
Study Phase:	4
Study Drug:	EXPAREL® (bupivacaine liposome injectable suspension)
Date:	07-May-2018
Study Sites:	Multicenter study in North America
Sponsor:	Pacira Pharmaceuticals, Inc. 5 Sylvan Way Parsippany, NJ 07054 Tel: (973) 254-3560

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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, 1.3%, 13.3 mg/mL		

Title of Study: A Multicenter, Randomized, Double-blind, Active-controlled Study to Evaluate the Safety and Efficacy of EXPAREL Plus Bupivacaine When Administered via Infiltration into the Transversus Abdominis Plane (TAP) Versus Bupivacaine Alone in Subjects Undergoing Elective Cesarean Section

Principal investigator: To be determined

Study Center(s): Multicenter study in North America

Publications (Reference): None

Objectives:

Primary objective: The primary objective of this study is to compare total opioid consumption through 72 hours following EXPAREL+bupivacaine HCl infiltration into the transversus abdominis plane (TAP) after spinal anesthesia to active bupivacaine HCl TAP infiltration after spinal anesthesia in subjects undergoing an elective cesarean section (C-section).

Secondary objective: The secondary objectives are to assess efficacy and safety parameters and patient satisfaction.

Methodology:

This is a Phase-4, multicenter, randomized, double-blind, active-controlled study in approximately 152 adult subjects undergoing elective C-section. All subjects will remain in the hospital for up to 72 hours postsurgery.

Obtaining Informed Consent

Potential participants may provide informed consent up to 30 days before their scheduled surgery. If a subject can only be screened on the day of surgery, the consent process must be started at least 24 hours prior to the day of surgery in order to ensure ample time for the subject to review the ICF and have all her questions answered by the investigator/study staff prior to providing informed consent. Screening procedures that are standard of care (SOC) at the institution may be completed prior to written informed consent. Any screening procedures that are not SOC, must be completed after written informed consent is provided and prior to surgery.

Screening

Subjects will be screened within 30 days prior to surgery; screening on the day of surgery will be allowed but is discouraged. If a subject can only be screened on the day of surgery, the informed consent process must still be started at least 24 hours prior to the conduct of any screening procedures that are not considered SOC at the institution and such procedures may not be performed until written informed consent is provided All screening procedures that are not SOC must be performed and documented within the 30-day time window (inclusive of the day of surgery for those subjects who can only be screened on the day of surgery) as described here. 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 history, surgical history, physical examination, 12-lead electrocardiogram (ECG), vital sign measurements, alcohol breath test and urine drug screen, and clinical laboratory tests (hematology and chemistry) will be performed.

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Day of Surgery

***Pre-operative medications**:* Use of pre-operative analgesics (eg, opioid medications, acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs]) is prohibited.

Eligible subjects will be randomized in a blinded 1:1 ratio to either:

- Group 1: EXPAREL+bupivacaine TAP infiltration following spinal anesthesia
- Group 2: Active bupivacaine HCl TAP infiltration following spinal anesthesia

On Day 1, prior to the C-section, all subjects will receive a intrathecal injection of 150 mcg preservative-free morphine for spinal injection (eg, Duramorph®) in conjunction with single-shot spinal anesthesia using 1.4-1.6 mL bupivacaine HCl 0.75% and 15 mcg fentanyl. If preservative-free morphine for spinal injection (eg, Duramorph) is unavailable because of a drug shortage, subjects may instead receive an intrathecal injection of 75 mcg preservative-free hydromorphone in conjunction with single-shot spinal anesthesia using 1.4-1.6 mL bupivacaine HCl 0.75% and 15 mcg fentanyl. A combined spinal epidural (CSE) anesthesia technique may also be used provided the epidural component is not used. Subjects who receive the epidural component of the CSE anesthesia must be immediately withdrawn from the study.

Intraoperative medications: The intraoperative use of the following medications is discouraged, but may be permitted if clinically indicated based on the investigator's discretion (all medications must be appropriately recorded [ie, drug, dose, and route of administration]): ketamine and midazolam (Versed®). Prophylactic use of dexamethasone for prevention of nausea and vomiting is prohibited.

After delivery of the baby and prior to the TAP infiltration, a small amount of lidocaine (<2 mL) may be administered subcutaneously to form a skin wheal over the area of the needle insertion site. A 2-point classic TAP block, in 2 steps (see below), must be performed under ultrasound guidance and must be performed no more than 90 minutes after skin incision closure of the C-section. A confirmatory ultrasound picture or video will be taken of each side of the abdomen after the TAP needle position has been established and following infiltration of study drug.

TAP infiltration: The TAP infiltration includes two steps: (1) TAP needle placement and saline hydrodissection and (2) study drug mixture infiltration into the TAP. Each step is briefly described below for one side of the abdomen and must be repeated on the contralateral side to complete the bilateral, 2-point TAP required for the study. For complete, step-by-step instructions on performing the TAP infiltration under ultrasound guidance, please refer to the Pharmacy Binder.

(1) TAP needle placement and saline hydrodissection: For subjects in both study groups, use ultrasound guidance to place the TAP needle into the desired location and use a 10-mL syringe pre-filled with normal saline to perform hydrodissection of the TAP. (Note: it is not necessary to use the full 10 mL of normal saline for hydodissection.) An ultrasound image of the TAP needle must be captured after saline hydrodissection.

(2) Study drug mixture infiltration into the TAP: Subjects randomized to the EXPAREL+bupivacaine group (Group 1) will receive 30 mL of a study drug mixture containing 10 mL EXPAREL (133 mg) combined with 10 mL bupivacaine HCl 0.25% (25 mg) and 10 mL normal saline (total mixture 30 mL) infiltrated into the TAP. An ultrasound image of the TAP needle placement must be captured after study drug infiltration.

Subjects randomized to the active bupivacaine group (Group 2) will receive 30 mL of a study drug mixture containing 10 mL bupivacaine HCl 0.25% (25 mg) combined with 20 mL normal saline (total mixture 30 mL) infiltrated into the TAP. An ultrasound image of the TAP needle placement must be captured after study drug mixture infiltration.

Repeat the above steps on the contralateral side to complete the bilateral, 2-point TAP required for the study.

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

Postsurgical Analgesia: **Patient-controlled analgesia is not permitted.**

The following multimodal pain regimen will be used:

At the time of skin incision closure (Note: it is very important that these be administered at the time of wound closure and not prior to or before the end of surgery)

- Intravenous (IV) ketorolac 15 mg (1 dose)
- IV acetaminophen 1000 mg (1 dose)

Beginning 6 hours after skin incision closure

- Scheduled oral (PO) acetaminophen 650 mg beginning 6 hours from the administration of the single dose of IV acetaminophen at the end of surgery and then every 6 hours (q6h) for up to 72 hours or hospital discharge
- Scheduled PO ibuprofen 600 mg beginning 6 hours from the administration of the single dose of IV ketorolac at the end of surgery and then q6h for up to 72 hours or hospital discharge

This multi-modal pain regimen **is a requirement for all subjects in the study** and is not subject to investigator discretion. The date, time, and dose of all standardized multimodal pain medications administered must be recorded. Note: The scheduled PO medication will be administered on a q6h schedule only through hospital discharge.

Rescue Medication**:** Subjects should only receive opioid rescue pain medication upon request for breakthrough pain. Postsurgical rescue medication will comprise PO immediate-release oxycodone (initiated at 5-10 mg every 4 hours [q4h] or as needed [PRN]). If a subject is unable to tolerate PO medication or fails the PO oxycodone rescue, IV morphine (initiated at 1-2 mg) or hydromorphone (initiated at 0.3-0.5 mg) may be administered q4h or PRN. All surgical and postsurgical opioid and other analgesics (pain medications) administered must be documented through Day 14 postsurgery. Additionally, an unscheduled pain intensity score using a 10-cm visual analog scale (VAS; see Appendix 1) must be completed immediately prior to any rescue medication while in the hospital.

Permitted medications for the prevention and treatment of possible medication side effects include the following and may be used at the discretion of the study site principal investigator:

- Ondansetron 4 mg IV immediately after delivery of the baby.
- Ondansetron 4 mg IV (should not exceed a maximum of 12 mg in a 24-hour period) for intraoperative and postoperative nausea and vomiting
- Metoclopramide 10 mg PO PRN for nausea and vomiting
- Nalbuphine IV 2.5 mg PRN for pruritus
- Naloxone IV 50-100 mcg PRN for pruritus.

Postsurgical Assessments

Subjects will remain in the hospital for up to 72 hours postsurgery. Postsurgical assessments will include:

- Opioid use
- Time of first unassisted ambulation
- Pain intensity scores using a 10-cm VAS (see Appendix 1) at rest
- Discharge readiness (see Appendix 2)
- Subject's satisfaction with postsurgical pain control (see Appendix 3)
- Overall benefit of anesthesia score (OBAS) questionnaire (see Appendix 4)
- Quality of recovery 15-item questionnaire (QoR-15; see Appendix 5)

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While in the hospital, subjects will be provided with a Patient Binder and will use the binder to record all scheduled and unscheduled VAS scores. For all scheduled assessments and unscheduled assessments in the hospital, subjects will assess, "How much pain are you experiencing right now" and a vertical mark will be placed on the VAS line to indicate the level of pain experienced at the time of assessment. If a subject is discharged prior to a scheduled VAS assessment, a member of the study site staff will contact the subject to remind her to complete the scheduled VAS assessment at the scheduled time and to record the assessment in the Participant Diary, which will be provided to the subject at the time of hospital discharge.

At hospital discharge, the subject will be instructed to record in the Participant Diary VAS pain intensity score daily and all pain medications taken following hospital discharge through Day 14.

At home, the subject will assess pain intensity at rest each day at noon (± 4 hours). This assessment should capture her average pain at rest in the prior 24 hours by assessing "What has been your average pain since your last pain assessment?" (ie, from noon on the previous day to the current assessment). At the same time, the subject should record any pain medication (medication name, date, time, and dose) taken in the prior 24 hours.

A phone call will be made to each subject on Day 14 for safety purposes and to inquire as to whether the subject has made any unscheduled phone calls or office visits related to pain; experienced any hospital readmission; or experienced an emergency room visit since hospital discharge. Adverse events (AEs) and serious adverse events (SAEs) will be recorded from the time the ICF is signed through Day 14.

Number of Subjects (Planned): Approximately 152 subjects are planned for enrollment into the study. Subjects who are withdrawn or discontinued prior to completing the study may be replaced.

Eligibility Criteria:

Note: Based on the World Health Organization's Guidance: Breastfeeding and Maternal Medication, Recommendations for Drugs in the Eleventh WHO Model List of Essential Drugs, bupivacaine is compatible with breastfeeding and, therefore, there are no restrictions in this study regarding the participation of women who wish to breastfeed following treatment with study drug.

Inclusion Criteria:

1. Females 18 years of age and older at screening.
2. Term pregnancies of 37 to 42 weeks gestation, scheduled to undergo elective C-section.
3. American Society of Anesthesiology (ASA) physical status 1, 2, or 3.
4. Able to provide informed consent, adhere to the study visit schedule, and complete all study assessments.

Exclusion Criteria:

1. Subjects who, in the opinion of the study site principal investigator, have a high-risk pregnancy (eg, multiple gestations, pregnancy resulting from in vitro fertilization, gestational diabetes, end-term prolonged bed rest required for medical reasons).
2. Subjects with a pregnancy-induced medical condition or complication (eg, hypertension, pre-eclampsia, chorioamnionitis).
3. Subjects with 3 or more prior C-sections.
4. Pre-pregnancy body mass index >50 kg/m^2 or otherwise not anatomically appropriate to undergo a TAP block.
5. Allergy, hypersensitivity, intolerance, or contraindication to any of the study medications for which an alternative is not named in the protocol (eg, amide-type local anesthetics, opioids, bupivacaine, NSAIDs, spinal anesthesia).
6. Planned concurrent surgical procedure with the exception of salpingo-oophorectomy or tubal ligation.

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7. Severely impaired renal or hepatic function (eg, serum creatinine level >2 mg/dL [176.8 µmol/L], blood urea nitrogen level >50 mg/dL [17.9 mmol/L], serum aspartate aminotransferase [AST] level >3 times the upper limit of normal [ULN], or serum alanine aminotransferase [ALT] level >3 times the ULN.)
8. Subjects at an increased risk for bleeding or a coagulation disorder (defined as platelet count less than $80{,}000 \times 10^3/mm^3$ or international normalized ratio greater than 1.5)
9. Concurrent painful physical condition that may require analgesic treatment (such as long-term, consistent use of opioids) in the postsurgical period for pain that is not strictly related to the surgery and which may confound the postsurgical assessments.
10. Clinically significant medical disease in either the mother or baby that, in the opinion of the investigator, would make participation in a clinical study inappropriate. This includes any psychiatric or other disease in the mother that would constitute a contraindication to participation in the study or cause the mother to be unable to comply with the study requirements.
11. History of, suspected, or known addiction to or abuse of illicit drug(s), prescription medicine(s), or alcohol within the past 2 years.
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
13. Previous participation in an EXPAREL study.

In addition, the subject will be ineligible to receive study drug and will be withdrawn from the study if she meets the following criteria during surgery:

14. Any clinically significant event or condition uncovered during the surgery (eg, excessive bleeding, acute sepsis) that might render the subject medically unstable or complicate the subject's postsurgical course.
15. Receives the epidural component of CSE anesthesia during participation in the study.

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

Name: EXPAREL (bupivacaine liposome injectable suspension) and bupivacaine HCl 0.25% (Group 1)

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

Dosage: Single infiltration of EXPAREL 266 mg in 20 mL admixed with bupivacaine HCl 0.25% in 20 mL and normal saline 20 mL (total volume 60 mL)

Lot Number: To be determined

Mode of Administration: Infiltration into the TAP under ultrasound guidance

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

Name: Bupivacaine HCl 0.25% (Group 2)

Active Ingredient: Bupivacaine

Dosage: Single infiltration of bupivacaine HCl 0.25% in 20 mL and normal saline 40 mL (total volume 60 mL)

Lot Number: To be determined

Mode of Administration: Infiltration into the TAP under ultrasound guidance

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, 1.3%, 13.3 mg/mL		

Duration of Subject Participation in Study:

Participation will begin upon signing of the ICF. No more than ~~7~~ 30 days should pass between signing the ICF and surgery. A follow-up telephone call will occur on Day 14 (± 3 days). Therefore, each subject may participate in the study for a maximum of ~~44~~ 47 days.

Efficacy Assessments:

The following efficacy measurements will be conducted at the times specified after completion of the last C-section wound incision stitch (ie, time of closure of the C-section wound):

- Date, time of administration, and amount of all postsurgical opioid rescue medication taken through Day 14
- Pain intensity scores at rest using a 10-cm VAS at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours (see Appendix 1) and once daily (at noon ± 4 hours) through Day 14. † For pain intensity scores at 18, 24, 30, 36, or 42 hours, if the subject is sleeping, do not wake her to assess pain. If she awakens within the assessment window (ie, 1 hour for the 18- and 24-hour assessments and 2 hours for the 30-, 36-, and 42-hour assessments), a pain score may be collected then.

  Please note that an unscheduled VAS score is also required immediately prior to administration of any rescue medication while in the hospital.
- Date and time of first unassisted ambulation
- OBAS questionnaire at 24, 48, and 72 hours (see Appendix 4). †
- Subject satisfaction with postsurgical pain control (using a 5-point Likert scale) at 72 hours or hospital discharge (see Appendix 3)
- Discharge readiness at 24, 48, and 72 hours or until the subject attains a score of 9, whichever occurs first (see Appendix 2)
- QoR-15 questionnaire at 72 hours or hospital discharge (Appendix 5)
- Unscheduled phone calls or office visits related to pain after discharge through Day 14

†If a subject is discharged prior to any of the scheduled VAS assessments collected at 6 to 72 hours postsurgery or a scheduled OBAS assessment collected at 24 to 72 hours postsurgery, a member of the study site staff will contact the subject at the appropriate scheduled times (ie, the time of each assessment scheduled to be collected that occurs after hospital discharge) to remind her to complete the VAS and OBAS assessments and to record the scheduled assessments in the Participant Diary. This will ensure that for any subject discharged prior to 72 hours, all VAS and OBAS assessments required for calculation of the study endpoints are captured. These phone calls will only occur if a subject is discharged prior to 72 hours.

Efficacy Endpoints:

The **primary** efficacy endpoint is the total postsurgical opioid consumption in morphine equivalents through 72 hours.

The **secondary** efficacy endpoints include:

- Time to first postsurgical opioid rescue medication
- The VAS pain intensity scores (at rest) from ~~0~~ 6 to 72 hours
- Percentage of opioid-free subjects through 72 hours

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Tertiary efficacy endpoints may include (but may not be limited to):

- Percentage of opioid-free subjects through 24 and 48 hours.
- The VAS pain intensity scores (at rest) from 6 to 12 hours, 6 to 24 hours, 6 to 48 hours, 24 to 48 hours, and 48 to 72 hours.
- Integrated rank assessment using the VAS pain intensity score (at rest) at 24, 48, and 72 hours and the total amount of postsurgical opioids consumed through 24, 48, and 72 hours.
- OBAS at each assessed timepoint.
- Time spent in the post-anesthesia care unit (PACU).
- Time to first unassisted ambulation.
- Proportion of subjects meeting Modified Postanesthesia Discharge Scoring System criteria for discharge readiness at each assessed timepoint.
- Overall assessment of the subject's satisfaction with postsurgical pain control (using a 5-point Likert scale) at 72 hours after surgery (or at hospital discharge if earlier than 72 hours).
- Responses to the QoR-15 questionnaire at 72 hours after surgery (or at hospital discharge if earlier than 72 hours).
- Number of unscheduled phone calls or office visits related to pain from discharge through Day 14.

Safety Assessments:

Adverse events (AEs/SAEs) will be recorded from the time the ICF is signed through Day 14.

Safety Endpoints:

Incidence of AEs/SAEs that start after the start of anesthesia through Day 14.

Statistical Methods:

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

Safety endpoints will be summarized descriptively by treatment group.

Sample size for this study was based on Quale et al (2016). The coefficient of variation (CV) from this poster was approximately 60%. Assuming a log-normal distribution for total opioid consumption with a 60% CV, 5% alpha, a 1:1 randomization ratio, and 80% power, a total of 72 subjects per treatment group will be sufficient to detect a 30% difference between treatments. Assuming 5% of the subjects are not evaluable, a total sample size of approximately 152 subjects is needed to ensure 144 evaluable subjects.

Interim Analysis

An unblinded interim analysis will be conducted by an independent statistician when approximately 80 treated subjects under protocol amendment 2 have completed the 72-hour follow-up for the primary efficacy assessments. The objective of this interim analysis is three-fold: (1) to stop the trial for futility if it is improbable to show a significant reduction in the primary efficacy endpoints; (2) to stop the trial for early success if a clear benefit is demonstrated; and (3) to allow for the possibility of increasing the study sample size if the original sample size assumptions are determined to be not viable. Full details and all thresholds for stopping or trial expansion will be covered in a prospective interim analysis plan that will become part of the study SAP.

Table 1. Time and Events Schedule of Study Procedures – Through 72 Hours After Surgery

Study Procedure	Within 30 days of scheduled surgery	Screening (within 7d of surgery)	Day 1					Hours After Surgery					
			OR	PACU	6 hr (± 30m)	12 hr (± 1hr)	18 hr (± 1hr)	24 hr (± 1hr)	30 hr (± 2hr)	36 hr (± 2hr)	42 hr (± 2hr)	48 hr (± 2hr)	72 hr (± 4hr)
Explain study purpose and procedures; obtain signed ICF	X[13]	X[13]											
Assess/confirm eligibility		X	X										
Record/confirm medical and surgical history		X	X										
Record prior and concomitant medications		X	X										
Record demographics and baseline characteristics		X											
Measure vital signs (blood pressure and heart rate)		X[12]	X	X									X[3]
Physical exam (according to the investigational site's standard of care)		X	X										
Drug screen/Alcohol test		X											
Clinical laboratory tests (hematology and chemistry; Appendix 6)[4]		X[5]											
Perform 12-lead ECG		X											
Explain Patient Binder and Participant Diary and expectations of the subject regarding the binder and diary		X											
Randomize subject and prepare study drug			X										

Table 1. Time and Events Schedule of Study Procedures – Through 72 Hours After Surgery

Study Procedure	Within 30 days of scheduled surgery	Screening (within 7d of surgery)	Day 1		Hours After Surgery								
			OR	PACU	6 hr (± 30m)	12 hr (± 1hr)	18 hr (± 1hr)	24 hr (± 1hr)	30 hr (± 2hr)	36 hr (± 2hr)	42 hr (± 2hr)	48 hr (± 2hr)	72 hr (± 4hr)
Administer intrathecal preservative-free morphine/preservative-free hydromorphone injection in conjunction with single-shot spinal anesthesia (Section 13.3)[11]			X										
Record surgery start and stop times			X										
Perform TAP needle placement and saline hydrodissection under ultrasound guidance using up to 10-mL normal saline				X									
Capture ultrasound image of the TAP needle placement after saline hydrodissection				X									
Perform 2-point classic TAP infiltration no more than 90 minutes after skin incision closure of the C-section				X									
Take ultrasound picture of the 2-point classic TAP needle placement after study drug infiltration				X									
Record start and stop times of study drug infiltration				X									
Record intraoperative opioids administered and doses			X										

Table 1. Time and Events Schedule of Study Procedures – Through 72 Hours After Surgery

Study Procedure	Within 30 days of scheduled surgery	Screening (within 7d of surgery)	Day 1					Hours After Surgery					
			OR	PACU	6 hr (± 30m)	12 hr (± 1hr)	18 hr (± 1hr)	24 hr (± 1hr)	30 hr (± 2hr)	36 hr (± 2hr)	42 hr (± 2hr)	48 hr (± 2hr)	72 hr (± 4hr)
Record date, time in and out of the PACU				X									
Record **scheduled** 10-cm VAS pain intensity score (Appendix 1) at rest[8,9]					X	X	X[10]	X	X	X	X[10]	X	X
Record 10-cm VAS pain intensity **immediately prior to any postsurgical opioid medication** administered while in the hospital (Appendix 1)													
Record date, time, and dose of all postsurgical pain medication[1]													
Record date, time, and dose of all standardized multimodal pain medications administered													
Record date and time of first unassisted ambulation													
Record overall rating of subject's satisfaction with postsurgical pain control (Appendix 3)													X[3]
Record OBAS (Appendix 4)[9]								X				X	X
Administer QoR-15 questionnaire (Appendix 5)													X[3]
Assess discharge readiness[7] (Appendix 2)								X				X	

Table 1. Time and Events Schedule of Study Procedures – Through 72 Hours After Surgery

Study Procedure	Within 30 days of scheduled surgery	Screening (within 7d of surgery)	Day 1		Hours After Surgery								
			OR	PACU	6 hr (± 30m)	12 hr (± 1hr)	18 hr (± 1hr)	24 hr (± 1hr)	30 hr (± 2hr)	36 hr (± 2hr)	42 hr (± 2hr)	48 hr (± 2hr)	72 hr (± 4hr)
Provide the Participant Diary, addressed and stamped envelope, and instructions for use													
Record date and time of hospital discharge													
Document whether the subject has made any unscheduled phone calls or office visits related to pain; experienced any hospital readmission; or experienced an emergency room visit since hospital discharge.													
Remind subject to return the Participant Diary in the provided addressed and stamped envelope													
Record concomitant medications for treatment of AEs													
Record AEs/SAEs (starting at signing of ICF)													

AE = Adverse event; d=Day (s); ECG = Electrocardiogram; hr=Hour(s); ICF = Informed consent form; m=Minute(s); OBAS = Overall benefit of analgesia score; OR = Operating room; PACU = Post-anesthesia care unit; QoR-15 = Quality of Recovery 15-item Questionnaire; SAE = Serious adverse event; VAS=Visual analog scale

Note: No more than ~~7~~ 30 days should pass between signing of the ICF and performance of the surgery. Screening on the day of surgery will be permitted but is discouraged.

Note: The end of surgery is defined as the time of closure of the C-section wound.

1 Subjects should only receive opioid pain medication (eg, morphine, hydromorphone [Dilaudid], oxycodone) upon request for breakthrough pain.

2 Captured after hospital discharge at rest each day at noon (± 4 hours) through Day 14 in the Participant Diary

3 At 72 hours postsurgery or prior to hospital discharge, whichever occurs first.

4 Clinical laboratory tests will be conducted in accordance with the investigator's standard of care including direct bilirubin and either gamma-glutamyl transpeptidase (GGT) and lactate dehydrogenase (LDH) OR alanine transaminase (ALT) and aspartate transaminase (AST). Note: if clinical laboratory test results are available from with 14 days of surgery, laboratory tests do not have to be repeated at screening

5 If clinical laboratory test results are available from within 14 days of surgery, laboratory tests do not have to be repeated at screening

6 Following hospital discharge, the subject will record her daily use of pain medication, if any, in the Participant Diary

7 Discharge readiness will be assessed at 24, 48, and 72 hours or until the subject attains a score of 9, whichever occurs first

8 To assess pain intensity (VAS) at rest, the subject should rest quietly in a supine or seated position that does not exacerbate her postsurgical pain for 3-5 minutes before entering the pain score.

9 If a subject is discharged prior to any of the scheduled VAS assessments collected at 6 to 72 hours postsurgery or a scheduled OBAS assessment collected at 24 to 72 hours postsurgery, a member of the study site staff will contact the subject at the appropriate scheduled times (ie, the time of each assessment scheduled to be collected that occurs after hospital discharge) to remind her to complete the VAS and OBAS assessments and to record the scheduled assessments in the Participant Diary. This will ensure that for any subject discharged prior to 72 hours, all VAS and OBAS assessments required for calculation of the study endpoints are captured. These phone calls will only occur if a subject is discharged prior to 72 hours.

10 For pain intensity scores at 18, 24, 30, 36, or 42 hours, if the subject is sleeping, do not wake her to assess pain. If she awakens within the assessment window (ie, 1 hour for the 18- and 24-hour assessments and 2 hours for the 30-, 36-, and 42-hour assessments), a pain score may be collected then.

11 If preservative-free morphine for spinal injection (eg, Duramorph) is unavailable because of a drug shortage, subjects may instead receive an intrathecal injection of 75 mcg preservative-free hydromorphone in conjunction with single-shot spinal anesthesia using 1.4-1.6 mL bupivacaine HCl 0.75% and 15 mcg fentanyl.

12 Vital Signs will include Height and Weight at Screening.

13 Potential participants may provide informed consent up to 30 days before their scheduled surgery. If a subject can only be screened on the day of surgery, the consent process must be started at least 24 hours prior to the day of surgery in order to ensure ample time for the subject to review the ICF and have all her questions answered by the investigator/study staff prior to providing informed consent. Screening procedures that are standard of care (SOC) at the institution may be completed prior to written informed consent. Any screening procedures that are not SOC, must be completed after written informed consent is provided and prior to surgery.

If a subject can only be screened on the day of surgery, the informed consent process must still be started at least 24 hours prior to the conduct of any screening procedures that are not considered SOC at the institution and such procedures may not be performed until written informed consent is provided.

Table 2. Time and Events Schedule of Study Procedures – Hospital Discharge Through Day 14

Study Procedure	Hospital Discharge	Day 14 (±3 d) Call
Explain study purpose and procedures; obtain signed ICF		
Assess/confirm eligibility		
Record/confirm medical and surgical history		
Record prior and concomitant medications		
Record demographics and baseline characteristics		
Measure vital signs (blood pressure and heart rate)	X[3]	
Physical exam (according to the investigational site's standard of care)		
Drug screen/Alcohol test		
Clinical laboratory tests (hematology and chemistry; Appendix 6)[4]		
Perform 12-lead ECG		
Explain Patient Binder and Participant Diary and expectations of the subject regarding the binder and diary	X	
Randomize subject and prepare study drug		
Administer intrathecal preservative-free morphine/preservative-free hydromorphone injection in conjunction with single-shot spinal anesthesia (Section 13.3)[11]		
Record surgery start and stop times		
Perform TAP needle placement and saline hydrodissection under ultrasound guidance using up to 10-mL normal saline		
Capture ultrasound image of the TAP needle placement after saline hydrodissection		
Perform 2-point classic TAP infiltration no more than 90 minutes after skin incision closure of the C-section		
Take ultrasound picture of the 2-point classic TAP needle placement after study drug infiltration		
Record start and stop times of study drug infiltration		
Record intraoperative opioids administered and doses		

Table 2. Time and Events Schedule of Study Procedures – Hospital Discharge Through Day 14

Study Procedure	Hospital Discharge	Day 14 (±3 d) Call
Record date, time in and out of the PACU		
Record **scheduled** 10-cm VAS pain intensity score (Appendix 1) at rest[8,9]	←- - - - - -	- - - - - -→ [2]
Record 10-cm VAS pain intensity **immediately prior to any postsurgical opioid medication** administered while in the hospital (Appendix 1)		
Record date, time, and dose of all postsurgical pain medication[1]	- - - - - - - - - - - -	- - - - - -→ [6]
Record date, time, and dose of all standardized multimodal pain medications administered	- - - - - - - - - - - -	- - - - - - - - - →
Record date and time of first unassisted ambulation		
Record overall rating of subject's satisfaction with postsurgical pain control (Appendix 3)	X[3]	
Administer QoR-15 questionnaire (Appendix 5)	X[3]	
Assess discharge readiness[7] (Appendix 2)	X[3]	
Provide the ~~Patient~~ Participant Diary, addressed and stamped envelope, and instructions for use	X	
Record date and time of hospital discharge	X	
Document whether the subject has made any unscheduled phone calls or office visits related to pain; experienced any hospital readmission; or experienced an emergency room visit since hospital discharge.		X
Remind subject to return the ~~Patient~~ Participant Diary in the provided addressed and stamped envelope		X
Record concomitant medications for treatment of AEs	- - - - - - - - - - - -	- - - - - - - - - →
Record AEs/SAEs (starting at signing of ICF)	- - - - - - - - - - - -	- - - - - - - - - →

AE = Adverse event; d=Day (s); ECG = Electrocardiogram; hr=Hour(s); ICF = Informed consent form; m=Minute(s); QoR-15 = Quality of Recovery 15-item Questionnaire; SAE = Serious adverse event; VAS=Visual analog scale

Note: The end of surgery is defined as the time of closure of the C-section wound.

1 Subjects should only receive opioid pain medication (eg, morphine, hydromorphone [Dilaudid], oxycodone) upon request for breakthrough pain.

2 Captured after hospital discharge at rest each day at noon (± 4 hours) through Day 14 in the Participant Diary

3 At 72 hours postsurgery or prior to hospital discharge, whichever occurs first.

4 Clinical laboratory tests will be conducted in accordance with the investigator's standard of care including direct bilirubin and either gamma-glutamyl transpeptidase (GGT) and lactate dehydrogenase (LDH) OR alanine transaminase (ALT) and aspartate transaminase (AST). Note: if clinical laboratory test results are available from with 14 days of surgery, laboratory tests do not have to be repeated at screening

5 If clinical laboratory test results are available from within 14 days of surgery, laboratory tests do not have to be repeated at screening

6 Following hospital discharge, the subject will record her daily use of pain medication, if any, in the Participant Diary

7 Discharge readiness will be assessed at 24, 48, and 72 hours or until the subject attains a score of 9, whichever occurs first

8 To assess pain intensity (VAS) at rest, the subject should rest quietly in a supine or seated position that does not exacerbate her postsurgical pain for 3-5 minutes before entering the pain score.

9 For pain intensity scores at 18, 24, 30, 36, or 42 hours, if the subject is sleeping, do not wake her to assess pain. If she awakens within the assessment window (ie, 1 hour for the 18- and 24-hour assessments and 2 hours for the 30-, 36-, and 42-hour assessments), a pain score may be collected then.

10 If preservative-free morphine for spinal injection (eg, Duramorph) is unavailable because of a drug shortage, subjects may instead receive an intrathecal injection of 75 mcg preservative-free hydromorphone in conjunction with single-shot spinal anesthesia using 1.4-1.6 mL bupivacaine HCl 0.75% and 15 mcg fentanyl.

11 Vital Signs will include Height and Weight at Screening.

12 Potential participants may provide informed consent up to 30 days before their scheduled surgery. If a subject can only be screened on the day of surgery, the consent process must be started at least 24 hours prior to the day of surgery in order to ensure ample time for the subject to review the ICF and have all her questions answered by the investigator/study staff prior to providing informed consent. Screening procedures that are standard of care (SOC) at the institution may be completed prior to written informed consent. Any screening procedures that are not SOC, must be completed after written informed consent is provided and prior to surgery.

If a subject can only be screened on the day of surgery, the informed consent process must still be started at least 24 hours prior to the conduct of any screening procedures that are not considered SOC at the institution and such procedures may not be performed until written informed consent is provided.

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4. LIST OF ACRONYMS/ABBREVIATIONS

AE	Adverse event
ALT	Alanine transaminase
ANOVA	Analysis of variation
ASA	American Society of Anesthesiology
AST	Aspartate transaminase
CSE	Combined spinal epidural
C-section	Cesarean section
CFR	Code of Federal Regulations
CI	Confidence interval
C_{max}	Maximum plasma concentration
CRF	Case Report Form
CV	Coefficient of variation
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive response technology
IV	Intravenous
LDH	Lactate dehydrogenase
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numeric rating scale
NSAIDs	Non-steroidal anti-inflammatory drugs
OBAS	Overall benefit of analgesia score
OR	Operating room
PACU	Post-anesthesia care unit
PO	Oral (per os)
PRN	As needed (Pro re nata)
PTAE	Pretreatment adverse event
PVC	Premature ventricular contraction
q4h	Every 4 hours
q6h	Every 6 hours
QoR-15	Quality of recovery 15-item questionnaire
SAE	Serious adverse event

SAP	Statistical analysis plan
SNRIs	Selective norepinepherine reuptake inhibitors
SSRIs	Selective serotonin reuptake inhibitors
TAP	Transversus abdominis plane
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States (of America)
VAS	Visual analog scale
wWOCF	Windowed Worst-Observation-Carried-Forward

5. ETHICS

5.1. Institutional Review Board/Independent Ethics Committee

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

5.2. Ethical Conduct of the Study

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

5.3. Subject Information and Consent

Before a subject undergoes any study-specific screening procedures, the investigator or designee will thoroughly explain to the subject the purpose of the study, the associated procedures, and any expected effects and potential adverse reactions. A copy of the IRB-approved ICF will be provided to the subject, who will be given sufficient time and opportunity to inquire about the details of the study and decide whether or not to participate. The subject, and the study staff with whom 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 she is completely free to decline entry into the study and may withdraw from the study at any time, for any reason, without risking her medical care. Similarly, the investigator and/or Pacira Pharmaceuticals, Inc. (Pacira) will be free to withdraw the subject at any time for safety or administrative reasons. Any other requirements necessary for the protection of the human rights of the subject will also be explained, according to the current ICH GCP (E6) and the Declaration of Helsinki (1964, and as amended through 2000 [Edinburgh]).

6. INVESTIGATORS AND STUDY ADMINISTRATION STRUCTURE

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

7. INTRODUCTION

7.1. Indication

EXPAREL® was developed to extend pain relief with a single dose administration without the use of indwelling catheters and to decrease the requirement for supplemental opioid medications. 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 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.

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 adverse events (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 is a widely used delivery system for morphine sulfate. Adverse events related to opioid administration (eg, 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 (eg, 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, New Jersey) is a bupivacaine liposome injectable suspension. It consists of microscopic spherical, multivesicular liposomes (DepoFoam® drug delivery system), organized in a honeycomb-like structure comprising numerous non-concentric internal aqueous chambers containing a bupivacaine base at a concentration of 13.3 mg/mL. Each chamber is separated from adjacent chambers by lipid membranes. The lipids (phospholipids, cholesterol, and triglycerides) are naturally occurring or close analogs of endogenous lipids. Bupivacaine is slowly released from the DepoFoam particles by a complex mechanism involving reorganization of the barrier lipid membranes and subsequent diffusion of the drug over an extended period of time.

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

- Bupivacaine 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 EXPAREL has a slightly different mixture of lipid components than that used in DepoCyt.

7.4. Summary of Human Experience with EXPAREL

Pacira has conducted more than 36 clinical studies and one observational follow-up study to investigate EXPAREL. Across these studies, over 1800 human subjects received EXPAREL at doses ranging from 2 mg to 665 mg (equivalent to 2 mg to 750 mg bupivacaine HCl) administered by various routes: local infiltration into the surgical site, subcutaneous, perineural (or "nerve block"), and epidural. 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 the central nervous or cardiovascular systems 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 both wound infiltration pivotal studies (SKY0402-C-316 and SKY0402-C-317) 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) (Sterlicht 2014, Feierman 2014) and intraoperative wound infiltration or instillation. Additionally, as of June 2017, more than 3 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 Objective

The primary objective of this study is to compare total opioid consumption through 72 hours following EXPAREL+bupivacaine HCl infiltration into the TAP after spinal anesthesia to active bupivacaine infiltration in the TAP after spinal anesthesia in subjects undergoing elective cesarean section (C-section).

8.2. Secondary Objectives

The secondary objectives are to assess efficacy and safety parameters and patient satisfaction.

9. OVERALL STUDY DESIGN AND PLAN

9.1. Study Design

This is a Phase-4, multicenter, randomized, double-blind, active-controlled study in approximately 152 adult subjects undergoing elective C-section.

Obtaining Informed Consent

Potential participants may provide informed consent up to 30 days before their scheduled surgery. If a subject can only be screened on the day of surgery, the consent process must be started at least 24 hours prior to the day of surgery in order to ensure ample time for the subject to review the ICF and have all her questions answered by the investigator/study staff prior to providing informed consent. Screening procedures that are standard of care (SOC) at the institution may be completed prior to written informed consent. Any screening procedures that are not SOC, must be completed after written informed consent is provided and prior to surgery. (see Section 13.3).

Screening

Subjects will be screened within ~~7~~30 days prior to surgery; screening on the day of surgery will be allowed but is discouraged. If a subject can only be screened on the day of surgery, the informed consent process must still be started at least 24 hours prior to the conduct of any screening procedures that are not considered SOC at the institution and such procedures may not be performed until written informed consent is provided All screening procedures that are not SOC must be performed and documented within the ~~7~~30-day time window (inclusive of the day of surgery for those subjects who can only be screened on the day of surgery) as described here. 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 history, surgical history, physical examination, 12-lead electrocardiogram (ECG), vital sign measurements, clinical laboratory tests (hematology and chemistry), alcohol breath test, and urine drug screen will be performed.

Day of Surgery

Pre-operative medications: Use of pre-operative analgesics (eg, opioid medications, acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs]) is prohibited.

Eligible subjects will be randomized in a blinded 1:1 ratio to either:

- Group 1: EXPAREL+bupivacaine TAP infiltration following spinal anesthesia
- Group 2: Active bupivacaine TAP infiltration following spinal anesthesia

On Day 1, prior to the C-section, all subjects will receive a intrathecal injection of 150 mcg preservative-free morphine for spinal injection (eg, Duramorph®) in conjunction with single-shot spinal anesthesia using 1.4-1.6 mL bupivacaine HCl 0.75% and 15 mcg fentanyl. If preservative-free morphine for spinal injection (eg, Duramorph) is unavailable because of a drug shortage, subjects may instead receive an intrathecal injection of 75 mcg preservative-free hydromorphone in conjunction with single-shot spinal anesthesia using 1.4-1.6 mL bupivacaine HCl 0.75% and 15 mcg fentanyl. A combined spinal epidural (CSE) anesthesia technique may also be used provided the epidural component is not used. Subjects who receive the epidural component of the CSE anesthesia must be immediately withdrawn from the study.

Intraoperative medications: The intraoperative use of the following medications is discouraged, but may be permitted if clinically indicated based on the investigator's discretion (all medications must be appropriately recorded [ie, drug, dose, and route of administration]): ketamine and midazolam (Versed®). Prophylactic use of dexamethasone for prevention of nausea and vomiting is prohibited.

After delivery of the baby and prior to the TAP infiltration, a small amount of lidocaine (<2 mL) may be administered subcutaneously to form a skin wheal over the area of the needle insertion site. A 2-point classic TAP block, in 2 steps (see below), must be performed under ultrasound guidance and must be performed no more than 90 minutes after skin incision closure of the

C-section. A confirmatory ultrasound picture or video will be taken of each side of the abdomen after the TAP needle position has been established and after infiltration of study drug.

TAP infiltration: The TAP infiltration includes two steps: (1) TAP needle placement and saline hydrodissection and (2) study drug mixture infiltration into the TAP. Each step is briefly described below for one side of the abdomen and must be repeated on the contralateral side to complete the bilateral, 2-point TAP required for the study. For complete, step-by-step instructions on performing the TAP infiltration under ultrasound guidance, please refer to the Pharmacy Binder.

(1) TAP needle placement and saline hydrodissection: For subjects in both study groups, use ultrasound guidance to place the TAP needle into the desired location and use a 10-mL syringe pre-filled with normal saline to perform hydrodissection of the TAP. (Note: it is not necessary to use the full 10 mL of normal saline for hydodissection.) An ultrasound image of the TAP needle placement must be captured after saline hydrodissection.

(2) Study drug mixture infiltration into the TAP: Subjects randomized to the EXPAREL+bupivacaine group (Group 1) will receive 30 mL of a study drug mixture containing 10 mL EXPAREL (133 mg) combined with 10 mL bupivacaine HCl 0.25% (25 mg) and 10 mL normal saline (total mixture 30 mL) administered into the TAP. An ultrasound image of the TAP needle placement must be captured after study drug infiltration.

Subjects randomized to the active bupivacaine group (Group 2) will receive 30 mL of a study drug mixture containing 10 mL bupivacaine HCl 0.25% (25 mg) combined with 20 mL normal saline (total mixture 30 mL) administered into the TAP. An ultrasound image of the TAP needle placement must be captured after study drug mixture infiltration.

Repeat the above steps on the contralateral side to complete the bilateral, 2-point TAP required for the study.

Postsurgical Analgesia: **Patient-controlled analgesia is not permitted**

The following multimodal pain regimen will be used:

At the time of skin incision closure (Note: it is very important that these be administered at the time of wound closure and not prior to or before the end of surgery)

- Intravenous (IV) ketorolac 15 mg (1 dose)
- IV acetaminophen 1000 mg (1 dose)

Beginning 6 hours after skin incision closure

- Scheduled oral (PO) acetaminophen 650 mg beginning 6 hours from the administration of the single dose of IV acetaminophen at the end of surgery and then every 6 hours (q6h) for up to 72 hours or hospital discharge

- Scheduled PO ibuprofen 600 mg beginning 6 hours from the administration of the single dose of IV ketorolac at the end of surgery and then q6h for up to 72 hours or hospital discharge

This multi-modal pain regimen **is a requirement for all subjects in the study** and is not subject to investigator discretion. The date, time, and dose of all standardized multimodal pain medications administered must be recorded. Note: The scheduled PO medication will be administered on a q6h schedule only through hospital discharge.

Rescue Medication: Subjects should only receive opioid rescue pain medication upon request for breakthrough pain. Postsurgical rescue medication will comprise PO immediate-release oxycodone (initiated at 5-10 mg every 4 hours [q4h] or as needed [PRN]). If a subject is unable to tolerate PO medication or fails the PO oxycodone rescue, IV morphine (initiated at 1-2 mg) or hydromorphone (initiated at 0.3-0.5 mg) may be administered q4h or PRN. All surgical and postsurgical opioid and other analgesics (pain medications) administered must be documented through Day 14 postsurgery. Additionally, an unscheduled pain intensity score using a 10-cm visual analog scale (VAS; see Appendix 1) must be completed immediately prior to any rescue medication while in the hospital.

Permitted medications for the prevention and treatment of possible medication side effects include the following and may be administered at the discretion of the study site principal investigator:

- Ondansetron 4 mg IV immediately after delivery of the baby.
- Ondansetron 4 mg IV (should not exceed a maximum of 12 mg in a 24-hour period) for intraoperative and postoperative nausea and vomiting
- Metoclopramide 10 mg PO PRN for nausea and vomiting
- Nalbuphine IV 2.5 mg PRN for pruritus
- Naloxone IV 50-100 mcg PRN for pruritus.

Postsurgical Assessments

Subjects will remain in the hospital for up to 72 hours after surgery. Postsurgical assessments will include:

- Opioid use
- Time of first unassisted ambulation
- Pain intensity scores at rest using a 10-cm VAS (see Appendix 1)
- Discharge readiness (see Appendix 2)
- Subject's satisfaction with postsurgical pain control (see Appendix 3)
- Overall benefit of anesthesia score (OBAS) questionnaire (see Appendix 4)
- The Quality of recovery 15-item questionnaire (QoR-15; see Appendix 5)

A phone call will be made to each subject on Day 14 for safety purposes and to inquire as to whether the subject made any unscheduled phone calls or office visits related to pain;

experienced any hospital readmission; or experienced an emergency room visit since hospital discharge. Adverse events and serious adverse events (SAEs) will be recorded from the time the ICF is signed through Day 14. Any concomitant medications to treat AEs through Day 14 will also be recorded.

9.1.1. Duration of the Study and Subject Participation

Participation will begin at the signing of the ICF. No more than ~~7~~ 30 days should pass between signing of the ICF and performance of the surgery. The time from study drug administration through the end of participation is 14 ± 3 days. Therefore, subjects may participate in the study for up to ~~44~~ 47 days.

9.1.2. Study Stopping Rules

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

The Pacira Medical Monitor and Pharmacovigilance team review all SAEs reported from Pacira clinical studies on an ongoing basis and in real time (ie, as the events are reported). The Medical Monitor is responsible for temporarily halting the study if the type, frequency, or seriousness/severity of such events suggests a potential threat to the safety of the study participants. If such action is taken, a thorough review of all available data will be conducted. Based on the results of this review and discussions with investigators and/or regulatory authorities as warranted, the study may be restarted or permanently terminated.

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

9.2. Discussion of Study Design

EXPAREL is approved for infiltration into a surgical wound. This Phase-4, multicenter, double-blind study will evaluate the efficacy and safety of EXPAREL+bupivacaine infiltration into the TAP compared to active bupivacaine infiltration into the TAP following bupivacaine HCl spinal anesthesia in subjects undergoing elective C-section. The double-blind study design is intended to avoid potential bias resulting from subject or investigator knowledge of the assigned treatment.

The physiology of pain involves multiple complex pathways and mechanisms and the successful management of pain requires the use of a combination of pain medications in a “balanced” or multimodal approach to achieve a state of balanced analgesia (White 2010).

The practice of multimodal analgesia is being adopted across different patient-care pathways and is becoming the standard of care at major surgery centers globally. There is quite a variety of options of medications within the multimodal approach either in different combinations or when used alone. In all cases, the goal is to reduce postoperative pain associated with surgery and

reduce opioid use and opioid-related adverse events. In some cases, such an approach may also reduce the average length of hospital stay (Elvir-Lazo 2010).

EXPAREL (liposomal bupivacaine) is an amide local anesthetic indicated for single-dose infiltration into the surgical site to produce postsurgical analgesia. This study is designed to assess the effectiveness of EXPAREL administered as a TAP in a multimodal setting to reduce total postsurgical opioid consumption. All subjects in the study will be eligible to receive an opioid analgesic, if needed, to control breakthrough postsurgical pain as part of the multimodal approach to pain management.

10. STUDY POPULATION

Note: Based on the World Health Organization's Guidance: Breastfeeding and Maternal Medication, Recommendations for Drugs in the Eleventh WHO Model List of Essential Drugs (WHO 2002), bupivacaine is compatible with breastfeeding and, therefore, there are no restrictions in this study regarding the participation of women who wish to breastfeed following treatment with study drug.

10.1. Inclusion Criteria

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

1. Females 18 years of age and older at screening.
2. Term pregnancies of 37 to 42 weeks gestation, scheduled to undergo elective C-section.
3. ASA physical status 1, 2, or 3.
4. 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 she meets any one of the following criteria:

1. Subjects who, in the opinion of the investigator, have a high-risk pregnancy (eg, multiple gestations, pregnancy resulting from in vitro fertilization, gestational diabetes).
2. Subjects with a pregnancy-induced medical condition or complication (eg, hypertension, pre-eclampsia, chorioamnionitis).
3. Subjects with 3 or more prior C-sections
4. Pre-pregnancy body mass index >50 kg/m^2 or otherwise not anatomically appropriate to undergo a TAP block.
5. Allergy, hypersensitivity, intolerance, or contraindication to any of the study medications for which an alternative is not named in the protocol (eg, amide-type local anesthetics, opioids, bupivacaine, NSAIDs, spinal anesthesia).

6. Planned concurrent surgical procedure with the exception of salpingo-oophorectomy or tubal ligation.
7. Severely impaired renal or hepatic function (eg, serum creatinine level >2 mg/dL [176.8 µmol/L], blood urea nitrogen level >50 mg/dL [17.9 mmol/L], serum aspartate aminotransferase [AST] level >3 times the upper limit of normal [ULN], or serum alanine aminotransferase [ALT] level >3 times the ULN.)
8. Subjects at an increased risk for bleeding or a coagulation disorder (defined as platelet count less than 80, 000 × 10^3/mm^3 or international normalized ratio greater than 1.5)
9. Concurrent painful physical condition that may require analgesic treatment (such as long-term, consistent use of opioids) in the postsurgical period for pain that is not strictly related to the surgery and which may confound the postsurgical assessments.
10. Clinically significant medical disease in either the mother or baby that, in the opinion of the investigator, would make participation in a clinical study inappropriate. This includes any psychiatric or other disease in the mother that would constitute a contraindication to participation in the study or cause the mother to be unable to comply with the study requirements.
11. History of, suspected, or known addiction to or abuse of illicit drug(s), prescription medicine(s), or alcohol within the past 2 years.
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
13. Previous participation in an EXPAREL study.

In addition, the subject will be ineligible to receive study drug and will be withdrawn from the study if she meets the following criteria during surgery:

14. Any clinically significant event or condition uncovered during the surgery (eg, excessive bleeding, acute sepsis) that might render the subject medically unstable or complicate the subject's postsurgical course.
15. Receives the epidural component of CSE anesthesia during participation in the study.

10.3. Removal of Subjects from Therapy or Assessment

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

If any clinically significant event or condition is uncovered during the surgery (eg, excessive bleeding, acute sepsis) the subject should be withdrawn from study and the event or condition should be reported as an AE or SAE.

Additionally, any subjects who receive the epidural component of the CSE anesthesia must be immediately withdrawn from the study.

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

10.3.1. Withdrawal Secondary to Adverse Events

If a subject experiences an AE that renders her incapable of continuing with the remaining assessments, 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. If such a subject discontinues prior to hospital discharge, all assessments to be conducted at 72 hours/hospital discharge should be conducted as part of this final examination. If such a subject discontinues following hospital discharge, all information captured in the ~~Patient~~ Participant Diary should be collected and a final telephone call for safety should be made.

Any subject who discontinues because of an AE should be instructed to notify the study personnel of any abnormalities and to come to the study site if medical evaluation is needed and the urgency of the situation permits. Any subject exhibiting undesirable side effects will receive appropriate treatment at the discretion of the investigator until resolution of the effect.

This study involves a single infiltration of study drug; therefore, subjects should not be terminated from the ongoing study assessments as long as they are willing and able to continue with the follow-up schedule according to the protocol. For emergencies and other unscheduled visits to a medical facility other than the study site, medical records must be obtained by the investigator and appropriate information captured in the subject's case report form (CRF).

10.3.2. Voluntary or Study Investigator Withdrawal

Subjects are free to discontinue from the study at any time, without prejudice to future treatment. A subject may be discontinued from the study if she refuses EXPAREL infiltration or refuses to comply with study procedures. Subjects should be encouraged to complete the study safety assessments. Reasons for discontinuation from the study will be recorded.

If a subject is discontinued by the investigator or voluntarily withdraws from the study after receiving study drug, the subject will be asked to complete a final evaluation so that she can be withdrawn in a safe and orderly manner. If such a subject discontinues prior to hospital discharge, all assessments to be conducted at 72 hours/hospital discharge should be conducted as part of this final examination. If such a subject discontinues following hospital discharge, all information captured in the Participant Diary should be collected and a final telephone call for safety should be made.

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

11. TREATMENTS

11.1. Treatment to be Administered

There will be two treatment groups; eligible subjects will be randomized in a blinded 1:1 ratio to either:

- Group 1: EXPAREL+bupivacaine TAP infiltration following spinal anesthesia
- Group 2: Active bupivacaine TAP infiltration following spinal anesthesia

On Day 1, prior to the C-section, all subjects will receive a intrathecal injection of 150 mcg preservative-free morphine for spinal injection (eg, Duramorph) in conjunction with single-shot spinal anesthesia using 1.4-1.6 mL bupivacaine HCl 0.75% and 15 mcg fentanyl. If preservative-free morphine for spinal injection (eg, Duramorph) is unavailable because of a drug shortage, subjects may instead receive an intrathecal injection of 75 mcg preservative-free hydromorphone in conjunction with single-shot spinal anesthesia using 1.4-1.6 mL bupivacaine HCl 0.75% and 15 mcg fentanyl. A CSE anesthesia technique may also be used provided the epidural component is not used. Subjects who receive the epidural component of the CSE anesthesia must be immediately withdrawn from the study.

After delivery of the baby and prior to the TAP infiltration, a small amount of lidocaine (<2 mL) may be administered subcutaneously to form a skin wheal over the area of the needle insertion site. A 2-point classic TAP block, in 2 steps (see below), must be performed under ultrasound guidance and must be performed no more than 90 minutes after skin incision closure of the C-section. A confirmatory ultrasound picture or video will be taken of each side of the abdomen after the TAP needle position has been established and after infiltration of study drug.

TAP infiltration: The TAP infiltration includes two steps: (1) TAP needle placement and saline hydrodissection and (2) study drug mixture infiltration into the TAP. Each step is briefly described below for one side of the abdomen and must be repeated on the contralateral side to complete the bilateral, 2-point TAP required for the study. For complete, step-by-step instructions on performing the TAP infiltration under ultrasound guidance, please refer to the Pharmacy Binder.

(1) TAP needle placement and saline hydrodissection: For subjects in both study groups, use ultrasound guidance to place the TAP needle into the desired location and use a 10-mL syringe pre-filled with normal saline to perform hydrodissection of the TAP. (Note: it is not necessary to use the full 10 mL of normal saline for hydodissection.) An ultrasound image of the TAP needle must be captured after saline hydrodissection.

(2) Study drug mixture infiltration into the TAP: Subjects randomized to the EXPAREL+bupivacaine group (Group 1) will receive 30 mL of a study drug mixture containing 10 mL EXPAREL (133 mg) combined with 10 mL bupivacaine HCl 0.25% (25 mg) and 10 mL normal saline (total mixture 30 mL) administered into the TAP. An

ultrasound image of the TAP needle placement must be captured after study drug infiltration.

Subjects randomized to the active bupivacaine group (Group 2) will receive 30 mL of a study drug mixture containing 10 mL bupivacaine HCl 0.25% (25 mg) combined with 20 mL normal saline (total mixture 30 mL) administered into the TAP. An ultrasound image of the TAP needle placement must be captured after study drug mixture infiltration.

Repeat the above steps on the contralateral side to complete the bilateral, 2-point TAP required for the study.

11.1.1. Infiltration Instructions/Procedure

On Day 1, prior to the C-section, all subjects will receive an intrathecal injection of 150 mcg preservative-free morphine for spinal injection (eg, Duramorph) in conjunction with single-shot spinal anesthesia using 1.4-1.6 mL bupivacaine HCl 0.75% and 15 mcg fentanyl. If preservative-free morphine for spinal injection (eg, Duramorph) is unavailable due to a drug shortage, subjects may instead receive an intrathecal injection of 75 mcg preservative-free hydromorphone in conjunction with single-shot spinal anesthesia using 1.4-1.6 mL bupivacaine HCl 0.75% and 15 mcg fentanyl. A CSE anesthesia technique may also be used provided the epidural component is not used. Subjects who receive the epidural component of the CSE anesthesia must be immediately withdrawn from the study.

The TAP infiltration includes two steps: (1) TAP needle placement and saline hydrodissection and (2) study drug mixture infiltration into the TAP. Each step is briefly described below for one side of the abdomen and must be repeated on the contralateral side to complete the bilateral, 2-point TAP required for the study. For complete, step-by-step instructions on performing the TAP infiltration under ultrasound guidance, please refer to the Pharmacy Binder.

(1) TAP needle placement and saline hydrodissection: For subjects in both study groups, use ultrasound guidance to place the TAP needle into the desired location and use a 10-mL syringe pre-filled with normal saline to perform hydrodissection of the TAP. (Note: it is not necessary to use the full 10 mL of normal saline for hydodissection.) An ultrasound image of the TAP needle must be captured after saline hydrodissection.

(2) Study drug mixture infiltration into the TAP: Subjects randomized to the EXPAREL+bupivacaine group (Group 1) will receive 30 mL of a study drug mixture containing 10 mL EXPAREL (133 mg) combined with 10 mL bupivacaine HCl 0.25% (25 mg) and 10 mL normal saline (total mixture 30 mL) administered into the TAP. An ultrasound image of the TAP needle placement must be captured after study drug infiltration.

Subjects randomized to the active bupivacaine group (Group 2) will receive 30 mL of a study drug mixture containing 10 mL bupivacaine HCl 0.25% (25 mg) combined with

20 mL normal saline (total mixture 30 mL) administered into the TAP. An ultrasound image of the TAP needle placement must be captured after study drug mixture infiltration.

Repeat the above steps on the contralateral side to complete the bilateral, 2-point TAP required for the study.

The maximum dosage of EXPAREL should not exceed 266 mg. Product handling and storage procedures will be in accordance with the product package insert (see also Section 11.1.2).

11.1.2. EXPAREL Administration Considerations

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

Administration of additional local anesthetics, including lidocaine, is prohibited and no agents other than bupivacaine HCl 0.25% in 20 mL are to be admixed with EXPAREL. Lidocaine and other local anesthetics are not permitted to be locally administered during the surgery because they are known to interact with EXPAREL resulting in the displacement of bupivacaine and elevated plasma levels.

EXPAREL may not be administered to a subject if the vial has been open for more than 4 hours. In order to prevent EXPAREL from settling, gently inverting and re-inverting the syringe prior to administration is recommended.

11.1.3. Intrathecal Morphine/Hydromorphone Administration Considerations

The most serious adverse experience encountered during administration of intrathecal morphine/ hydromorphone, respiratory depression and/or respiratory arrest, may be severe and could require intervention. Naloxone injection and resuscitative equipment should be immediately available for administration in case of life-threatening or intolerable side effects and whenever intrathecal morphine/ hydromorphone therapy is being initiated.

Intrathecal morphine/ hydromorphone is contraindicated in patients with medical conditions that would preclude the administration of opioids via the IV route, including an allergy to morphine/ hydromorphone or other opiates, acute bronchial asthma, or upper airway obstruction. Morphine/ hydromorphone, like all opioid analgesics, may cause severe hypotension in individuals whose ability to maintain blood pressure is compromised by a depleted blood volume or a concurrent administration of drugs, such as phenothiazines or general anesthetics.

11.2. Identity of the Investigational Products

11.2.1. Description of EXPAREL

EXPAREL (bupivacaine liposome injectable suspension) is formulated as a sterile, non-pyrogenic, white to off-white, preservative-free homogenous suspension of bupivacaine

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

11.2.2. Description of Reference Product

The reference product is 20 mL bupivacaine HCl 0.25% and 40 mL normal saline (total volume 60 mL) administered as an infiltration into the TAP under ultrasound guidance after spinal anesthesia. Bupivacaine HCl is a long-acting local anesthetic, used for surgical anesthesia and acute pain management. It is an alternative to NSAIDs and opioids.

11.3. Method of Assigning Subjects to Treatment

11.3.1. Randomization Scheme

Subjects will be randomized in a 1:1 ratio. 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 will be reused once assigned.

11.3.2. Randomization Procedures

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

11.3.3. Replacement of Subjects

Subjects who withdraw from the study before being randomized 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.

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 100 mg. Clinical studies have shown that for wound infiltration a total dose of 266 mg (20 mL) of EXPAREL is safe and efficacious. Based on this experience, the FDA-approved marketed dose of 266 mg was deemed appropriate for this study.

Intrathecal preservative-free morphine for spinal injection (eg, Duramorph) is commonly used during C-section, usually at a dose between 0.1 mg and 0.2 mg (Sviggum 2106). The midpoint of

0.15 mg (150 mcg) is preferred by some anesthesiologists because it balances duration of analgesia (which may be shorter with a lower dose) and incidence of opioid-related adverse events such as nausea and vomiting (which may increase with a higher dose). If preservative-free morphine for spinal injection (eg, Duramorph) is unavailable because of a drug shortage, preservative-free hydromorphone may also be used in C-section, usually at a dose that is 50% lower than that for intrathecal morphine. The study dose of 0.15 mg (150 mcg) of intrathecal morphine or 0.075 mg (75 mcg) of intrathecal hydromorphone is also supported by a recent dose-finding study that sought to determine the effective analgesic dose for 90% of patients (ED_{90}) for both intrathecal morphine and hydromorphone in patient undergoing C-section (Sviggum 2106).

11.5. Blinding

11.5.1. Blinding Procedures

To maintain the double-blind study design, only the unblinded study personnel who are NOT involved with protocol-specific, postsurgical assessments may prepare and administer the study drug. Staff members conducting study-specific, postsurgical assessments and the subjects will remain blinded to the assigned treatment throughout the study. If a subject experiences an SAE, Pacira will only unblind the subject's treatment if doing so is necessary to manage the treatment of the SAE. Expedited SAEs will be unblinded by Pacira for regulatory reporting purposes.

At each site, only the designated unblinded pharmacist will receive the unblinded randomization assignments and be responsible for preparing study drug.

Assignment of blinded and unblinded responsibilities regarding the preparation of study drug should take into account that **EXPAREL must be administered within 4 hours of opening the vial**. Syringes containing study drug will need to be gently inverted several times to re-suspend any settling of the study drug that may have occurred prior to administration.

The individuals preparing and administering study drug will not be allowed to perform any of the study assessments or reveal the assigned study treatment to any other members of the study team at any time. The infiltration of study drug will be recorded using the minimal amount of information necessary to avoid unblinding staff who will be participating in blinded procedures (see Pharmacy Binder for additional details).

No crossover will be permitted between the blinded and unblinded study site personnel during the study period. The assignment of site monitors will also be segregated. Blinded monitors will review 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 (eg, randomization, study drug preparation, study drug accountability, study drug infiltration) 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 it is felt that subject safety warrants such unblinding. However, if possible, the investigator should discuss the safety issues with the Pacira Medical Monitor before attempting such unblinding. Any unblinding will be documented through immediate notification of the Pacira study team and the investigator within the interactive response technology (IRT) system used for randomization. The reason for unblinding will be documented. Any accidental unblinding events (ie, 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 Therapy and Medications

Use of any of the following medications within the times specified before surgery is prohibited: 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.

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, she must be on a stable dose for at least 1 month prior to study drug administration.

11.6.2. Restricted Therapy and Medications During Surgery

As described in the EXPAREL package insert, no agents are to be admixed with EXPAREL (eg, epinephrine, dexamethasone, clonidine) other than bupivacaine. Lidocaine and other local anesthetics are not permitted to be locally administered during the surgery because they are known to interact with EXPAREL resulting in the displacement of bupivacaine and elevated plasma levels. When a topical antiseptic is applied to the surgical site, the solutions are not to come in contact with each other (eg, the area must be dry before EXPAREL is administered). Upon discovering use of any prohibited therapy and/or medication during or after surgery, the investigator should document all events that led to the deviation, write a note to file, and notify the Pacira Medical Monitor accordingly.

11.6.3. Permitted Therapy or Medications after Surgery

Patient-controlled analgesia is not permitted.

The following multimodal pain regimen will be used:

At the time of skin incision closure (Note: it is very important that these be administered at the time of wound closure and not prior to or before the end of surgery.)

- Intravenous (IV) ketorolac 15 mg (1 dose)
- IV acetaminophen 1000 mg (1 dose)

Beginning 6 hours after skin incision closure

- Scheduled PO acetaminophen 650 mg beginning 6 hours from the administration of the single dose of IV acetaminophen at the end of surgery and then q6h for up to 72 hours or hospital discharge
- Scheduled PO ibuprofen 600 mg beginning 6 hours from the administration of the single dose of IV ketorolac at the end of surgery and then q6h for up to 72 hours or hospital discharge

This multi-modal pain regimen **is a requirement for all subjects in the study** and is not subject to investigator discretion. The date, time, and dose of all standardized multimodal pain medications administered must be recorded.

Subjects should only receive opioid rescue pain medication upon request for breakthrough pain. Postsurgical rescue medication will comprise PO immediate-release oxycodone (initiated at 5-10 mg q4h or PRN). If a subject is unable to tolerate PO medication or fails the PO oxycodone rescue, IV morphine (initiated at 1-2 mg) or hydromorphone (initiated at 0.3-0.5 mg) may be administered q4h or PRN. **Patient-controlled analgesia is not permitted.** All surgical opioid and postsurgical opioid and other analgesics (pain medications) administered must be documented through Day 14 postsurgery. Additionally, an unscheduled pain intensity score using the VAS (see Appendix 1) must be completed immediately prior to any rescue medication while in the hospital.

Permitted medications for the prevention and treatment of possible medication side effects include the following and may be administered at the discretion of the study site principal investigator:

- Ondansetron 4 mg IV immediately after delivery of the baby.
- Ondansetron 4 mg IV (should not exceed a maximum of 12 mg in a 24-hour period) for intraoperative and postoperative nausea and vomiting
- Metoclopramide 10 mg PO PRN for nausea and vomiting
- Nalbuphine IV 2.5 mg as needed PRN for pruritus
- Naloxone IV 50-100 mcg PRN for pruritus.

11.7. Treatment Compliance

Study drug will be administered by the study staff and, thus, treatment compliance is ensured.

11.8. Accountability of Study Drug

Shipment of EXPAREL for the study will contain an investigational drug transmittal and receipt form to assist the investigator or designee (eg, 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/or 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 Measurements

The following efficacy measurements will be conducted at the times specified after completion of the last C-section wound incision stitch (ie, time of closure of the C-section wound):

- Date, time of administration, and amount of all postsurgical opioid rescue medication taken through Day 14.
- Pain intensity scores at rest using a 10-cm VAS at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours (see Appendix 1) at rest and once daily (at noon ± 4 hours) through Day 14. For pain intensity scores at 18, 24, 30, 36, or 42 hours, if the subject is sleeping, do not wake her to assess pain. If she awakens within the assessment window (ie, 1 hour for the 18- and 24-hour assessments and 2 hours for the 30-, 36-, and 42-hour assessments), a pain score may be collected then.†
- Discharge readiness at 24, 48, and 72 hours or until the subject attains a score of 9, whichever occurs first.
- Date and time of first unassisted ambulation.
- Subject satisfaction with postsurgical pain control (using a 5-point Likert scale) at 72 hours (or prior to hospital discharge).
- Quality of Recovery 15-item questionnaire at 72 hours (or prior to hospital discharge).
- OBAS questionnaire at 24, 48, and 72 hours.†

- Unscheduled phone calls or office visits related to pain after discharge through Day 14.

† If a subject is discharged prior to any of the scheduled VAS assessments collected at 6 to 72 hours postsurgery or a scheduled OBAS assessment collected at 24 to 72 hours postsurgery, a member of the study site staff will contact the subject at the appropriate scheduled times (ie, the time of each assessment scheduled to be collected that occurs after hospital discharge) to remind her to complete the VAS and OBAS assessments and to record the scheduled assessments in the Participant Diary. This will ensure that for any subject discharged prior to 72 hours, all VAS and OBAS assessments required for calculation of the study endpoints are captured. These phone calls will only occur if a subject is discharged prior to 72 hours.

12.2. Efficacy Endpoints

The **primary** efficacy endpoint is the total postsurgical opioid consumption in morphine equivalents through 72 hours.

The **secondary** efficacy endpoints include:

- Time to first postsurgical opioid rescue medication
- The VAS pain intensity scores at rest from 6 to 72 hours
- Percentage of opioid-free subjects through 72 hours

Tertiary efficacy endpoints may include (but may not be limited to):

- Percentage of opioid-free subjects through 24 and 48 hours.
- The VAS pain intensity scores at rest from 6 to 12 hours, 6 to 24 hours, 6 to 48 hours, 24 to 48 hours, and 48 to 72 hours.
- Integrated rank assessment using the VAS pain intensity score at rest at 24, 48, and 72 hours and the total amount of postsurgical opioids consumed through 24, 48, and 72 hours (Silverman 1993).
- Overall benefit of analgesia scores at each assessed timepoint.
- Time spent in the post-anesthesia care unit (PACU).
- Time to first unassisted ambulation.
- Proportion of subjects meeting Modified Postanesthesia Discharge Scoring System criteria for discharge readiness at each assessed timepoint.
- Overall assessment of the subject's satisfaction with postsurgical pain control (using a 5-point Likert scale) at 72 hours after surgery (or at hospital discharge if earlier than 72 hours).
- Responses to the QoR-15 questionnaire at 72 hours after surgery (or at hospital discharge if earlier than 72 hours).

- Number of unscheduled phone calls or office visits related to pain from discharge through Day 14.

12.3. Safety Assessments

Adverse events will be monitored from the time the ICF is signed through Day 14.

12.4. Safety Endpoints

Incidence of treatment-emergent AEs (TEAEs) and SAEs will be assessed through Day 14.

12.5. Appropriateness of Measures

Endpoints selected for this study were based on well-established clinical measurements used in peer-reviewed studies.

13. STUDY PROCEDURES

A time and events schedule for all study procedures is provided in Table 1 and Table 2.

13.1. Instructions for Conducting Procedures and Measures

All assessments conducted after baseline will be timed from when the last C-section wound incision stitch is completed (ie, time of closure of the C-section wound). 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 closure of the C-section wound. Postsurgical is defined as after the end of surgery.

Subjects will be hospitalized for up to 72 hours after surgery. Postsurgical analgesia and collection of study data through hospital discharge will take place under the supervision of study staff. Following hospital discharge, the subject will record use of pain medication, if any, in the Participant Diary. Additionally, the subject will record a daily (at noon ± 4 hours) 10-cm VAS pain score at rest in the Participant Diary daily from hospital discharge through Day 14. This assessment should capture her average pain at rest in the prior 24 hours by assessing, "What has been your average pain since your last pain assessment?" (ie, from noon on the previous day to the current assessment). At the same time, the subject should record any pain medication (medication name, dose, date, and time) taken in the prior 24 hours.

Because the Day-14 assessment is a phone call, subjects will be provided with an addressed and stamped envelope in which to return the Participant Diary to the investigator.

13.1.1. Patient Binder and Participant Diary

The Patient Binder will be given to the subject at the first scheduled assessment (ie, 6 hours) following surgery. While in the hospital, the subject will use the binder to record all scheduled VAS (ie, at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours) and OBAS (ie, at 24, 48, and 72 hours) assessments. She will also use the binder while in the hospital to record any unscheduled VAS assessments prior to receiving rescue medication.

If a subject is discharged prior to any of the scheduled VAS assessments collected at 6 to 72 hours postsurgery or a scheduled OBAS assessment collected at 24 to 72 hours postsurgery, a member of the study site staff will contact the subject at the appropriate scheduled times (ie, the time of each assessment scheduled to be collected that occurs after hospital discharge) to remind her to complete the VAS and OBAS assessments and to record the scheduled assessments in the Participant Diary, which will be provided to the subject at the time of hospital discharge. This will ensure that for any subject discharged prior to 72 hours, all VAS and OBAS assessments required for calculation of the study endpoints are captured. These phone calls will only occur if a subject is discharged prior to 72 hours.

At hospital discharge, study personnel will use the Participant Diary to record any pain medication provided to the subject for home use and any prescription provided for any pain medication to be filled following discharge. This information should include medication name, dose, and instructions for use.

At hospital discharge, the subject will be instructed to record a daily VAS pain intensity score and all pain medications taken following hospital discharge through Day 14 in the Participant Diary.

At home, the subject will assess pain intensity at rest each day at noon (± 4 hours). This assessment should capture her average pain at rest in the prior 24 hours by assessing, "What has been your average pain since your last pain assessment?" (ie, from noon on the previous day to the current assessment). At the same time, the subject should record any pain medication (date, time, and dose) taken in the prior 24 hours.

13.1.2. Pain Intensity Assessments

Pain intensity scores at rest using a 10-cm VAS at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours (see Appendix 1) at rest and once daily (at noon ± 4 hours) through Day 14. For pain intensity scores at 18, 24, 30, 36, or 42 hours, if the subject is sleeping, do not wake her to assess pain. If she awakens within the assessment window (ie, 1 hour for the 18- and 24-hour assessments and 2 hours for the 30-, 36-, and 42-hour assessments), a pain score may be collected then. See Section 13.1.1 regarding subjects discharged prior to 72 hours.

To assess pain intensity (VAS) at rest, the subject should rest quietly in a supine or seated position that does not exacerbate her postsurgical pain for 3-5 minutes before entering the pain score.

13.1.3. Overall Benefit of Analgesia Score Questionnaire

The OBAS questionnaire (Lehmann 2010; see Appendix 4) will be completed at 24, 48, and 72 hours. See Section 13.1.1 regarding subjects discharged prior to 72 hours.

13.1.4. Subject Satisfaction with Postsurgical Pain Control

The subject's satisfaction with postsurgical pain control will be assessed at 72 hours (or hospital discharge, whichever occurs first; see Appendix 3).

13.1.5. Discharge Readiness

The subject's discharge readiness will be assessed using the Modified Postanesthesia Discharge Scoring System criteria (Chung 1995a; Chung 1995b; see Appendix 2). The discharge readiness assessment will be used for data collection only and is not intended to interfere with the investigational site's policy for determining when the subject should be discharged from the hospital. Discharge readiness will be assessed at 24, 48, and 72 hours or hospital discharge or until the subject attains a score of 9, whichever occurs first.

13.1.6. Quality of Recovery

The subject's quality of recovery will be assessed using the QoR-15 questionnaire at 72 hours, (or hospital discharge, whichever occurs first; see Appendix 5).

13.2. Obtaining Informed Consent

Potential participants may provide informed consent up to 30 days before their scheduled surgery. If a subject can only be screened on the day of surgery, the consent process must be started at least 24 hours prior to the day of surgery in order to ensure ample time for the subject to review the ICF and have all her questions answered by the investigator/study staff prior to providing informed consent. Screening procedures that are standard of care (SOC) at the institution may be completed prior to written informed consent. Any screening procedures that are not SOC, must be completed after written informed consent is provided and prior to surgery. (see Section 13.3).

13.3. Screening/Baseline Procedures

Subjects will be screened within 30 days prior to surgery; screening on the day of surgery will be allowed but is discouraged. If a subject can only be screened on the day of surgery, the informed consent process must still be started at least 24 hours prior to the conduct of any screening procedures that are not considered SOC at the institution and such procedures may not be performed until written informed consent is provided All screening procedures that are not SOC must be performed and documented within the 30-day time window (inclusive of the day of surgery for those subjects who can only be screened on the day of surgery) as described here.

The following screening/baseline procedures should be performed within 30 days prior to administration of study drug. Screening on the day of surgery will be permitted but is discouraged.

- Explain study purpose and procedures
- Obtain signed ICF, if not provided earlier

- Assess eligibility
- Record medical/surgical history
- Record prior and concomitant medications
- Record demographics and baseline characteristics
- Explain to the subject that she will be provided with a Patient Binder while in the hospital and that she will be expected to capture specific information in the binder while in the hospital.
- Explain to the subject that she will be provided with a Participant Diary upon discharge from the hospital and that she will be expected to capture specific information in the diary after discharge through Day 14.
- Measure vitals (blood pressure, height, weight, and heart rate)
- Perform physical exam according to the investigational site's standard of care
- Perform 12-lead ECG
- Conduct urine drug screen and breath alcohol test
- Clinical laboratory tests in accordance with the investigator's standard of care including (Appendix 6):

    1. Direct bilirubin
    2. Gamma-glutamyl transpeptidase (GGT) and lactate dehydrogenase (LDH)

    OR

    ALT and AST.

  Note: if clinical laboratory test results are available from with 14 days of surgery, laboratory tests do not have to be repeated at screening
- Record AEs starting when the ICF is signed
- Record concomitant medications for treatment of AEs

13.4. Day 1 - Operating Room

- Assess/confirm eligibility
- Confirm medical/surgical history
- Update prior and concomitant medications
- Measure vital signs (blood pressure and heart rate)
- Perform physical exam according to the investigational site's standard of care
- Randomize subject and prepare study drug
- Administer an intrathecal injection of 150 mcg preservative-free morphine for spinal injection (eg, Duramorph®) in conjunction with single-shot spinal anesthesia using

1.4-1.6 mL bupivacaine HCl 0.75% and 15 mcg fentanyl. If preservative-free morphine for spinal injection (eg, Duramorph) is unavailable because of a drug shortage, subjects may instead receive an intrathecal injection of 75 mcg preservative-free hydromorphone in conjunction with single-shot spinal anesthesia using 1.4-1.6 mL bupivacaine HCl 0.75% and 15 mcg fentanyl. A CSE anesthesia technique may also be used provided the epidural component is not used. Subjects who receive the epidural component of the CSE anesthesia must be immediately withdrawn from the study.

- Record start and stop time of surgery (Note: end of surgery is defined as the closure of the C-section wound)
- Record intraoperative opioids administered and doses
- Record any AEs or SAEs
- Record concomitant medications for treatment of AEs

13.5. Day 1 - Post-anesthesia Care Unit

- Perform TAP needle placement and saline hydrodissection under ultrasound guidance
- Capture ultrasound image of the TAP needle placement after saline hydrodissection
- Perform 2-point classic TAP infiltration no more than 90 minutes after skin incision closure of the C-section
- Collect ultrasound image of two-point TAP needle placement after infiltration of study drug
- Record start and stop time of study drug infiltration

13.6. Day 1 - Prior to PACU Discharge

- Record date, time in and out of the PACU
- Measure vital signs (blood pressure and heart rate)
- Record an unscheduled VAS pain intensity score before any postsurgical opioid medication while in the hospital.
- Record date, time, and dose of all postsurgical opioid and other pain medication. Note: Subjects should only receive opioid pain medication (eg, morphine, hydromorphone [Dilaudid], oxycodone) upon request for breakthrough pain.
- Record date, time, and dose of all standardized multimodal pain medications administered

13.7. Days 1-3 (0-72 Hours After Surgery/Hospital Discharge)

- At the first scheduled assessment (ie, 6 hours) provide the Patient Binder
- Record scheduled pain intensity scores at rest using a 10-cm VAS (see Appendix 1) at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours. For pain intensity scores at 18, 24, 30, 36, or 42 hours, if the subject is sleeping, do not wake her to assess pain. If she awakens within the assessment window (ie, 1 hour for the 18- and 24-hour assessments and 2 hours for the 30-, 36-, and 42-hour assessments), a pain score may be collected then. See Section 13.1.1 regarding subjects discharged prior to 72 hours.
- Record date, time, and dose of all standardized multimodal pain medications administered
- Record an unscheduled VAS pain intensity score immediately before any postsurgical opioid medication while in the hospital.
- Record date, time, and dose of all postsurgical opioid and other pain medications administered through 72 hours. Note: Subjects should only receive opioid pain medication (morphine, hydromorphone [Dilaudid], oxycodone) upon request for breakthrough pain, PRN.
- Record date and time of subject's first unassisted ambulation
- Record OBAS (see Appendix 4) at 24, 48, and 72 hours. See Section 13.1.1 regarding subjects discharged prior to 72 hours.
- Record discharge readiness (see Appendix 2) at 24, 48, and 72 hours or hospital discharge, or until the subject attains a score of 9, whichever occurs first
- Record overall rating of subject's satisfaction with postsurgical pain control at 72 hours (or hospital discharge, whichever occurs first; see Appendix 3)
- Record QoR-15 data at 72 hours (or hospital discharge, whichever occurs first; see Appendix 5)
- Record date and time of hospital discharge
- Record any AEs or SAEs
- Record any concomitant medications for treatment of AEs

13.8. After Hospital Discharge Through Day 14

- Record VAS pain intensity scores at rest (see Appendix 1) in the Participant Diary at noon (± 4 hours) each day through Day 14. This assessment should capture the subject's average pain at rest in the prior 24 hours by assessing, "What has been your average pain since your last pain assessment?" (ie, from noon on the previous day to the current assessment).

- Record the use of pain medication, if any, in the Participant Diary daily through Day 14

13.9. Day 14 Phone Call

- Document whether the subject has made any unscheduled phone calls or office visits related to pain; experienced any hospital readmission; or experienced an emergency room visit since hospital discharge.
- Record any AEs or SAEs
- Record any concomitant medications for treatment of AEs
- Remind subject to return the Participant Diary in the provided addressed and stamped envelope

14. ADVERSE EVENT REPORTING

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

The concepts of AE and SAE 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 primarily used 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 (eg, 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 (eg, 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 the 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 (eg, migraine) is considered an AE.

An AE that occurs after the ICF has been 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 a 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 investigational new drug (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 (ie, PTAEs and TEAEs) with an onset after the subject signs the ICF. For the purpose of this study, all AEs that occur through Day 14 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; ie, lined through and initialed). Whenever possible, abnormal laboratory results should be reported as their clinical corollary (eg, low potassium should be recorded as hypokalemia).

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

Any condition noted before the subject signs the ICF will be listed as Medical History and is considered a pre-existing condition. If a pre-existing condition changes (ie, becomes more severe or more frequent) at any time after the ICF is signed, or after study drug administration, it is considered an AE. Note: A change in treatment for a pre-existing condition (eg, 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 study drug, action taken for the AE, and the outcome of the AE, including the date and time of resolution, if applicable.

14.1.3. Severity of Adverse Events

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

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

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

Severe: An AE that prevents normal everyday activities.

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

14.1.4. Relationship of Adverse Events to Study Drug

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

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

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

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

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

Definite: The pharmacological properties of the study drug(s) or of the substance class, and the course of the AE after dechallenge and, if applicable, after rechallenge, and/or specific test indicate involvement of the study drug(s) in the occurrence/worsening of the AE, and no indication of other causes exists.

14.1.5. Outcome of Adverse Events

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

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

14.1.6. Action Taken with Subject Because of an Adverse Event

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

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

14.2. Serious Adverse Events

14.2.1. Definition of a Serious Adverse Event

Definition of an 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 (ie, 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 14, whether or not related to EXPAREL, must be reported by the investigator or designee to Pacira Drug Safety either email (drugsafety@pacira.com) or fax to 973-201-0649 within 24 hours of discovery. In addition, the Investigator or designee is encouraged to contact the Medical Monitor to discuss the case, as needed.

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

If the investigator is made aware of any SAEs after Day 14, these should also be reported to Pacira Drug Safety or designee provided the SAE is considered related to EXPAREL. The site would then provide a completed SAE form within 1 business day and the event would be followed until resolution, or until adequate stabilization is met.

15. STATISTICAL METHODS

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

15.1. Study Objective

The primary objective of this study is to compare total opioid consumption through 72 hours following EXPAREL+bupivacaine HCl infiltration into TAP after spinal anesthesia to active bupivacaine HCl infiltration into the TAP after spinal anesthesia in subjects undergoing elective C-section.

15.2. Study Endpoints

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

15.3. Determination of Sample Size

Sample size for this study was based Quale et al (2016). The coefficient of variation (CV) from this poster was approximately 60%. Assuming a log-normal distribution for total opioid consumption with a 60% CV, 5% alpha, a 1:1 randomization ratio, and 80% power 72 subjects per treatment arm is sufficient to detect a 30% difference between treatments. Assuming 5% of the subjects are not evaluable a total sample size of approximately 152 subjects are needed to ensure 144 evaluable subjects.

15.4. Analysis Populations

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

The efficacy analysis set will include all randomized subjects who undergo C-section. All analyses based on the efficacy analysis set will be by randomized treatment regardless of treatment actually received.

The per-protocol efficacy analysis set will include all subjects in the efficacy analysis set who do not have any important protocol deviations. All analyses based on the per-protocol analysis set will be by randomized treatment regardless of treatment actually received.

15.5. Handling Subject Dropouts and Discontinuations

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 descriptively by treatment group.

15.6.2. Study Compliance

The percentage of subject 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

A comprehensive statistical analysis plan (SAP) will be developed for this study. All efficacy endpoint analyses will be conducted for the efficacy analysis set. The primary efficacy endpoint will also be analyzed using the per-protocol analysis set as a sensitivity analysis.

Summary statistics (n, mean, median, standard deviation, minimum, maximum) will be shown for each continuous measure of efficacy by treatment group. Number and percentage of subjects in each category will be shown for each categorical measure of efficacy by treatment group. For time to event measures of efficacy, medians and Kaplan-Meier estimates will be shown by treatment group.

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

All assessments will be listed in subject data listings.

15.6.3.1. Primary Efficacy Endpoint

The analysis of total postsurgical opioid consumption through 72 hours will be described in the SAP.

15.6.3.2. Secondary Efficacy Endpoints

The analyses of the secondary efficacy endpoints will be described in the SAP.

15.6.3.3. Tertiary Efficacy Endpoint(s)

The analyses of the tertiary efficacy endpoints will be described in the SAP.

15.6.4. Safety Analyses

Adverse event verbatim terms will be mapped to preferred terms and related system/organ class using the Medical Dictionary for Regulatory Activities (MedDRA). All summaries of AEs will include AEs that occur after the beginning of anesthesia. All summaries of AEs will be based on the safety analysis set. Events that start prior to anesthesia will be identified in listings only. Incidence rates of AEs after the start of anesthesia and the proportion of subjects prematurely withdrawn from the study due to an AE will be shown for each treatment group. Incidence rates will also be shown for each treatment group for study drug-related AEs after the start of

anesthesia and by severity. Incidence rates of SAEs will also be shown for each treatment group. All incidence rates will be categorized and shown by system/organ class and preferred term.

15.7. Significance Testing

Significance testing will be described in the SAP.

15.8. Interim Analyses

An unblinded interim analysis will be conducted by an independent statistician when approximately 80 treated subjects under protocol amendment 2 have completed the 72-hour follow-up for the primary efficacy assessments. The objective of this interim analysis is three-fold:

1. To stop the trial for futility if it is improbable to show a significant reduction in the primary efficacy endpoints;
2. To stop the trial for early success if a clear benefit is demonstrated
3. To allow for the possibility of increasing the study sample size if the original sample size assumptions are determined to be not viable.

If the predictive probability at the current maximum sample size is less than a predetermined threshold, then the trial will terminate for futility. A group sequential stopping boundary will be used for the early success stopping analysis. If the trial stops early for neither success nor futility, predictive probabilities will be calculated for the current maximum sample size (144 treated subjects) and larger sample sizes up to 200 subjects. The sample size may be extended to a number that achieves higher predictive probability of trial success (Saville 2017). The final decision to stop, continue or increase the sample size will be made by Pacira. Full details and all thresholds for stopping or trial expansion will be covered in a prospective interim analysis plan that will become part of the study SAP.

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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 (eg, the investigator's Brochure);
- To ensure that all persons assisting me with the conduct of this study are adequately informed about the investigational product(s) and about their study-related duties and functions as described in this protocol;
- That I am aware that regulatory authorities may require investigators to disclose all information about significant ownership interests and/or financial ties related to the Sponsor and/or the investigational product(s). Consequently, I agree to disclose all such significant financial information to Pacira and to update this information promptly if any relevant changes occur during the course of the study through 1 year following completion of the study. I also agree that any information regarding my significant financial interest related to Pacira and/or the investigational product(s) will be disclosed to the regulatory authorities by Pacira.

_____ _____

Signature of investigator Date

18. APPENDICES

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

Subjects will be evaluated for pain intensity scores at rest using the 10-cm VAS at rest at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours after surgery and then once daily (at noon ± 4 hours) through Day 14. For pain intensity scores at 18, 24, 30, 36, or 42 hours, if the subject is sleeping, do not wake her to assess pain. If she awakens within the assessment window (ie, 1 hour for the 18- and 24-hour assessments and 2 hours for the 30-, 36-, and 42-hour assessments), a pain score may be collected then.

If a subject is discharged prior to any of the scheduled VAS assessments collected at 6 to 72 hours postsurgery, a member of the study site staff will contact the subject at the appropriate scheduled times (ie, the time of each assessment scheduled to be collected from 6 to 72 hours that occurs after hospital discharge) to remind her to complete the VAS assessment and to record the scheduled assessment in the Participant Diary. This will ensure that for any subject discharged prior to 72 hours, all VAS assessments required for calculation of the study endpoints are captured. These phone calls will only occur if a subject is discharged prior to 72 hours.

While in the hospital, subjects will also record an unscheduled VAS pain score immediately before any requested opioid pain medication.

To assess pain intensity (VAS) at rest, the subject should rest quietly in a supine or seated position that does not exacerbate her postsurgical pain for 3-5 minutes before entering the pain score.

While in the hospital, subjects are to assess, "How much pain are you experiencing right now?" and a vertical mark will be placed on the line below to indicate the level of pain experienced at the time of assessment.

At home, the subject will assess pain intensity at rest each day at noon (± 4 hours). This assessment should capture her average pain at rest in the prior 24 hours by assessing, "What has been your average pain since your last pain assessment?" (ie, from noon on the previous day to the current assessment).

Visual Analog Scale (VAS)

No Pain — Pain as Bad as it Could Possible Be

(**For reference only; not for clinical use**.)

Appendix 2: Discharge Readiness

The subject's discharge readiness will be assessed using the Modified Postanesthesia Discharge Scoring System below (Chung 1995a; Chung 1995b).

The discharge readiness assessment will be used for data collection only and is not intended to interfere with the investigational site's policy for determining when the subject should be discharged from the hospital.

Discharge readiness will be assessed at 24, 48, and 72 hours, or hospital discharge, or until the subject attains score of 9, whichever comes first. Once a score of 9 is reached, no further discharge readiness assessments are required

Modified Postanesthesia Discharge Scoring System

Parameter	Score
Vital Signs: measure systolic blood pressure, heart rate, respiratory rate, temperature	
• All 4 vital signs are within 20% of the preoperative values	2
• Any of the 4 vital signs are within 20-40% of the preoperative values and none exceeds 40% of the preoperative value	1
• Any of the 4 vital signs are >40% of the preoperative values	0
Ambulation	
• Steady gait/no dizziness	2
• With assistance	1
• None/dizziness	0
Nausea and Vomiting	
• Minimal: no nausea/vomiting or nausea not requiring treatment	2
• Moderate: nausea without vomiting and can tolerate liquids	1
• Severe: nausea/vomiting and unable to tolerate oral liquids	0
Pain	
• Minimal: requiring one or less pain rescue in the prior 12 hours	2
• Moderate: requiring more than one pain rescue in the prior 12 hours	1
• Severe: requiring supplemental IV analgesia for pain rescue	0
Surgical Bleeding	
• Minimal: no action required	2
• Moderate: requires dressing change because it has soaked through or a compressive dressing	1
• Severe: requires a suture or a return to the operating room	0

Appendix 3: Subject Satisfaction with Postsurgical Pain Control (Likert Scale)

The subject's satisfaction with postsurgical pain control will be conducted at 72 hours after surgery (or at hospital discharge, whichever occurs first).

Please circle the number below that best describes your overall satisfaction with your pain control, pain management and treatment after surgery. (Select one number only.)

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

Appendix 4: Overall Benefit of Analgesia Score Questionnaire

The OBAS questionnaire will be completed at 24, 48, and 72 hours after surgery (ie, closure of the C-section wound).

Note: If a subject is discharged prior to any of the scheduled OBAS assessments collected at 24 to 72 hours postsurgery, a member of the study site staff will contact the subject at the appropriate scheduled times (ie, the time of each assessment scheduled to be collected from 24 to 72 hours that occurs after hospital discharge) to remind her to complete the OBAS questionnaire and to record her answers to the questionnaire in the Participant Diary. This will ensure that for any subject discharged prior to 72 hours, all OBAS assessments required for calculation of the study endpoints are captured. These phone calls will only occur if a subject is discharged prior to 72 hours.

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

Appendix 5: Quality of Recovery 15-item Questionnaire

The QoR-15 will be conducted at 72 hours after surgery (or at hospital discharge, whichever occurs first).

Part A

How have you been feeling in the last 24 hours?

(0 to 10, where: 0 = none of the time [poor] and 10 = all of the time [excellent])

1.	Able to breathe easily	None of the time 0 1 2 3 4 5 6 7 8 9 10 All of the time
2.	Been able to enjoy food	None of the time 0 1 2 3 4 5 6 7 8 9 10 All of the time
3.	Feeling rested	None of the time 0 1 2 3 4 5 6 7 8 9 10 All of the time
4.	Have had a good sleep	None of the time 0 1 2 3 4 5 6 7 8 9 10 All of the time
5.	Able to look after personal toilet and hygiene unaided	None of the time 0 1 2 3 4 5 6 7 8 9 10 All of the time
6.	Able to communicate with family or friends	None of the time 0 1 2 3 4 5 6 7 8 9 10 All of the time
7.	Getting support from hospital doctors and nurses	None of the time 0 1 2 3 4 5 6 7 8 9 10 All of the time

8.	Able to return to work or usual home activities	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
9.	Feeling comfortable and in control	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
10.	Having a feeling of general well-being	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time

Part B

Have you had any of the following in the last 24 hours?

(10 to 0, where: 10 = none of the time [excellent] and 0 = all of the time [poor])

11.	Moderate pain	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time
12.	Severe pain	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time
13.	Nausea or vomiting	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time
14.	Feeling worried or anxious	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time
15.	Feeling sad or depressed	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time

Total Score

Appendix 6: Clinical Laboratory Tests

Clinical laboratory tests (hematology and chemistry) will be conducted at screening in accordance with the investigator's standard of care including:

1. Direct bilirubin
2. Gamma-glutamyl transpeptidase (GGT) and lactate dehydrogenase (LDH)
   OR
   Alanine transaminase (ALT) and aspartate transaminase (AST).